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DESCRIPCIÓN

Compuestos Heterocíclicos de Fenoximetilo

5 Antecedentes

Las fosfodiesterasas cíclicas son enzimas intracelulares que, a través de la hidrólisis de los nucleótidos cíclicos AMPc y GMPc, regulan los niveles de estos nucleótidos monofosfato que sirven como segundos mensajeros en la cascada de señalización de los receptores acoplados a proteína G. En las neuronas, las PDE también juegan un papel en la regulación de las quinasas dependientes de GMPc y AMPc aguas abajo que desfosforilan proteínas implicadas en la regulación de la transmisión sináptica y la homeostasis. Hasta la fecha, se han identificado nueve familias de PDE diferentes que están codificadas por 21 genes. Las PDE contienen un dominio regulador N-terminal variable y un dominio catalítico C-terminal altamente conservado y difieren en su especificidad de sustrato, expresión y localización en los compartimentos celulares y tisulares, incluyendo el SNC.

El descubrimiento de una nueva familia de PDE, PDE10, fue referido simultáneamente por tres grupos en 1999 (Soderling et al. "Isolation and characterization of a dual-substrate phosphodiesterase gene family: PDE10A" Proc. Natl Sci. 1999, 96, 7071-7076; Loughney et al. "Isolation and characterization of PDE10A, a novel human 3',5'-cyclic nucleotide phosphodiesterase" Gene 1999, 234, 109-117; Fujishige et al. "Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A)" J. Biol. Chem. 1999, 274, 18438-18445). La secuencia de PDE10 humana es altamente homóloga en las variantes tanto de rata como de ratón con una identidad de aminoácidos total de 95%, y una identidad de 98% conservada en la región catalítica.

La PDE10 se expresa principalmente en el cerebro (núcleo caudado y putamen) y está altamente localizada en las neuronas espinosas medianas del cuerpo estriado, que es una de las entradas principales hacia los ganglios basales. Esta localización de PDE10 ha conducido a la suposición de que pueden influir en las rutas dopaminérgica y glutamatérgica ambas las cuales juegan papeles en la patología de diversos trastornos psicóticos y neurodegenerativos.

La PDE10 hidroliza tanto AMPc ($K_m = 0,05 \mu M$) como GMPc ($K_m = 3 \mu M$) (Soderling et al. "Isolation and Characterization de a dual-substrate phosphodiesterase gene family: PDE10," Proc. Natl Sci. USA 1999, 96(12), 7071-7076). Además, PDE10 tiene una V_{max} cinco veces mayor para GMPc que para AMPc y estos datos cinéticos *in vitro* han conducido a la suposición de que PDE10 puede actuar como una GMPc fosfodiesterasa inhibida por AMPc *in vivo* (Soderling y Beavo "Regulation of AMPc and GMPc signaling: New phosphodiesterases y new functions", Curr. Opin. Cell Biol., 2000, 12, 174-179).

La PDE10 también es uno de los cinco miembros de fosfodiesterasa que contienen un dominio GAF en tándem en su extremo N. Se diferencia por el hecho de que las otras PDE que contienen GAF (PDE2, 5, 6, y 11) se unen a GMPc sin bien datos recientes apuntan a la unión estrecha del AMPc al dominio GAF de PDE10 (Handa et al. "Crystal structure of the GAF-B domain from human phosphodiesterase 10A complexed con its ligand, AMPc" J. Biol. Chem. 2008, May 13^a, ePub).

Se han descrito inhibidores de PDE10 para el tratamiento de una variedad de trastornos neurológicos y psiquiátricos incluyendo la enfermedad de Parkinson, la esquizofrenia, la enfermedad de Huntington, los trastornos delirantes, las psicosis inducidas por fármacos, los trastornos obsesivo compulsivos y de pánico (Solicitud de Patente de los Estados Unidos Núm. 2003/0032579). Estudios en ratas (Kostowski et. al "Papaverine drug induced stereotypy and catalepsy and biogenic aminas in the brain of the rat" Pharmacol. Biochem. Behav. 1976, 5, 15-17) han mostrado que la papaverina, un inhibidor selectivo de PDE10, reduce las estereotipias inducidas por apomorfina y los niveles de dopamina en cerebro de rata e incrementa la catalepsia inducida por haloperidol. Este experimento confiere apoyo al uso de un inhibidor de PDE10 como antipsicótico puesto que se han observado tendencias similares con antipsicóticos comercializados, conocidos.

Las medicaciones con antipsicóticos son el fundamento del tratamiento actual para la esquizofrenia. Los antipsicóticos convencionales o clásicos, tipificados por el haloperidol, fueron introducidos a mediados de la década de 1950 y tienen un registro probado de resultados a lo largo de la última mitad del siglo en el tratamiento de la esquizofrenia. Si bien estos fármacos son eficaces contra los síntomas psicóticos, positivos de la esquizofrenia, muestran un pequeño beneficio en el alivio de los síntomas negativos de deterioro cognitivo asociado con la enfermedad. Además, fármacos tales como el haloperidol tienen efectos secundarios extremos tales como síntomas extrapiramidales (EPS) debido a su interacción específica con el receptor de dopamina D2, También puede presentarse una afección incluso más grave caracterizada por movimientos motores anómalos, prolongados, significativos conocida como discinesia tardía con el tratamiento prolongado con antipsicóticos clásicos.

En la década de 1990 se observó el desarrollo de algunos nuevos fármacos para la esquizofrenia, referidos como antipsicóticos atípicos, tipificados por la risperidona y la olanzapina y muy eficazmente, la clozapina. Estos

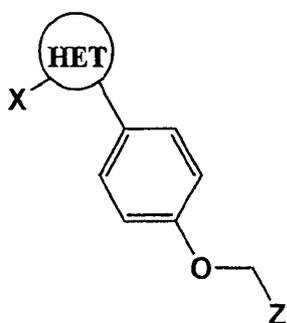
antipsicóticos atípicos están caracterizados generalmente por su eficacia para los síntomas tanto positivos como negativos asociados con la esquizofrenia, pero tienen poca eficacia contra las deficiencias cognitivas y el deterioro cognitivo persistente sigue constituyendo un grave problema de salud pública (Davis, J.M et al. "Dose response and dose equivalence of antipsychotics." Journal of Clinical Psychopharmacology, 2004, 24 (2), 192-208; Friedman, J.H. et al "Treatment of psychosis in Parkinson's disease: Safety considerations". Drug Safety, 2003, 26 (9), 643-659). Además, los agentes antipsicóticos atípicos, si bien son eficaces en el tratamiento de los síntomas positivos y, en cierto grado, de los síntomas negativos de la esquizofrenia, tienen efectos secundarios significativos. Por ejemplo, la clozapina que es uno de los fármacos antipsicóticos más eficaces clínicamente muestra agranulocitosis en aproximadamente 1,5% de los pacientes observándose mortalidad debida a este efecto secundario. Otros fármacos antipsicóticos atípicos tienen efectos secundarios significativos incluyendo efectos secundarios metabólicos (diabetes tipo 2, ganancia de peso significativa, y dislipidemia), disfunción sexual, sedación, y efectos secundarios cardiovasculares potenciales que comprometen su eficacia clínica. En el extenso estudio CATIE financiado por el NIH publicado recientemente, (Lieberman et al "The Clinical Antipsychotic Trials Of Intervention Effectiveness (CATIE) Schizophrenia Trial: clinical comparison of subgroups with and without the metabolic syndrome." Schizophrenia Research, 2005, 80 (1), 9-43) 74% de pacientes interrumpieron el uso de su medicación antipsicótica en el plazo de 18 meses debido a varios factores incluyendo una escasa tolerabilidad o una eficacia incompleta. Por lo tanto, todavía existe una necesidad clínica sustancial de medicaciones antipsicóticas más eficaces y mejor toleradas posiblemente a través del uso de inhibidores de PDE10,

El documento WO 2007/077490 A2 describe inhibidores de PDE10 heteroarílicos bicíclicos que contienen benzimidazol, benzotiazol y otros sistemas anulares nitrogenados fusionados.

Breve Resumen

La descripción se refiere a compuestos que son inhibidores de la fosfodiesterasa 10, La descripción se refiere adicionalmente a procedimientos, a composiciones farmacéuticas, a preparaciones farmacéuticas y al uso farmacéutico de los compuestos en el tratamiento de mamíferos, incluyendo seres humanos para trastornos del sistema nervioso central (CNS) y otros trastornos que pueden afectar a la función del SNC. La descripción también se refiere a compuestos para el tratamiento de trastornos neurológicos, neurodegenerativos y psiquiátricos incluyendo peso no limitados a aquellos que comprenden déficits cognitivos o síntomas esquizofrénicos.

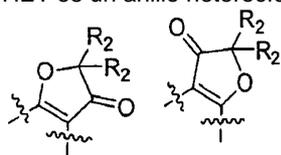
En la presente memoria se describen compuestos de Fórmula (I) que son inhibidores de al menos una fosfodiesterasa 10:



(I)

En donde:

HET es un anillo heterocíclico seleccionado entre las Fórmulas A29 y A31 de más abajo



A29

A31

y el radical más a la izquierda está conectado al grupo X;

X se selecciona entre arilo sustituido opcionalmente y heteroarilo sustituido opcionalmente;

Z es heteroarilo sustituido opcionalmente;

Cada R₂ se selecciona independientemente entre alquilo C₁-C₄, o dos grupos R₂ tomados junto con el carbono al que están anclados forman un anillo de cicloalquilo de 3 miembros;

En una realización, los grupos alquilo están completamente saturado ya estén presentes solos o como parte de otro grupo (p. ej. alquilamino o alcoxi).

En ciertas realizaciones, los grupos sustituyentes no están sustituidos adicionalmente.

En diversas realizaciones, cualquier grupo que esté definido por estar sustituido opcionalmente puede estar sustituido opcionalmente una sola vez o múltiples veces independientemente.

- 5 En una realización, HET se selecciona entre las Fórmulas A29 y A31,
- En otra realización, HET es la Fórmula A29,
- 10 En otra realización, HET es la Fórmula A31,
- En una realización, X se selecciona entre un heteroarilo monocíclico que tiene 5 átomos anulares seleccionados entre C, O, S y N siempre que el número total de heteroátomos anulares sea menor que o igual a cuatro y donde no más de uno del número total de heteroátomos es oxígeno o azufre, y un anillo aromático monocíclico que tiene 6
- 15 átomos seleccionados entre C y N siempre que no más de tres átomos anulares sean N, y donde dicho anillo puede estar sustituido opcionalmente e independientemente con hasta dos grupos seleccionados entre alquilo C₁-C₄, cicloalquilo, cicloalquiloxi, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro. Los ejemplos incluyen pero no están limitados a 1H-pirrolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, isotiazolilo, isoxazolilo, oxazolilo, tiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tetrazolilo, 1,2,3,4-oxatriazolilo, 1,2,3,5-oxatriazolilo, 1,2,3,4-tiatrizolilo, 1,2,3,5-tiatrizolilo, 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo, piridinilo, pirazinilo, piridazinilo y pirimidinilo.
- 20 En una realización adicional, X es un heteroarilo monocíclico que tiene 6 átomos anulares seleccionados entre C y N siempre que no más de tres átomos anulares sean N, y donde dicho anillo puede estar sustituido opcionalmente e independientemente con hasta dos grupos seleccionados entre alquilo C₁-C₄, cicloalquilo, cicloalquiloxi, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro. Los ejemplos incluyen pero no están limitados a 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo, piridinilo, pirazinilo, piridazinilo y pirimidinilo.
- 25 En una realización adicional, X es un heteroarilo monocíclico que tiene 5 átomos anulares seleccionados entre C, O, S, y N, siempre que el número total de heteroátomos anulares sea menor que o igual a cuatro y donde no más de uno del número total de heteroátomos es oxígeno o azufre y donde dicho anillo puede estar sustituido opcionalmente e independientemente con hasta dos grupos seleccionados entre alquilo C₁-C₄, cicloalquilo, cicloalquiloxi, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro. Los ejemplos incluyen pero no están limitados a 1H-pirrolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, isotiazolilo, isoxazolilo, oxazolilo, tiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tetrazolilo, 1,2,3,4-oxatriazolilo, 1,2,3,5-oxatriazolilo, 1,2,3,4-tiatrizolilo, 1,2,3,5-tiatrizolilo.
- 35 En una realización adicional, X es 4-piridinilo sustituido opcionalmente con un grupo seleccionado entre alquilo C₁-C₄, ciclopropilo, ciclopropiloxi, ciclopropilmetilo, alcoxi C₁-C₄, CF₃, amino, alquilamino, dialquilamino, tioalquilo, halógeno, alquilsulfonilo y ciano.
- 40 En una realización adicional, X es 4-piridinilo.
- En otra realización X se selecciona entre fenilo restringido.
- 50 En una realización adicional, X se selecciona entre un fenilo 3,4-disustituido, fenilo 4-sustituido y 4-piridinilo.
- En una realización adicional, X se selecciona entre un fenilo 3,4-disustituido y fenilo 4-sustituido.
- 55 En otra realización, X se selecciona entre 4-piridinilo y fenilo 4-sustituido.
- En una realización adicional, X es 4-sustituido fenilo.
- En una realización adicional, X es 4-metoxifenilo.
- 60 En otra realización, X es 4-clorofenilo.
- En otra realización, X es 4-cianofenilo.

5 En otra realización, Z se selecciona entre imidazo[1,2-a]piridin-2-ilo, imidazo[1,2-b]piridazin-2-ilo, e imidazo[1,2-b]piridazin-6-ilo todos los cuales pueden estar sustituidos opcionalmente con hasta 2 sustituyentes seleccionados independientemente entre alquilo C₁-C₄, cicloalquilo, cicloalquiloxi, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro.

10 En una realización adicional, Z se selecciona entre imidazo[1,2-a]piridin-2-ilo, imidazo[1,2-b]piridazin-2-ilo, e imidazo[1,2-b]piridazin-6-ilo todos los cuales pueden estar sustituidos opcionalmente con hasta 2 sustituyentes seleccionados independientemente entre alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalquil(C₃-C₆)oxi, cicloalquilalquilo, cicloalquilalcoxi, halógeno, alquilsulfonilo y ciano.

15 En una realización adicional, Z es imidazo[1,2-a]piridin-2-ilo sustituido con hasta 2 sustituyentes seleccionados independientemente entre alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalquil(C₃-C₆)oxi, cicloalquilalquilo, cicloalquilalcoxi, halógeno, alquilsulfonilo y ciano.

En una realización adicional, Z es imidazo[1,2-b]piridazin-2-ilo sustituido con hasta 2 sustituyentes seleccionados independientemente entre alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalquil(C₃-C₆)oxi, cicloalquilalquilo, cicloalquilalcoxi, halógeno, alquilsulfonilo y ciano.

20 En una realización adicional, Z es imidazo[1,2-b]piridazin-6-ilo sustituido con hasta 2 sustituyentes seleccionados independientemente entre alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalquil(C₃-C₆)oxi, cicloalquilalquilo, cicloalquilalcoxi, halógeno, alquilsulfonilo y ciano.

25 En una realización adicional, cualquier sustituyente Z puede estar insustituido.

En una realización, R₂ es C₁-C₄ alquilo.

En otra realización, R₂ es metilo.

30 En otra realización, dos grupos R₂ tomados juntos forman un anillo de cicloalquilo de 3 miembros.

Los compuestos de la descripción pueden contener centros asimétricos y existir en forma de diferentes enantiómeros o diastereómeros o una combinación de estos. Todas las formas enantioméricas, diastereoméricas de Fórmula (I) están incluidas en la presente memoria.

35 Los compuestos de la descripción pueden estar en forma de sales farmacéuticamente aceptables. La frase "farmacéuticamente aceptables" hace referencia a sales preparadas a partir de ácidos y bases no tóxicos farmacéuticamente aceptables, incluyendo bases inorgánicas y orgánicas y ácidos inorgánicos y orgánicos. Las sales derivadas de bases inorgánicas incluyen litio, sodio, potasio, magnesio, calcio y cinc. Las sales derivadas de bases orgánicas incluyen amoníaco, aminas primarias, secundarias y terciarias, y aminoácidos. Las sales derivadas de ácidos inorgánicos incluyen sulfúrico, clorhídrico, fosfórico, bromhídrico. Las sales derivadas de ácidos orgánicos incluyen ácidos alquil(C₁-C₆)carboxílicos, ácidos di-carboxílicos y ácidos tricarboxílicos tales como ácido acético, ácido propiónico, ácido fumárico, ácido maleico, ácido succínico, ácido tartárico, ácido adipico y ácido cítrico, y ácidos alquilsulfónicos tales como metanosulfónico, y ácidos arilsulfónicos tales como ácido para-toluenosulfónico y ácido bencenosulfónico

40 Los compuestos de la descripción pueden estar en forma de un solvato. Esto ocurre cuando un compuesto de Fórmula (I) tiene una interacción energéticamente favorable con un disolvente, cristaliza de una manera en la que incorpora moléculas de disolvente en la red cristalina o se forma un complejo con moléculas de disolvente en el estado sólido o líquido. Los ejemplos de los disolventes que forman solvatos son agua (hidratos), MeOH, EtOH, iPrOH, y acetona.

50 Los compuestos de la descripción pueden existir en diferentes formas cristalinas conocidas como formas polimorfas. Polimorfismo es la capacidad de una sustancia para existir en dos o más fases cristalinas que tienen diferentes ordenamientos y/o conformaciones de la molécula en la red cristalina.

55 Los compuestos de la descripción pueden existir en forma de compuestos marcados isotópicamente de Fórmula (I) donde uno o más átomos son remplazados por átomos que tienen el mismo número atómico pero una masa atómica diferente de la masa atómica que se observa predominantemente en la naturaleza. Los ejemplos de los isótopos incluyen, pero no están limitados a isótopos de hidrógeno (deuterio, tritio), isótopos de carbono (¹¹C, ¹³C, ¹⁴C) e isótopos de nitrógeno (¹³N, ¹⁵N). Por ejemplo, la sustitución por isótopos más pesados tales como deuterio (²H) puede ofrecer ciertas ventajas terapéuticas resultantes de una mayor estabilidad metabólica que podría ser preferible y conducir a una vida media *in vivo* más prolongada o una reducción de la dosis en un mamífero o ser humano.

Los profármacos de los compuestos abarcados por la Fórmula (I) también se describen en la presente memoria. Derivados concretos de los compuestos de Fórmula (I) que pueden tener por sí mismos una actividad farmacológica pequeña o casi inexistente, cuando se administran a un mamífero o ser humano, pueden ser convertidos en compuestos de Fórmula (I) que tienen la actividad biológica deseada.

Los compuestos de la descripción y sus sales farmacéuticamente aceptables, se pueden utilizar también para tratar ciertos trastornos alimentarios, obesidad, ludopatía compulsiva, trastornos sexuales, narcolepsia, trastornos del sueño, diabetes, síndrome metabólico, trastornos neurodegenerativos y trastornos/afecciones del SNC así como en el tratamiento de la cesación del hábito de fumar.

En una realización el tratamiento de los trastornos y afecciones del SNC por medio de los compuestos de la descripción puede incluir la enfermedad de Huntington, la esquizofrenia y las afecciones esquizo-afectivas, los trastornos delirantes, las psicosis inducidas por fármacos, el pánico y los trastornos obsesivo compulsivos, los trastornos de estrés post-traumático, el deterioro cognitivo relacionado con la edad, el trastorno de déficit de atención/hiperactividad, los trastornos bipolares, los trastornos de la personalidad de tipo paranoide, los trastornos de la personalidad de tipo esquizoide, la psicosis inducida por alcohol, anfetaminas, fenciclidina, alucinógenos opiáceos u otras psicosis inducidas por fármacos, discinesia o afecciones coreiformes incluyendo discinesia inducida por agonistas de dopamina, terapias dopaminérgicas, psicosis asociada con la enfermedad de Parkinson, síntomas psicóticos asociados con otros trastornos neurodegenerativos incluyendo enfermedad de Alzheimer, afecciones distónicas tales como la distonía idiopática, la distonía inducida por fármacos, la distonía por torsión, y la discinesia tardía, trastornos del estado de ánimo incluyendo episodios depresivos mayores, la depresión post-ictus, trastorno depresivo menor, trastorno disfórico premenstrual, demencia incluyendo pero no limitada a demencia por infarto múltiple, demencia relacionada con el SIDA, y demencia neurodegenerativa.

En otra realización, los compuestos de la descripción se pueden utilizar para el tratamiento de trastornos alimentarios, obesidad, ludopatía compulsiva, trastornos sexuales, narcolepsia, trastornos del sueño así como en el tratamiento de la cesación del hábito de fumar.

En una realización adicional, los compuestos de la descripción se pueden utilizar para el tratamiento de la obesidad, la esquizofrenia, las afecciones esquizo-afectivas, la enfermedad de Huntington, las afecciones distónicas y la discinesia tardía.

En otra realización, los compuestos de la descripción se pueden utilizar para el tratamiento de la esquizofrenia, las afecciones esquizo-afectivas, la enfermedad de Huntington y la obesidad.

En una realización adicional, los compuestos de la descripción se pueden utilizar para el tratamiento de la esquizofrenia y las afecciones esquizo-afectivas.

En una realización adicional, los compuestos de la descripción se pueden utilizar para el tratamiento de la enfermedad de Huntington.

En otra realización, los compuestos de la descripción se pueden utilizar para el tratamiento de la obesidad y del síndrome metabólico.

Los compuestos de la descripción también se pueden utilizar en mamíferos y seres humanos junto con medicaciones antipsicóticas convencionales incluyendo pero no limitadas a Clozapina, Olanzapina, Risperidona, Ziprasidona, Haloperidol, Aripiprazol, Sertindol y Quetiapina. La combinación de un compuesto de Fórmula (I) con una dosis subterapéutica de una medicación antipsicótica convencional anteriormente mencionada puede proporcionar ciertas ventajas de tratamiento incluyendo perfiles de efectos secundarios mejorados y requerimientos de dosificación inferiores.

Definiciones

Se pretende que alquilo denote un hidrocarburo C₁-C₈ alifático saturado o insaturado lineal o ramificado que puede estar sustituido opcionalmente con hasta 3 átomos de flúor y, si se especifica, sustituido con otros grupos. La insaturación en forma de un enlace carbono-carbono doble o triple puede ser interna o estar localizada terminalmente y en el caso de un enlace doble están incluidos los isómeros cis y trans. Los ejemplos de los grupos alquilo incluyen pero no están limitados a metilo, trifluorometilo, etilo, trifluoroetilo, isobutilo, neopentilo, cis- y trans-2-butenilo, isobutenilo, propargilo. Alquilo C₁-C₄ es el subgrupo de alquilo limitado a un total de hasta 4 átomos de carbono.

En cada caso en el que se describe un rango de tamaño para el número de átomos en un anillo o cadena, se describen todos los subgrupos. De este modo, C_x-C_y incluye todos los subgrupos, p. ej., C₁-C₄ incluye C₁-C₂, C₂-C₄, C₁-C₃ etc.

5 Acilo es un grupo alquil-C(O)- en donde alquilo se define como antes. Los ejemplos de los grupos acilo incluyen acetilo y propionilo.

Alcoxi es un grupo alquil-O- en donde alquilo se define como antes. Alcoxi C₁-C₄ es el subgrupo de alquil-O- donde el subgrupo de alquilo está limitado a total de hasta 4 átomos de carbono. Los ejemplos de los grupos alcoxi incluyen metoxi, trifluorometoxi, etoxi, trifluoroetoxi, y propoxi.

10 Alcoxialquilo es un grupo alquil-O-(alquil C₁-C₄)- en donde alquilo se define como antes. Los ejemplos de los grupos alcoxialquilo incluyen metoximetilo y etoximetilo.

15 Alcoxialquiloxi es un grupo alcoxi-alquil-O- en donde alcoxi y alquilo se definen como antes. Los ejemplos de los grupos alcoxialquiloxi incluyen los grupos metoximetiloxi (CH₃OCH₂O-) y metoxietiloxi (CH₃OCH₂CH₂O-).

Alquiltio es un grupo alquil-S- en donde alquilo se define como antes. Alquiltio incluye alquiltio C₁-C₄.

20 Alquilsulfonilo es alquil-SO₂- en donde alquilo se define como antes. Alquilsulfonilo incluye alquil(C₁-C₄)sulfonilo.

Alquilamino es alquil-NH- en donde alquilo se define como antes. Alquilamino incluye alquil(C₁-C₄)amino.

Dialquilamino es (alquil)₂-N- en donde alquilo se define como antes.

25 Amido es H₂NC(O)-.

Alquilamido es alquil-NHC(O)- en donde alquilo se define como antes.

30 Dialquilamido es (alquil)₂-NC(O)- en donde alquilo se define como antes.

Aromático es heteroarilo o arilo en donde heteroarilo y arilo se definen a continuación.

35 Arilo es un grupo fenilo o naftilo. Los grupos arilo pueden estar sustituidos opcionalmente e independientemente con hasta tres grupos seleccionados entre halógeno, CF₃, CN, NO₂, OH, alquilo, cicloalquilo, cicloalquilalquilo, alcoxi, alcoxialquilo, ariloxi, alcoxialquiloxi, heterocicloalquilo, heterocicloalquilalquilo, heterocicloalquiloxi, heteroarilo, heteroariloxi, -OCH₂CH₂OCH₃, -OC(O)R_a, -OC(O)OR_a, -OC(O)NHR_a, -OC(O)N(R_a), -SR_a, -S(O)R_a, -NH₂, -NHR_a, -N(R_a)(R_b), -NHC(O)R_a, -N(R_a)C(O)R_b, -NHC(O)OR_a, -N(R_a)C(O)OR_b, -N(R_a)C(O)NH(R_b), -N(R_a)C(O)NH(R_b)₂, -C(O)NH₂, -C(O)NHR_a, -C(O)N(R_a)(R_b), -CO₂H, -CO₂R_a, -COR_a en donde R_a y R_b se seleccionan independientemente entre alquilo, alcoxialquilo, -CH₂CH₂OH, -CH₂CH₂OMe, cicloalquilo, cicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterocicloalquilo, y heterocicloalquilalquilo, cada uno de los cuales está sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre solamente halógeno, Me, Et, ⁱPr, ^tBu, ciclopropilo no sustituido, ciclobutilo no sustituido, CN, NO₂, NH₂, CF₃, NHMe, NMe₂, OMe, OCF₃, cada uno de los cuales está anclado a través de enlaces sencillos carbono-carbono o carbono-nitrogeno o carbono-oxígeno; o R_a y R_b tomados junto con el átomo o los átomos a los que están anclados forman un anillo de 5-6 miembros.

Arilalquilo es un grupo aril-alquil- en donde arilo y alquilo se definen como antes.

50 Ariloxi es un grupo aril-O- en donde arilo se define como antes.

Arilalcoxi es un grupo aril-(alquil C₁-C₄)-O- en donde arilo se define como antes.

55 Carboxi es un grupo CO₂H o CO₂R_c en donde R_c se selecciona independientemente entre, alquilo, alquilo C₁-C₄, cicloalquilo, arilalquilo, cicloalquilalquilo, CF₃, y alcoxialquilo, en donde alquilo se define como antes.

Cicloalquilo es un hidrocarburo no aromático cíclico C₃-C₇ que puede contener un único doble enlace y está sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre alquilo, alcoxi, hidroxilo y oxo. Los ejemplos de los grupos cicloalquilo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopentenilo y ciclohexanonilo.

60 Cicloalquiloxi es un grupo cicloalquil-O- en donde cicloalquilo se define como antes. Los ejemplos incluyen ciclopropiloxi, ciclobutiloxi y ciclopentiloxi. Cicloalquil(C₃-C₆)oxi es el subgrupo de cicloalquil-O- donde cicloalquilo contiene 3-6 átomos de carbono. Cicloalquilalquilo es un grupo cicloalquil-(alquilo C₁-C₄)-. Los ejemplos incluyen ciclopropilmetilo, ciclobutilmetilo, ciclohexilmetilo y ciclohexilmetilo.

Cicloalquilalcoxi es un grupo cicloalquil-(alquil C₁-C₄)-O- en donde cicloalquilo y alquilo se definen como antes. Los ejemplos de los grupos cicloalquilalcoxi incluyen ciclopropilmetoxi, ciclopentilmetoxi y ciclohexilmetoxi. Halógeno es F, Cl, Br o I.

5 Heteroarilo es a tetrazol, 1,2,3,4-oxatriazol, 1,2,3,5-oxatriazol, un sistema anular aromático mono o bicíclico, o un sistema anular heterobíciclico con teniendo un anillo aromático de 5 a 10 átomos anulares seleccionados independientemente entre C, N, O y S, siempre que no más de 3 átomos anulares en cualquier anillo individual sean distintos de C. Los ejemplos de los grupos heteroarilo incluyen pero no están limitados a tiofenilo, furanilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, pirrazolilo, imidazolilo, 1,2,3-triazolilo, 1,3,4-triazolilo, pirimidinilo, pirazinilo, indolilo, quinolilo, tetrahidroquinolilo, isoquinolilo, tetrahidroisoquinolilo, indazolilo, benzotiadiazolilo, benzoxadiazolilo y benzimidazolilo. Los grupos heteroarilo pueden estar sustituidos opcionalmente e independientemente con hasta 3 sustituyentes seleccionados independientemente entre halógeno, CF₃, CN, NO₂, OH, alquilo, cicloalquilo, cicloalquilalquilo, alcoxi, alcoxialquilo, ariloxi, alcoxialquilo, heterocicloalquilo, heterocicloalquilalquilo, heterocicloalquiloxi, heteroarilo, heteroariloxi, -OCH₂CH₂OCH₃, -OC(O)R_a, -OC(O)OR_a, -OC(O)NHR_a, -OC(O)N(R_a), -SR_a, -S(O)R_a, -NH₂, -NHR_a, -N(R_a)(R_b), -NHC(O)R_a, -N(R_a)C(O)R_b, -NHC(O)OR_a, -N(R_a)C(O)OR_b, -N(R_a)C(O)NH(R_b), -N(R_a)C(O)NH(R_b)₂, -C(O)NH₂, -C(O)NHR_a, -C(O)N(R_a)(R_b), -CO₂H, -CO₂R_a, -COR_a en donde R_a y R_b se seleccionan independientemente entre alquilo, alcoxialquilo, -CH₂CH₂OH, -CH₂CH₂OMe, cicloalquilo, cicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterocicloalquilo, y heterocicloalquilalquilo, cada uno de los cuales está sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre solamente halógeno, Me, Et, ⁱPr, ^tBu, ciclopropilo no sustituido, ciclobutilo no sustituido, CN, NO₂, NH₂, CF₃, NHMe, NMe₂, OMe, OCF₃, cada uno de los cuales está anclado a través de enlaces carbono-carbono, carbono-nitrógeno o carbono-oxígeno; o R_a y R_b tomados junto con el átomo o los átomos a los que están anclados forman un anillo de 5-6 miembros.

Heteroarilalquilo es un grupo heteroaril-(alquilo C₁-C₄)- en donde heteroarilo y alquilo se definen como antes. Los ejemplos de los grupos heteroarilalquilo incluyen 4-piridinilmetilo y 4-piridiniletilo.

30 Heteroariloxi es un grupo heteroaril-O en donde heteroarilo se define como antes.

Heteroarilalcoxi es un grupo heteroaril-(alquil C₁-C₄)-O- en donde heteroarilo y alcoxi se definen como antes. Los ejemplos de los grupos heteroarilalquilo incluyen 4-piridinilmetoxi y 4-piridiniletoxi.

35 Sistema anular heterobíciclico es un sistema anular que tiene 8-10 átomos seleccionados independientemente entre C, N, O y S, siempre que no más de 3 átomos anulares en cualquier anillo sencillo sean distintos de carbono y siempre que al menos uno de los anillos sea aromático; dicho anillo bicíclico puede estar sustituido opcionalmente e independientemente con hasta 3 sustituyentes seleccionados independientemente entre alquilo, alcoxi, cicloalquilo, cicloalquil(C₃-C₆)oxi, cicloalquilalquilo, halógeno, nitro, alquilsulfonilo y ciano. Los ejemplos de los sistemas anulares heterobíciclicos de 8-10 miembros incluyen pero no están limitados a 1,5-naftiridilo, 1,2,3,4-tetrahidro-1,5-naftiridilo 1,6-naftiridilo, 1,2,3,4-tetrahidro-1,6-naftiridilo 1,7-naftiridilo, 1,2,3,4-tetrahidro-1,7-naftiridinilo 1,8-naftiridilo, 1,2,3,4-tetrahidro-1,8-naftiridilo, 2,6-naftiridilo, 2,7-naftiridilo, cinolilo, isoquinolilo, tetrahidroisoquinolilo, ftalazilo, quinazolilo, 1,2,3,4-tetrahidroquinazolinilo, quinolilo, tetrahidroquinolinilo, quinoxalilo, tetrahidroquinoxalinilo, benzo[d][1,2,3]triazilo, benzo[e][1,2,4]triazilo, pirido[2,3-b]pirazilo, pirido[2,3-c]piridazilo, pirido[2,3-d]pirimidilo, pirido[3,2-b]pirazilo, pirido[3,2-c]piridazilo, pirido[3,2-d]pirimidilo, pirido[3,4-b]pirazilo, pirido[3,4-c]piridazilo, pirido[3,4-d]pirimidilo, pirido[4,3-b]pirazilo, pirido[4,3-c]piridazilo, pirido[4,3-d]pirimidilo, quinazolilo, 1H-benzo[d][1,2,3]triazolo, 1H-benzo[d]imidazoilo, 1H-indazoilo, 1H-indoilo, 2H-benzo[d][1,2,3]triazolo, 2H-pirazolo[3,4-b]piridinilo, 2H-pirazolo[4,3-b]piridinilo, [1,2,3]triazolo[1,5-a]piridinilo, [1,2,4]triazolo[1,5-a]piridinilo, [1,2,4]triazolo[4,3-a]piridinilo, benzo[b]tienilo, benzo[c][1,2,5]oxadiazilo, benzo[c][1,2,5]tiadiazolilo, benzo[d]isotiazolo, benzo[d]isoxazoilo, benzo[d]oxazoilo, benzo[d]tiazolo, benzofurilo, imidazo[1,2-a]pirazilo, imidazo[1,2-a]piridinilo, imidazo[1,2-a]pirimidilo, imidazo[1,2-b]piridazilo, imidazo[1,2-c]pirimidilo, imidazo[1,5-a]pirazilo, imidazo[1,5-a]piridinilo, imidazo[1,5-a]pirimidilo, imidazo[1,5-b]piridazilo, imidazo[1,5-c]pirimidilo, indolizilo, pirazolo[1,5-a]pirazilo, pirazolo[1,5-a]piridinilo, pirazolo[1,5-a]pirimidilo, pirazolo[1,5-b]piridazina, pirazolo[1,5-c]pirimidina, pirrolo[1,2-a]pirazina, pirrolo[1,2-a]pirimidilo, pirrolo[1,2-b]piridazilo, pirrolo[1,2-c]pirimidilo, 1H-imidazo[4,5-b]piridinilo, 1H-imidazo[4,5-c]piridinilo, 1H-pirazolo[3,4-b]piridinilo, 1H-pirazolo[3,4-c]piridinilo, 1H-pirazolo[4,3-b]piridinilo, 1H-pirazolo[4,3-c]piridinilo, 1H-pirrolo[2,3-b]piridinilo, 1H-pirrolo[2,3-c]piridinilo, 1H-pirrolo[3,2-b]piridinilo, 1H-pirrolo[3,2-c]piridinilo, 2H-indazoilo, 3H-imidazo[4,5-b]piridinilo, 3H-imidazo[4,5-c]piridinilo, benzo[c]isotiazilo, benzo[c]isoxazilo, furo[2,3-b]piridinilo, furo[2,3-c]piridinilo, furo[3,2-b]piridinilo, furo[3,2-c]piridinilo, isotiazolo[4,5-b]piridinilo, isotiazolo[4,5-c]piridinilo, isotiazolo[5,4-b]piridinilo, isotiazolo[5,4-c]piridinilo, isoxazolo[4,5-b]piridinilo, isoxazolo[4,5-c]piridinilo, isoxazolo[5,4-b]piridinilo, isoxazolo[5,4-c]piridinilo, oxazolo[4,5-b]piridinilo, oxazolo[4,5-c]piridinilo, oxazolo[5,4-b]piridinilo, oxazolo[5,4-c]piridinilo, tiazolo[4,5-b]piridinilo, tiazolo[4,5-c]piridinilo, tiazolo[5,4-b]piridinilo, tiazolo[5,4-c]piridinilo, tieno[2,3-b]piridinilo, tieno[2,3-c]piridinilo, tieno[3,2-b]piridinilo y tieno[3,2-c]piridinilo.

Heterocicloalquilo es un sistema anular saturado o parcialmente insaturado monocíclico o bicíclico no aromático que comprende 5-10 átomos anulares seleccionados entre C, N, O y S, siempre que no más de 2 átomos anulares en cualquier anillo sencillo sean distintos de C. En el caso en el que el grupo heterocicloalquilo contiene un átomo de nitrógeno el nitrógeno puede estar sustituido con un grupo alquilo, acilo, -C(O)O-alquilo, -C(O)NH(alquilo) o un grupo -C(O)N(alquilo)₂. Los grupos heterocicloalquilo puede estar sustituidos opcionalmente e independientemente con grupos hidroxilo, alquilo y alcoxi y pueden contener hasta dos grupos oxo. Los grupos heterocicloalquilo se pueden conectar al resto de la molécula a través de átomos anulares de carbono o nitrógeno. Los ejemplos de los grupos heterocicloalquilo incluyen tetrahidrofuranilo, tetrahidrotienilo, tetrahidro-2H-pirano, tetrahidro-2H-tiopirano, pirrolidinilo, pirrolidonilo, succinimidilo, piperidinilo, piperazinilo, N-metilpiperazinilo, morfolinilo, morfolin-3-ona, tiomorfolinilo, tiomorfolin-3-ona, 2,5-diazabicyclo[2,2,2]octanilo, 2,5-diazabicyclo[2,2,1]heptanilo, octahidro-1H-piridol[1,2-a]pirazina, 3-tia-6-azabicyclo[3,1,1]heptano y 3-oxa-6-azabicyclo[3,1,1]heptanilo.

Heterocicloalquilalquilo es un grupo heterocicloalquil-(alquilo C₁-C₄)- en donde heterocicloalquilo se define como antes.

Heterocicloalquiloxi es un grupo heterocicloalquil-O- en donde heterocicloalquilo se define como antes.

Heterocicloalquilalcoxi es un grupo heterocicloalquil-(alquil C₁-C₄)-O- en donde heterocicloalquilo se define como antes.

Oxo es un grupo -C(O)-.

Fenilo es un anillo de benceno que puede estar sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre halógeno, CF₃, CN, NO₂, OH, alquilo, cicloalquilo, cicloalquilalquilo, alcoxi, alcoxialquilo, ariloxi, alcoxialquiloxi, heterocicloalquilo, heterocicloalquilalquilo, heterocicloalquiloxi, heteroarilo, heteroariloxi, -OCH₂CH₂OCH₃, -OC(O)R_a, -OC(O)OR_a, -OC(O)NHR_a, -OC(O)N(R_a), -SR_a, -S(O)R_a, -NH₂, -NHR_a, -N(R_a)(R_b), -NHC(O)R_a, -N(R_a)C(O)R_b, -NHC(O)OR_a, -N(R_a)C(O)OR_b, -N(R_a)C(O)NH(R_b), -N(R_a)C(O)NH(R_b)₂, -C(O)NH₂, -C(O)NHR_a, -C(O)N(R_a)(R_b), -CO₂H, -CO₂R_a, -COR_a en donde R_a y R_b se seleccionan independientemente entre alquilo, alcoxialquilo, -CH₂CH₂OH, -CH₂CH₂OMe, cicloalquilo, cicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterocicloalquilo, y heterocicloalquilalquilo, cada uno de los cuales está sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre solamente halógeno, Me, Et, ¹Pr, ¹Bu, ciclopropilo no sustituido, ciclobutilo no sustituido, CN, NO₂, NH₂, CF₃, NHMe, NMe₂, OMe, OCF₃, cada uno de los cuales está anclado a través de enlaces carbono-carbono, carbono-nitrógeno o carbono-oxígeno; o R_a y R_b tomados junto con el átomo o los átomos a los que están anclados forman un anillo de 5-6 miembros.

Fenilo restringido es un anillo de benceno que puede estar sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre halógeno, CF₃, CN, alcoxi, alcoxialquilo, ariloxi, alcoxialquiloxi, heterocicloalquilo, heterocicloalquiloxi, heteroarilo, heteroariloxi, -OCH₂CH₂OCH₃, -OC(O)R_a, -OC(O)OR_a, -OC(O)N(R_a), -N(R_a)(R_b), -NHC(O)R_a, -N(R_a)C(O)R_b, -NHC(O)OR_a, -N(R_a)C(O)OR_b, -C(O)N(R_a)(R_b), -COR_a en donde R_a y R_b se seleccionan independientemente entre alquilo, alcoxialquilo, -CH₂CH₂OH, -CH₂CH₂OMe, cicloalquilo, cicloalquilalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterocicloalquilo, y heterocicloalquilalquilo, cada uno de los cuales está sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre solamente halógeno, Me, Et, ¹Pr, ¹Bu, ciclopropilo no sustituido, ciclobutilo no sustituido, CN, NO₂, NH₂, CF₃, NHMe, NMe₂, OMe, OCF₃, cada uno de los cuales está anclado a través de enlaces carbono-carbono, carbono-nitrógeno o carbono-oxígeno; o R_a y R_b tomados junto con el átomo o los átomos a los que están anclados forman un anillo de 5-6 miembros.

Las abreviaturas utilizadas en los siguientes ejemplos y preparaciones incluyen:

Ac

Acilo (Me-C(O)-)

AcN

Acetonitrilo

BINAP

2,2'-bis(difenilfosfino)-1,1'-binaftilo

Bn

Bencilo

Celite®

Tierra de diatomeas

DBU

1,8-Diazabicyclo[5,4,0]undec-7-eno

DCC

N,N', Diciclohexilcarbodiimida

DCM

Diclorometano

	DIEA	Di-isopropiletilamina
	DIPEA	Di-isopropiletilamina
5	DMAP	4-Dimetilaminopiridina
	DMF	Dimetilformamida
10	DMP	Peryodinano de Dess Martin
	DMSO	Dimetilsulfóxido
	Dppf	1,4-Bis(difenilfosfino)ferroceno
15	EDC	Hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida
	Et ₃ N	Trietilamina
20	g	gramos
	h	Horas
	hr	Horas
25	HATU	Hexafluorofosfato de 2-(7-aza-1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio
	HMDS	Hexametildisilazida
30	HOBt	1-Hiroxibenzotriazol
	HPLC	Cromatografía Líquida de Alta Presión
	HRMS	Espectrometría de masas de alta resolución
35	i.v.	Intravenoso
	KHMDS	Hexametildisilazida potásica
40	LDA	Di-isopropilamiduro de litio
	m	Multiplete
	m-	<i>meta</i>
45	MEM	Metoxietoximetilo
	MeOH	Alcohol Metílico o Metanol
50	min	Minutos
	mmol	milimoles
	mmoles	milimoles
55	Ms	Mesilato
	MS	Espectrometría de Masas
60	MW	Peso Molecular
	NBS	N-Bromosuccinamida
	NIS	N-yodosuccinamida

	NMR	Resonancia Magnética Nuclear
	NMM	N-Metil Morfolina
5	NMP	N-Metil-2-pirrolidona
	O	<i>orto</i>
	o/n	durante la noche
10	p	<i>para</i>
	PCC	Clorocromato de Piridinio
15	PEPPSI	Dicloruro 1,3-bis(2,6-diisopropilfenil)imidazolidin)(3-cloropiridinil)paladio(II)
	PhNTf ₂	1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonyl)metanosulfonamida
20	POPd	Diclorobis(di-terc-butilfosfinito-kp)paladato (2-) de hidrógeno
	p.s.i.	Libras por pulgada cuadrada
	PPA	Poli(ácido fosfórico)
25	PPAA	Anhídrido Cíclico de Ácido 1-Propanofosfónico
	PTSA	Ácido p-toluenosulfónico
30	PyBOP®	Hexafluorofosfato de benzotriazol-1-il-oxitripirrolidino fosfonio
	RT (o rt)	temperatura ambiente (aproximadamente 20-25°C)
	s	Singlete
35	sat.	Saturado
	t	Triplete
40	TBAF	Fluoruro de tetra-butil amonio
	TEA	Trietilamina
	TFA	Ácido trifluoroacético
45	THF	Tetrahidrofurano
	TLC	Cromatografía en capa fina
50	TMS	Trimetilsililo
	Tf	Triflato
	Tof-MS	Espectrometría de Masas por Tiempo de Vuelo
55	Ts	Tosilato
	v/v	volumen/volumen
60	p/v	peso/volumen

Descripción Detallada

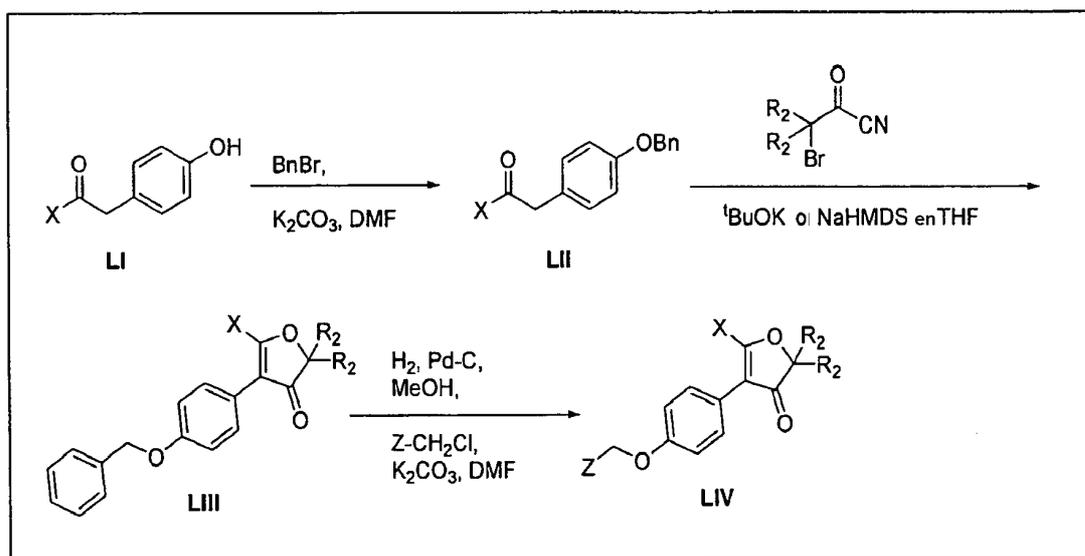
Los compuestos heterocíclicos 1,2-disustituídos de Fórmula I pueden ser preparados a partir de rutas de síntesis orgánicas de múltiples etapas a partir de sustancias de partida asequibles comercialmente por un experto en la técnica de la síntesis orgánica utilizando procedimientos sintéticos orgánicos bien establecidos. Se pueden elaborar ácidos fenilacéticos no asequibles comercialmente a partir de sustancias de partida asequibles comercialmente a través de métodos conocidos por un experto en la técnica de síntesis orgánicas. Tales métodos incluyen la síntesis a partir de los ácidos arílicos correspondientes a través de la trasposición de Wolff utilizando diazometano.

Los compuestos de la descripción donde HET es A29 y A31 se pueden preparar generalmente como se describe en los Esquemas 1-8 de más abajo.

Los compuestos de la descripción de Fórmula (I) en donde HET es A29 y X = fenilo o heteroarilo (cada uno sustituido opcionalmente respectivamente) que tienen por tanto la Fórmula general LIV se pueden preparar generalmente como se representa en el Esquema 1:

Esquema 1

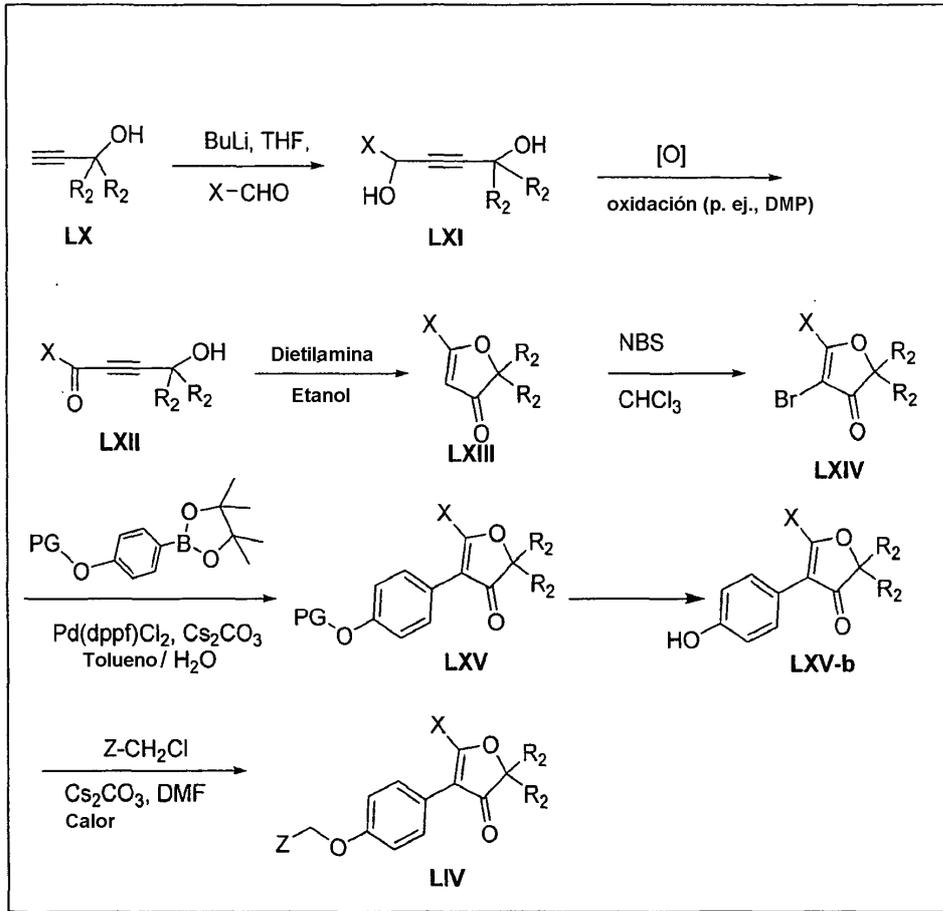
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Alternativamente, los compuestos de la descripción de Fórmula (I) en donde HET es A29 y X= fenilo o heteroarilo (cada uno sustituido opcionalmente respectivamente) y por tanto que tienen la Fórmula general LIV también se pueden preparar generalmente como se representa en el Esquema 2:

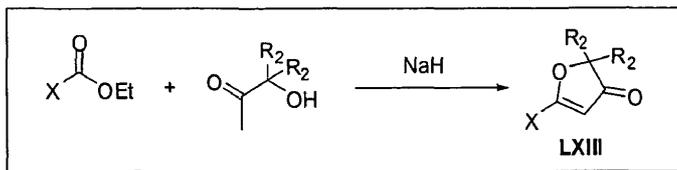
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Esquema 2



5 Los compuestos intermedios de Fórmula LXIII se pueden sintetizar alternativamente como se representa en el Esquema 3.

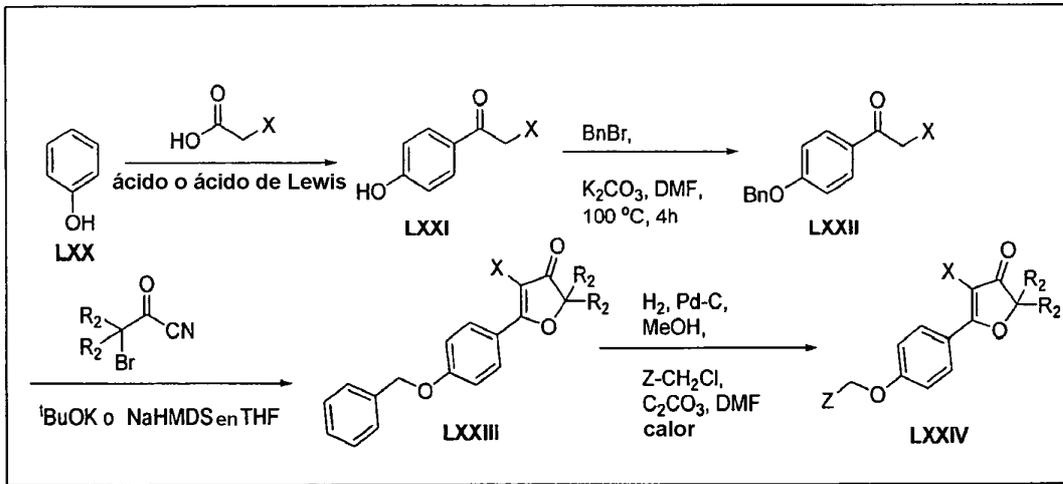
Esquema 3



10 Los compuestos de la descripción de Fórmula (I) en donde HET es A31 y X = fenilo o heteroarilo (cada uno sustituido opcionalmente) que son los descritos previamente y tienen por tanto la Fórmula general LXXIV, se pueden preparar generalmente como se representa en el Esquema 4:

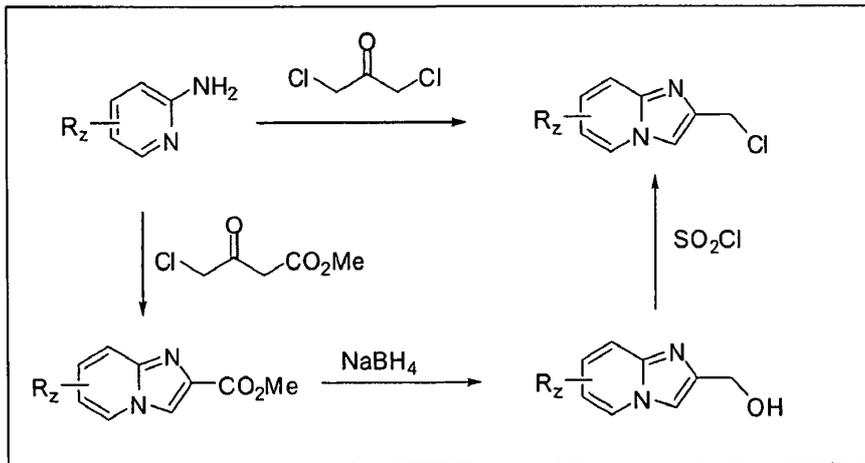
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Esquema 4



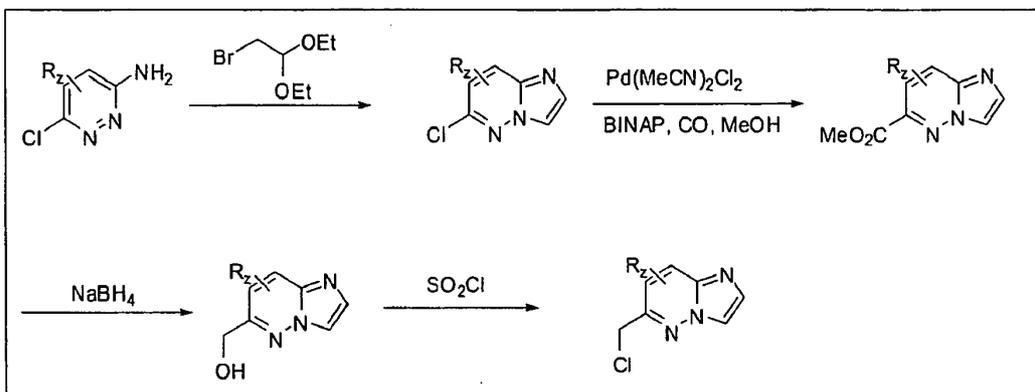
5 La síntesis general de los intermedios cloruro heterocíclicos (Z-CH₂-Cl) donde Z corresponde a un imidazo[1,2-a]pirid-2-ilo se representa en el Esquema 5.

Esquema 5



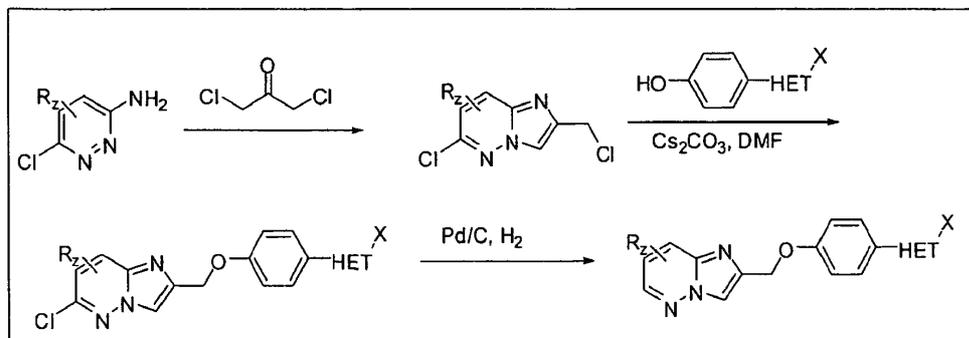
10 La síntesis general de los intermedios cloruro heterocíclicos (Z-CH₂-Cl) donde Z corresponde a un imidazo[1,2-b]piridazin-6-ilo se representa en el Esquema 6.

Esquema 6



La síntesis general de los intermedios cloruro heterocíclicos (Z-CH₂-Cl) donde Z corresponde a un imidazo[1,2-b]piridazin-2-ilo se representa en el Esquema 7.

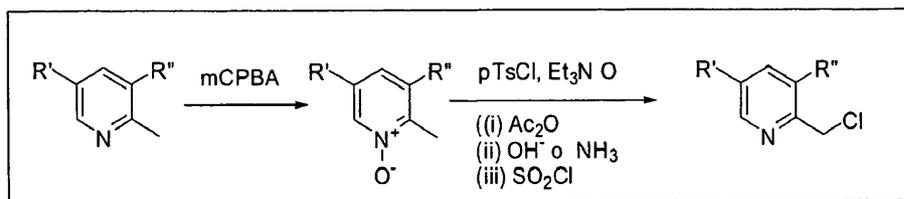
5 Esquema 7



La síntesis general de los intermedios cloruro heterocíclicos (Z-CH₂-Cl) donde Z corresponde a un 5-sustituido-piridin-2-ilo o un 3,5-disustituido-1piridin-2-ilo se representa en el Esquema 8.

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Esquema 8



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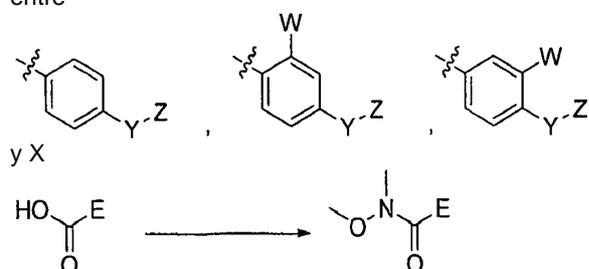
Los grupos reactivos no implicados en los procedimientos anteriores se pueden proteger con grupos protectores convencionales durante las reacciones y eliminar mediante procedimientos convencionales (T. W. Greene & P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Tercera Edición, Wiley-Interscience) conocidos por los expertos normales en la técnica. Los grupos protectores preferidos en la actualidad incluyen metilo, bencilo, MEM, acetato y tetrahidropirranilo para el radical hidroxilo, y BOC, Cbz, trifluoroacetamida y bencilo para el radical amino, ésteres metílico, etílico, terc-butílico y bencílico para el radical ácido carboxílico. Los profesionales expertos en la técnica también reconocerán que se puede cambiar el orden de ciertas reacciones químicas. Los profesionales expertos en la técnica también observarán que existen reactivos y condiciones alternativos para diversas etapas químicas.

20

25 **Procedimientos Experimentales**

La síntesis de N-metoxi-N-metilcarboxamidas a partir de sus ácidos carboxílicos correspondientes es conocida por los expertos normales en la técnica. Más abajo se describe un procedimiento representativo, donde se selecciona entre

30



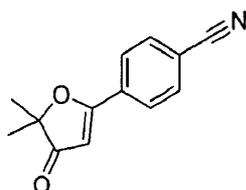
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A una disolución agitada de ácido carboxílico (1 eq., 3 mmoles) en DCM (50 mL) se le añadieron HATU (1,5 eq, 4,5 mmoles), N-metoximetilamina (1,5 eq, 4,5 mmoles) y TEA (3 eq., 9 mmoles) a RT en atmósfera de nitrógeno. La mezcla de reacción se agitó a continuación a RT durante 3 h. La mezcla de reacción se diluyó con agua y la capa acuosa se extrajo con DCM (3 x 50 mL). Los extractos orgánicos combinados se lavaron con agua (50 mL), salmuera (20 mL), se secaron sobre Na₂SO₄ anhidro, se filtraron y se evaporaron a presión reducida para proporcionar la correspondiente N-metoxi-N-metilcarboxamida.

Condiciones de la HPLC

<u>Condición A:</u>	Columna	: Acquity BEH C-18 (50x2,1mm, 1,7μ),
	Temp. de la Columna	: 25°C
	Fase Móvil A/B	: Acetonitrilo (TFA al 0,025%) y agua
	Velocidad de Flujo	: 0,50 mL/Min

5 4-(5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo

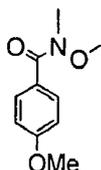


10 A una suspensión de NaH (0,9 g) en THF a RT se le añadieron 3-hidroxi-3-metil-2-butanona (1 g) y 4-cianobenzoato de etilmetilo (1,58 g). La mezcla resultante se sometió a reflujo durante la noche, después de lo cual la reacción se sofocó con HCl 12 N (6 mL). Se añadió MgSO₄ (exceso) hasta que la fase orgánica se volvió clara. Los sólidos se eliminaron mediante filtración y el producto filtrado se concentró a presión reducida. El residuo se purificó por medio de cromatografía en columna para proporcionar 4-(5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (0,63 g).

15

Síntesis de 4-(4-Hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona:

4-Metoxi-N-metoxi-N-metilbenzamida

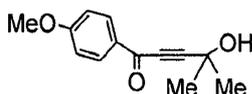


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25 A una disolución agitada de ácido 4-metoxibenzoico (10,0 g, 65,70 mmoles) en DCM (50 mL) se le añadieron EDCI (18,90 g, 98,60 mmoles), HOBT (10,0 g, 65,70 mmoles), N-metoxi metilamina (13,0 g, 131,40 mmoles) y DIPEA (34,3 mL, 197,20 mmoles) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 12 h. La mezcla de reacción se diluyó con agua y la capa acuosa se extrajo con DCM (3 x 100 mL). Los extractos orgánicos combinados se lavaron con agua (2 x 100 mL), salmuera (2 x 50 mL), se secaron sobre Na₂SO₄ anhidro, se filtraron y se evaporaron a presión reducida para proporcionar un producto bruto. La sustancia bruta se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en hexano y gel de sílice (Malla 230-400) para proporcionar N,4-dimetoxi-N-metilbenzamida (11,0 g, 86 %) en forma de un líquido incoloro.

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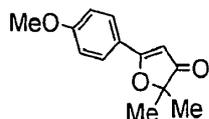
4-Hidroxil-1-(4-metoxifenil)-4-metilpent-2-in-1-ona



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40 A una disolución agitada de 2-metilbut-3-in-2-ol (2,15 g, 25,6 mmoles) en THF seco (80 mL) se le añadió n-BuLi (24,0 mL, 38,7 mmoles, 1,6 M en hexano) gota a gota a -20°C en una atmósfera inerte a lo largo de un período de 10 min. Después de agitar durante 30 min a -20°C, se añadió a la mezcla de reacción una disolución de N,4-dimetoxi-N-metilbenzamida (2,5 g, 12,8 mmoles) en THF seco (10 mL) y se continuó agitando durante 3h adicionales a -20°C. La mezcla de reacción se sofocó con una disolución saturada de NH₄Cl y se extrajo con EtOAc (2 x 100 mL). La capa orgánica combinada se lavó con agua (100 mL), salmuera (40 mL), se secó sobre Na₂SO₄, se filtró y se concentró a vacío para proporcionar 4-hidroxil-1-(4-metoxifenil)-4-metilpent-2-in-1-ona (2,25 g, 81 %) en forma de un líquido incoloro.

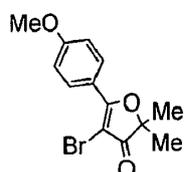
5-(4-Metoxifenil)-2, 2-dimetilfuran-3(2H)-ona



5 A 4-hidroxi-1-(4-metoxifenil)-4-metilpent-2-in-1-ona (10 g, 45,8 mmoles) se le añadió amoníaco metanólico (50 mL) a temperatura ambiente y la mezcla de reacción se agitó durante la noche. La mezcla se concentró a presión reducida y se añadió ácido acético acuoso al 50%. La mezcla resultante se calentó a reflujo durante 4 horas. El pH se ajustó a 8 con una disolución saturada de cloruro de amonio y se extrajo con DCM. Las sustancias orgánicas combinadas se lavaron con agua y una disolución de salmuera, se secaron sobre sulfato de sodio, se filtraron, se concentraron a presión reducida y se lavaron con heptano para proporcionar 5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (8,6 g, 86%) en forma de un sólido de color blanco. RMN H^1 (500 MHz, d_6 -DMSO): δ 7,99 (d, 2 H), 7,15 (d, 2 H), 6,20 (s, 1 H), 3,89 (s, 3 H), 1,42 (s, 6 H). MS: $[M + H]^+$: $m/z = 218,1$.

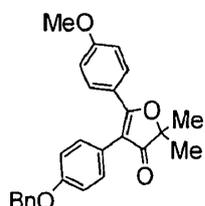
4-Bromo-5-(4-metoxifenil)-2, 2-dimetilfuran-3(2H)-ona

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20 A una disolución agitada de 5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (5,5 g, 0,025 moles) en $CHCl_3$ (100 mL) se le añadió NBS (6,733 g, 0,038 moles) en porciones a RT. La mezcla de reacción se agitó durante 2 h a RT. La mezcla de reacción se diluyó con DCM (100 mL), se lavó con agua (50 mL), salmuera (50 mL), se secó sobre Na_2SO_4 , se filtró y después se concentró a vacío para obtener el producto bruto. La sustancia bruta se purificó *por medio* de cromatografía en columna instantánea utilizando acetato de etilo al 25% en hexano y gel de sílice (Malla 230-400) para proporcionar 4-bromo-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (4,6 g, 65 %) en forma de un sólido.

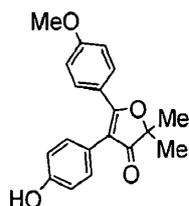
25 4-(4-(Benciloxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



30 La 4-bromo-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2 g, 6,7 moles), 2-(4-(benciloxi)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (2,43 g, 0,0067 moles), y Cs_2CO_3 (11 g, 0,034 moles) en tolueno (25 mL) y agua (8 mL) se desgasificaron, se añadió Pd (dppf) Cl_2 (1,1 g, 0,0013 moles) en una atmósfera inerte y la mezcla se desgasificó una vez más. La reacción se calentó a reflujo durante 3 h, después de lo cual la mezcla de reacción se filtró a través de un lecho de Celite® y el producto filtrado se diluyó con EtOAc (100 mL), se lavó con agua (50 mL), salmuera (50 mL), se secó sobre Na_2SO_4 , se filtró y se concentró a vacío para obtener el producto bruto. La sustancia bruta se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 30% en hexano y gel de sílice (Malla 230-400), $R_f = 0,30$ para proporcionar 4-(4-(benciloxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,3 g, 73 %) en forma de un sólido. RMN H^1 (500 MHz, d_6 -DMSO): δ 8,42 (d, $J = 7,6$ Hz, 1 H), 8,06-7,99 (m, 2 H), 7,95 (t, $J = 7,2$ Hz, 1 H), 7,72 (t, $J = 7,2$ Hz, 1 H), 7,63 (t, $J = 7,8$ Hz, 1 H), 7,56 (d, $J = 7,2$ Hz, 2 H); 7,18 (d, $J = 7,4$ Hz, 2 H), 7,12 (d, $J = 7,2$ Hz, 2 H), 6,89 (d, $J = 7,2$ Hz, 2 H), 5,38 (s, 2 H), 3,79 (s, 3 H). 1,42 (s, 6 H). MS: $[M + H]^+$: $m/z = 452,1$; $[M+Na]^+$: $m/z = 474,2$.

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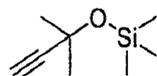
4-(4-Hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



Se añadió paladio sobre carbono al 5% (7,0 g) a una disolución 4-(4-(benziloxy)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (19 g, 42,1 mmoles) en metanol (25 ml) a RT en una atmósfera de nitrógeno. La atmósfera de nitrógeno se cambió a una atmósfera de hidrógeno. La mezcla de reacción se agitó en una atmósfera de hidrógeno a RT durante 4h (la reacción se verificó por medio de TLC). La mezcla de reacción se filtró a través de un lecho de Celite®, se lavó con metanol, se concentró a vacío y el residuo resultante se suspendió con heptano. El sólido se filtró y se secó a vacío para proporcionar 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (14,0 g, 95 %), en forma de un sólido de color amarillo claro. RMN H^1 , 500 MHz, DMSO- d_6 : δ 9,5 (s ancho, 1H), 7,55 (d, 2H), 7,05 (d, 2H), 7,0 (d, 2H), 6,75 (d, 2H), 3,8 (s, 3H), 1,4 (s, 6H). MS: [M + H]: m/z = 311,2. HPLC: (98,8%, Eclipse XDB-C₁₈, 150 X 4,6 mm, 5 μ m. Fase Móvil: TFA al 0,1% en Agua. (A).ACN (B), Velocidad de flujo: 1,5 ml/min).

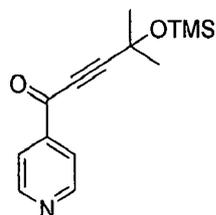
Síntesis de 5-(4-Hidroxifenil)-2, 2-dimetil-4-(piridin-4-il) furan-3(2H)-ona

15 Trimetil(2-metilbut-3-in-2-ilo)xilano



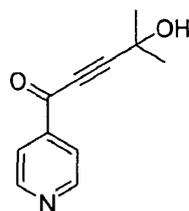
A una disolución agitada de 2-metilbut-3-in-2-ol (20 g, 0,23 moles) en HMDS (42,3 g, 0,261 moles) se le añadió $LiClO_4$ (38,03 g, 0,35 moles) a RT. La mezcla de reacción se agitó a continuación durante 30 minutos adicionales, se diluyó con agua (100 mL) y a continuación se extrajo con éter (3 x 200 mL). Las capas de éter combinadas se lavaron con agua (100 mL) y salmuera (100 mL), se secaron sobre Na_2SO_4 y se filtraron. El éter se separó mediante destilación a 80°C para proporcionar trimetil(2-metilbut-3-in-2-ilo)xilano (25 g) en forma de un aceite.

25 4-Metil-1-(piridin-4-il)-4-(trimetilsililoxi)pent-2-in-1-ona



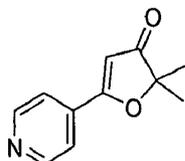
A una disolución agitada pre-refrigerada a -78°C de trimetil(2-metilbut-3-in-2-ilo)xilano (5,0 g, 0,03 moles) en THF seco (150 mL), se le añadió gota a gota $n-BuLi$ (23,82 mL, 0,03 moles, 1,6 M en hexano) a lo largo de un período de 10 minutos en una atmósfera inerte. La reacción se agitó durante 30 minutos a -78°C y a continuación se añadió a la mezcla de reacción una disolución de *N*-metoxi-*N*-metilisonicotinamida (6,34 g, 0,03 moles) en THF seco (30 mL) y se continuó agitando durante 40 min adicionales a -78°C. La mezcla de reacción se sofocó con una disolución saturada de NH_4Cl y se extrajo con EtOAc (2 x 100 mL). Las capas orgánicas combinadas se lavaron con agua (100 mL) y salmuera (100 mL), se secaron sobre Na_2SO_4 , se filtraron y finalmente se concentraron a vacío para obtener un residuo. El residuo se purificó a través de cromatografía en columna de gel de sílice eluyendo con EtOAc al 5% en hexanos para proporcionar 4-metil-1-(piridin-4-il)-4-(trimetilsililoxi)pent-2-in-1-ona (2,2 g, 27 %) en forma de un aceite.

40 4-Hidroxi-4-metil-1-(piridin-4-il) pent-2-in-1-ona



A una disolución agitada de 4-metil-1-(piridin-4-il)-4-(trimetilsililo) pent-2-in-1-ona (0,5 g, 1,915 mmoles) en DCM (10 mL) se le añadió PTSA (0,47 g, 2,49 mmoles) a RT y la mezcla de reacción se agitó durante 2 h. La mezcla de reacción se diluyó con DCM (50 mL). Las capas orgánicas se lavaron con una disolución saturada de NaHCO₃ y agua, se secaron sobre Na₂SO₄, se filtraron y después se concentraron a vacío para proporcionar 4-hidroxi-4-metil-1-(piridin-4-il) pent-2-in-1-ona (0,35 g, 96 %) en forma de un aceite.

2,2-Dimetil-5-(piridin-4-il) furan-3(2H)-ona



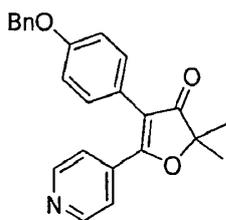
A una disolución agitada de 4-hidroxi-4-metil-1-(piridin-4-il)pent-2-in-1-ona (1,49 g, 0,007 moles) en etanol (15 mL), se le añadió gota a gota dietilamina (0,511 g, 0,007 moles) en EtOH (15 mL) a RT. La mezcla se agitó a continuación durante 40 min adicionales. El EtOH se evaporó y la mezcla se diluyó con EtOAc (100 mL). Las capas orgánicas se lavaron con agua (50 mL) y salmuera (20 mL), se secaron sobre Na₂SO₄, se filtró y se concentró a vacío para proporcionar 2, 2-dimetil-5-(piridin-4-il) furan-3(2H)-ona (1,4 g).

4-Bromo-2,2-dimetil-5-(piridin-4-il) furan-3(2H)-ona



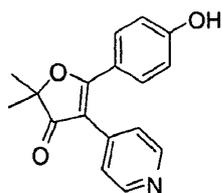
A una disolución agitada de 2, 2-dimetil-5-(piridin-4-il)furan-3(2H)-ona (0,81 g, 4,28 mmoles) en CHCl₃ (20 mL), se le añadió en porciones NBS (1,3 g, 7,28 mmoles) a RT. La mezcla de reacción se agitó a continuación durante 2 h y se diluyó con DCM (100 mL). Las capas orgánicas se lavaron con agua (50 mL) y salmuera (50 mL), se secaron sobre Na₂SO₄, se filtraron, y a continuación se concentraron a vacío para obtener el producto bruto. La sustancia bruta se purificó a través de cromatografía en columna de gel de sílice para proporcionar 4-bromo-2,2-dimetil-5-(piridin-4-il) furan-3(2H)-ona (0,25 g, 21%) en forma de un sólido.

4-(4-(Benciloxi)fenil)-2,2-dimetil-5-(piridin-4-il)furan-3(2H)-ona



Una disolución de 4-bromo-2,2-dimetil-5-(piridin-4-il)furan-3(2H)-ona (10,0 g, 37,2 mmoles), 2-(4-(benciloxi)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (13,8 g, 44,7 mmoles), y Cs₂CO₃ (36,27 g, 111,6 mmoles) en tolueno (100 mL) y agua (50 mL) se desgasificó. Se añadió dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(II) (2,7 g, 3,7 mmoles) en una atmósfera inerte y se desgasificó de nuevo. A continuación la reacción se sometió a reflujo durante 3 h y se verificó mediante TLC. Tras el consumo completo de la sustancia de partida, la mezcla de reacción se filtró a través de un lecho de Celite® lavando con acetato de etilo. La capa orgánica se lavó a continuación con agua, salmuera, se secó sobre Na₂SO₄, se filtró y se concentró a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en n-hexanos en una malla 230-400 de gel de sílice para proporcionar 4-(4-(benciloxi)fenil)-2,2-dimetil-5-(piridin-4-il)furan-3(2H)-ona (8,3 g, 60,2 %) en forma de un sólido de color naranja. RMN H¹, 500 MHz, DMSO-d₆: δ 8,2 (d, 2H), 7,85 (d, 2H), 7,6 (d, 4H), 7,4 (t, 1H), 7,15 (d, 2H), 7,05 (d, 2H), 5,1 (s, 2H), 1,45 (s, 6H). MS: [M + H]⁺: m/z = 396,0. HPLC: (97,5%, Columna: Eclipse XDB- C₁₈, 150 X 4,6 mm, 5 µm. Fase Móvil: TFA al 0,1% en Agua. (A).ACN (B), Velocidad de flujo: 1,5 ml/min).

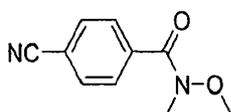
5-(4-Hidroxifenil)-2,2-dimetil-4-(piridin-4-il)furan-3(2H)-ona



5 A una disolución agitada de 5-(4-(benziloxy)fenil)-2, 2-dimetil-4-(piridin-4-il) furan-3(2H)-ona (620 mg, 0,001 mmoles) en MeOH (15 mL) se le añadió Pd(OH)₂ (120 mg, 0,85 mmoles) a RT en una atmósfera inerte. La mezcla de reacción se agitó en una atmósfera de hidrógeno durante 1 h. La mezcla de reacción se filtró a continuación a través de un lecho de Celite® y el producto filtrado se concentró a vacío para obtener el producto bruto. La sustancia bruta se purificó a través de cromatografía en columna de gel de sílice para proporcionar 5-(4-hidroxifenil)-2, 2-dimetil-4-(piridin-4-il)furan-3(2H)-ona (280 mg, 60 %) en forma de un sólido.

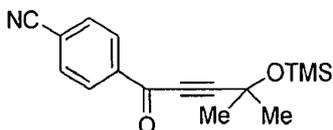
10 Síntesis de 4-(3-(4-Hidroxifenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo

4-Ciano-N-metoxi-N-metilbenzamida



15 A una disolución agitada de ácido 4-cianobenzoico (5,0 g, 34,0 mmoles) en DCM (75 mL) se le añadieron HATU (19,40 g, 51,0 mmoles), N-metoxi, N-metilamina (4,90 g, 51,0 mmoles) y TEA (14,30 mL, 102,0 mmoles) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a continuación a RT durante 3 h, se diluyó con agua y la capa acuosa se extrajo con DCM (3 x 100 mL). Los extractos orgánicos combinados se lavaron con agua (60 mL) y salmuera (30 mL), se secaron sobre Na₂SO₄ anhidros, se filtraron y se evaporaron a presión reducida para proporcionar 4-ciano-N-metoxi-N-metilbenzamida (6,2 g, 96 %) en forma de un sólido de color amarillo.

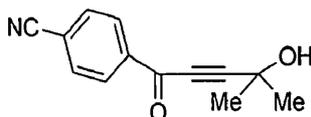
25 4-(4-Metil-4-(trimetilsililoxi) pent-2-inoil)benzonitrilo



30 A una disolución agitada a -78°C solución de trimetil(2-metilbut-3-in-2-ilo)xilano (3,3 g, 20,00 mmoles) en THF seco (45 mL), se le añadió gota a gota *n*-BuLi (4,1 mL, 9,00 mmoles, 1,6 M en hexano) a lo largo de 10 minutos en una atmósfera inerte. La mezcla de reacción se agitó durante 30 min a -78°C, y a continuación se añadió a la mezcla de reacción una disolución de 4-ciano-N-metoxi-N-metilbenzamida (2,0 g, 10,00 mmoles) en THF seco (15 mL) y se continuó agitando durante 1 h adicional a -78°C. La mezcla de reacción se sofocó con una disolución saturada de NH₄Cl y se extrajo con EtOAc (2 x 100 mL). Las capas orgánicas combinadas se lavaron con agua (50 mL) y salmuera (50 mL), se secaron sobre Na₂SO₄, se filtraron, y se concentraron a vacío para obtener el producto bruto.

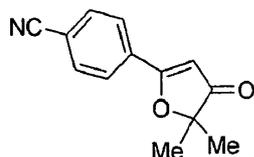
35 La sustancia bruta se purificó a través de cromatografía en columna de gel de sílice eluyendo con EtOAc al 15% en hexanos para proporcionar 4-(4-metil-4-(trimetilsililoxi)pent-2-inoil)benzonitrilo (3,8 g, 68 %) en forma de un aceite de color amarillo.

40 4-(4-Hidroxil-4-metilpent-2-inoil) benzonitrilo



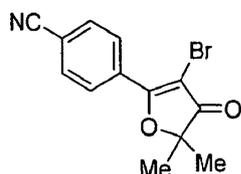
45 A una disolución agitada de 4-(4-metil-4-(trimetilsililoxi)pent-2-inoil)benzonitrilo (1,7 g, 5,00 mmoles) en DCM (15 mL) se le añadió PTSA (1,70 g, 8,90 mmoles) a RT y la mezcla de reacción se agitó durante 30 min. La mezcla de reacción se diluyó con agua (10 mL) y se extrajo con DCM (2 x 50 mL). Las capas orgánicas combinadas se lavaron con una disolución saturada de NaHCO₃ y agua, se secaron sobre Na₂SO₄, se filtraron, y a continuación se concentró a vacío para proporcionar 4-(4-hidroxil-4-metilpent-2-inoil)benzonitrilo (1,20 g) en forma de un aceite de color amarillo.

4-(5,5-Dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo



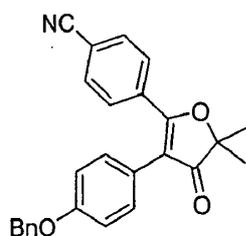
5 A una disolución agitada de 4-(4-hidroxi-4-metilpent-2-inoil)benzonitrilo bruto (1,2 g, 5,60 mmoles) en etanol (12 mL), se le añadió gota a gota una disolución de dietilamina (0,58 mL, 5,60 mmoles) en EtOH (5 mL) a RT. La mezcla de reacción se agitó a continuación durante 1 h adicional. El etanol se eliminó y la mezcla a continuación se diluyó con EtOAc (50 mL). Las capas orgánicas combinadas se lavaron con agua (10 mL), salmuera (10 mL), se secaron sobre Na₂SO₄, se filtraron, y se concentraron a vacío para proporcionar 4-(5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo bruto (1,2 g) en forma de un semisólido de color verde claro que se recogió para la siguiente etapa sin purificación adicional.

4-(3-Bromo-5, 5-dimetil-4-oxo-4, 5-dihidrofuran-2-il) benzonitrilo



15 A una disolución agitada de 4-(5, 5-dimetil-4-oxo-4, 5-dihidrofuran-2-il) benzonitrilo (1,2 g, 5,60 mmoles) en CHCl₃ (12 mL), se le añadió en porciones NBS (1,1 g, 6,00 mmoles) a RT. La mezcla de reacción se agitó a continuación durante 3 h y se diluyó con DCM (100 mL). Las capas orgánicas combinadas se lavaron con agua (30 mL) y salmuera (30 mL), se secaron sobre Na₂SO₄, se filtraron, y a continuación se concentraron a vacío para obtener el producto bruto. La sustancia bruta se purificó a través de cromatografía en columna de gel de sílice para proporcionar 4-(3-bromo-5, 5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (0,50 g, 31%) en forma de un sólido de color blanquecino.

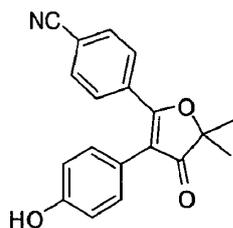
4-(3-(4-(benciloxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo



30 Una disolución de 4-(3-bromo-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (29,0 g, 107,4 mmoles), 2-(4-(benciloxi)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (34,7 g, 118,8 mmoles), y Cs₂CO₃ (104,7 g, 322,2 mmoles) en tolueno (200 mL) y agua (50 mL) se desgasificó. Se añadió dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(II) (8,5 g, 10 mmoles) en una atmósfera inerte y la disolución se desgasificó de nuevo. La reacción se sometió a reflujo a continuación durante 3 h y se verificó que se completaba por medio de TLC. Una vez que se hubo consumido completamente la sustancia de partida, la mezcla de reacción se filtró a través de un lecho de Celite® lavando con acetato de etilo. La capa orgánica se lavó a continuación con agua, salmuera, se secó sobre Na₂SO₄, se filtró y se concentró a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en n-hexano en una malla 230-400 de gel de sílice (R_f=0,3) para proporcionar 4-(3-(4-(benciloxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (31,5 g, 74,25%) en forma de un sólido. RMN H¹: 500 MHz, DMSO-d₆: δ 7,95 (d, 2H), 7,75 (d, 2H), 7,5 (d, 4H), 7,35 (t, 1H), 7,15 (d, 2H), 7,05 (d, 2H), 5,1 (s, 2H), 1,45 (s, 6H). MS: [M + H]⁺: m/z = 396,0. HPLC: (99,5%, Eclipse XDB- C₁₈, 150 X 4,6 mm, 5 μm. Fase Móvil: TFA al 0,1% en Agua. (A).ACN (B), Velocidad de flujo: 1,5 ml/min).

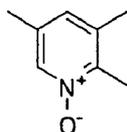
4-(3-(4-Hidroxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo

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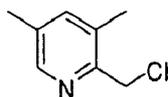
5 Se añadió tribromuro de boro (3,4 g, 15,8 mmoles) a una disolución de 4-(3-(4-(benziloxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (2,5 g, 6,3 mmoles) en DCM a 0°C y la mezcla se agitó durante 1h (la reacción se verificó por medio de TLC). Una vez que se hubo consumido completamente la sustancia de partida, la mezcla se sofocó con agua helada y se extrajo con DCM. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna para proporcionar 4-(3-(4-hidroxifenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (1,8 g, 93,2%), en forma de un sólido de color amarillo. RMN H¹: 500 MHz, CDCl₃: δ 9,6 (s, 1H), 7,95 (d, 2H), 7,75 (d, 2H), 7,0 (d, 2H), 6,75 (d, 2H), 1,5 (s, 6H).

1-Oxido de 2,3,5-trimetilpiridina



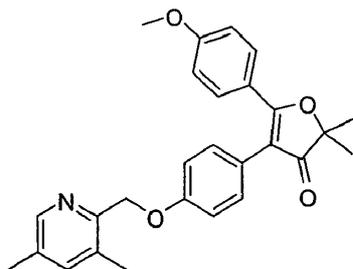
15 Se añadió ácido 3-cloroperbenzoico (10 g, 164,2 mmoles) a una disolución de 2,3,5-trimetilpiridina (10 g, 82,1 mmoles) en DCM a 0°C y la mezcla se agitó a RT durante 8h (la reacción se verificó por medio de TLC). La reacción se sofocó con una disolución de bicarbonato de sodio y se agitó durante 1h a RT. La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró y se concentró a presión reducida para proporcionar 1-oxido de 2,3,5-trimetilpiridina (6,5 g, 58,0 %), en forma de un sólido de color pardo. RMN H¹: 200 MHz, CDCl₃: δ 8,15 (s, 1H), 7,15 (s, 1H), 2,55 (s, 3H), 2,35 (s, 3H), 2,25 (s, 3H). MS: [M + H]⁺: m/z = 311,2.

2-(Clorometil)-3,5-dimetilpiridina



25 Se añadió cloruro de tosilo (12,5 g, 65,6 mmoles) a una disolución de 1-oxido de 2,3,5-trimetilpiridina (6,0 g, 43,7 mmoles), y trietilamina (6,6 g, 65,6 mmoles) en DCM (60 ml) a RT en una atmósfera de nitrógeno. La mezcla de reacción se calentó a reflujo y el reflujo se mantuvo durante 4 h (la reacción se verificó por medio de TLC). La reacción se sofocó con agua y se extrajo con DCM. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 10% en n-hexanos y gel de sílice (Malla 230-400) para proporcionar 2-(clorometil)-3,5-dimetilpiridina (4,5 g, 66,1%), en forma de un jarabe espeso de color pardo. RMN H¹: 200 MHz, CDCl₃: δ 8,15 (s, 1H), 7,45 (s, 1H), 4,75 (s, 2H), 2,35 (s, 3H), 2,25 (s, 3H). MS: [M + H]⁺: m/z = 156,3.

4-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



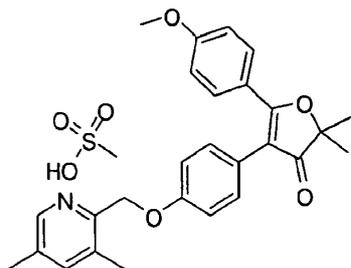
40 Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (3,0 g, 9,6 mmoles) a una mezcla de carbonato de cesio (12,6 g, 38,6 mmoles) y DMF (1000mL) a RT en una atmósfera de nitrógeno. La mezcla de

reacción se agitó a RT durante 30 min después de lo cual se añadió 2-(clorometil)-3,5-dimetilpiridina (2,25 g, 14,5 mmoles). La mezcla de reacción se calentó durante 4 h a 80°C (la reacción se verificó por medio de TLC). La mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 15% en n-hexano y gel de sílice (malla 230-400) para proporcionar 4-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (3,2 g, 65,3%), en forma de un sólido de color blanquecino. RMN H^1 : 500 MHz, DMSO- d_6 : δ 8,2 (s, 1H), 7,65 (d, 2H), 7,45 (s, 1H), 7,15 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,2 (s, 2H), 3,8 (s, 3H), 2,35 (s, 3H), 2,3 (s, 3H), 1,45 (s, 6H). MS: $[M + H]^+$: m/z = 430,4. HPLC (96,3%, Condición A).

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Metanosulfonato de 4-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



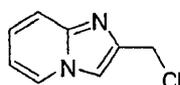
Se añadió ácido metanosulfónico (445,0 mg, 4,6 mmoles) a una disolución de 4-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,01 g, 4,6 mmoles) en DCM (3 ml) y éter dietílico (150 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4h y los sólidos se eliminaron mediante filtración. El sólido se lavó con DCM al 20% en éter dietílico y se secó a vacío para proporcionar metanosulfonato de 4-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,1 g, 87%) en forma de un sólido de color blanco. RMN H^1 : 500 MHz, DMSO- d_6 : δ 8,2 (s, 1H), 7,65 (d, 2H), 7,45 (s, 1H), 7,15 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,2 (s, 2H), 3,8 (s, 3H), 2,35 (s, 3H), 2,3 (s, 3H), 1,45 (s, 6H). HPLC: (98,9%, Condición A).

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2-(Clorometil)imidazo[1,2-a]piridina

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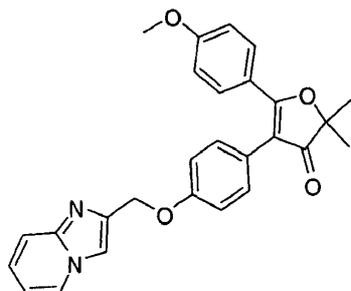


Se añadió 1,3-dicloroacetona (22,9 g, 180,3 mmoles) a una disolución de 2-aminopiridina (10 g, 106,3 mmoles) en acetonitrilo (200 ml). La mezcla se calentó a reflujo durante 14h (la reacción se verificó por medio de TLC). Una vez completada la reacción, las sustancias volátiles se eliminaron a presión reducida. El residuo se diluyó con agua y el pH se ajustó a 7,5 con una disolución de bicarbonato de sodio que se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 12% en n-hexanos y gel de sílice (malla 230-400) para proporcionar 2-(clorometil)imidazo[1,2-a]piridina (8,0 g, 47,9%), en forma de un sólido de color amarillo pálido. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,15 (d, 1H), 7,6 (dd, 2H), 7,1 (t, 1H), 6,8 (t, 1H), 4,75 (s, 2H). MS: $[M + H]^+$: m/z = 167,2.

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4-(4-(Imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona

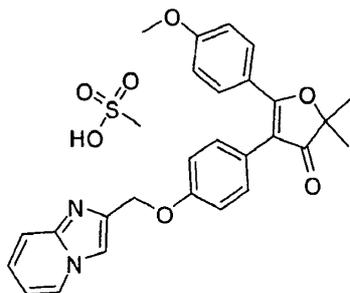


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Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,5 g, 8,06 mmoles) a una mezcla de carbonato de cesio (10,5 g, 32,2 mmoles) y DMF (20 mL) a RT en nitrógeno. La mezcla de reacción se agitó a RT durante 30 min, después de lo cual se añadió 2-(clorometil)imidazo[1,2-a]piridina (2,4 g, 12,0 mmoles). La mezcla se

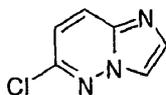
calentó a 80°C durante 4h (la reacción se verificó por medio de TLC). Se dejó que la mezcla de reacción se enfriara a RT, se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en n-hexano y gel de sílice (malla 230-400), para proporcionar 4-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,8 g, 77,7%), en forma de un sólido de color blanquecino. RMN ¹H: 500 MHz, DMSO-d₆: δ 8,55 (d, 1H), 8,0 (s, 1H), 7,55 (Ar, 3H), 7,3-6,85 (Ar, 8H), 5,15 (s, 2H) 3,85 (s, 3H), 1,25 (s, 6H). MS: [M + H]⁺: m/z = 441,2. HPLC: (97,3%, Condición A).

Metanosulfonato de 4-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



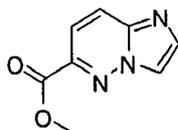
Se añadió ácido metanosulfónico (531 mg, 5,5 mmoles) a una disolución de 4-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,5 g, 5,5 mmoles) en DCM (5 ml) y éter dietílico (150 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó durante 4h adicionales a RT. Los sólidos se recogieron mediante filtración, se lavaron con DCM al 20% en éter dietílico y se secaron a vacío para proporcionar metanosulfonato de 4-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,4 g, 82,7%), en forma de un sólido de color blanco. RMN ¹H: 500 MHz, DMSO-d₆: δ 8,75 (d, 1H), 8,1 (s, 1H), 7,65 (Ar, 3H), 7,3-6,85 (Ar, 8H), 5,2 (s, 2H) 3,85 (s, 3H), 1,25 (s, 6H). HPLC: (98,8%, Condición A).

6-Cloroimidazo[1,2-b]piridazina



Se añadió dietilacetil de bromoacetaldehído (36,5 g, 216 mmoles) a una disolución ac. de cHBr (7,2 ml) y a continuación se calentó a reflujo durante 30 min. La mezcla se enfrió a continuación a 0°C, después de lo cual se añadieron etanol (236 ml), bicarbonato de sodio (8,09 g, 95 mmoles) y 6-cloropiridazin-3-amina (4 g, 30 mmoles). La mezcla se calentó a 80°C durante 3h (la reacción se verificó por medio de TLC) y a continuación se dejó que se enfriara a RT. La mezcla se concentró a presión reducida, se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 15% en n-hexano y gel de sílice (malla 230-400), para proporcionar 6-cloroimidazo[1,2-b]piridazina (4,0 g, 85,2%), en forma de un sólido de color blanquecino. RMN ¹H: 200 MHz, CDCl₃: δ 7,4-7,2 (Ar, 4H), 3,85 (c, 1H), 3,4 (c, 1H), 3,2 (c, 2H), 1,35 (t, 3H), 1,1 (t, 3H). MS: [M + H]⁺: m/z = 154,3.

Imidazo[1,2-b]piridazino-6-carboxilato de metilo

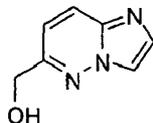


Se añadió 6-cloroimidazo[1,2-b]piridazina (5,0 g, 32 mmoles) a una disolución de metanol (75 ml) y acetonitrilo (75 ml) en una bomba de acero a RT haciendo burbujear nitrógeno. A continuación se añadieron a la mezcla trietilamina (4,0 g, 39,4 mmoles), BINAP (2,0 g, 3,0 mmoles) y dicloruro de paladio-bisacetonitrilo (0,854 g, 3,0 mmoles). La mezcla se calentó a 100°C que se mantuvo durante aproximadamente 10 horas (la reacción se verificó por medio de TLC). La mezcla de reacción se filtró a través de un lecho de Celite® lavando con acetato de etilo. Las sustancias orgánicas se lavaron con agua y salmuera, se secaron sobre sulfato de sodio y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 10% en n-hexano y gel de sílice (malla 230-400) para proporcionar imidazo[1,2-b]piridazina-6-carboxilato de metilo (2,5 g,

43%), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, DMSO- d_6 : δ 8,55 (s, 1H), 8,3 (d, 1H), 7,95 (s, 1H), 7,55 (d, 1H), 3,95 (s, 3H). MS: $[M + H]^+$: $m/z = 177,9$.

Imidazo[1,2-b]piridazin-6-ilmetanol

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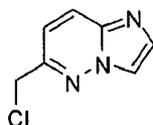


Se añadió borohidruro de sodio (1,1 g, 31,1 mmoles) a una disolución de imidazo[1,2-b]piridazina-6-carboxilato de metilo (2,4 g, 15,5 mmoles) en THF (35 mL) y metanol (2,5 ml) a RT. La mezcla de reacción se agitó a RT durante 2 h (la reacción se verificó por medio de TLC) después de lo cual la mezcla se concentró a presión reducida. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida para proporcionar imidazo[1,2-b]piridazin-6-ilmetanol (1,6 g, 81 %), en forma de un sólido de color blanco. RMN H^1 : 200 MHz, DMSO- d_6 : δ 8,5 (s, 1H), 8,3 (d, 1H), 7,9 (s, 1H), 7,55 (d, 1H), 5,65 (t, 1H), 4,6 (d, 2H). MS: $[M + H]^+$: $m/z = 311,2$.

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6-(Clorometil)imidazo[1,2-b]piridazina



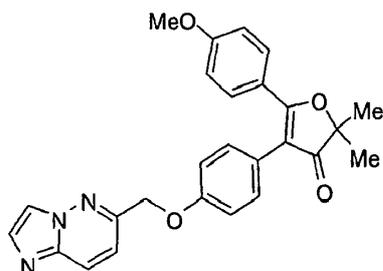
Se añadió cloruro de tionilo (10 ml) a imidazo[1,2-b]piridazin-6-ilmetanol (1,5 g, 9,0 mmoles) a 20°C en una atmósfera de nitrógeno a RT. La mezcla de reacción se agitó a reflujo durante 3h (la reacción se verificó por medio de TLC) después de lo cual las sustancias volátiles se eliminaron a presión reducida. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 15% en n-hexano y gel de sílice (malla 230-400) para proporcionar 6-(clorometil)imidazo[1,2-b]piridazina (1,2 g, 69 %), en forma de un sólido de color blanquecino. RMN H^1 , 200 MHz, DMSO- d_6 : δ 8,35 (s, 1H), 8,3 (d, 1H), 7,85 (s, 1H), 7,35 (d, 1H), 4,95 (s, 2H). MS: $[M + H]^+$: $m/z = 149,9$.

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4-(4-(Imidazo[1,2-b]piridazin-6-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona

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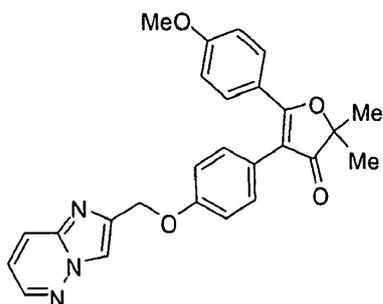


Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (1,2g, 3,8 mmoles) a una mezcla de carbonato de cesio (3,7 g, 11,6 mmoles) y DMF (25 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 30 min después de lo cual se añadió 6-(clorometil)imidazo[1,2-b]piridazina (0,96 g, 5 mmoles). La mezcla se calentó a 80°C durante 4h (la reacción se verificó por medio de TLC). La mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 30% en n-hexano y gel de sílice (malla 230-400) para proporcionar 4-(4-(imidazo[1,2-b]piridazin-6-ilmetoxi) fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (0,8 g, 47 %), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, DMSO- d_6 : δ 8,35 (s, 1H), 8,2 (d, 1H), 7,8 (s, 1H), 7,55 (d, 2H), 7,4 (d, 1H), 7,2 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,3 (s, 2H) 3,9 (s, 3H), 1,45 (s, 6H). MS: $[M + H]^+$: $m/z = 442,1$. HPLC:(95,8%, Condición A).

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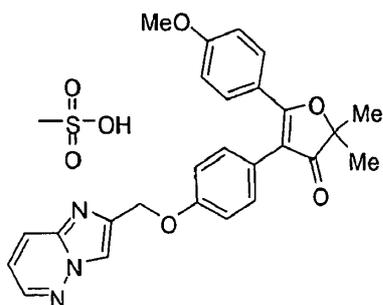
45 Metanosulfonato de 4-(4-(Imidazo[1,2-b]piridazin-6-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



5 Se añadió hidróxido de paladio (36 mg) a una disolución de 4-(4-((6-cloroimidazo[1,2-b]piridazin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (180 mg, 0,37 mmoles) y dietilamina (28 mg, 0,37) en metanol (25 ml) a RT en una atmósfera de nitrógeno. La atmósfera de nitrógeno se cambió por hidrógeno y se agitó a RT durante 2h (la reacción se verificó por medio de TLC). El compuesto se filtró a través de un lecho de Celite® lavando con metanol. El producto filtrado se concentró a presión reducida para proporcionar 4-(4-(imidazo [1, 2-b] piridazin-2-ilmetoxi) fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (160 mg, 96,7 %), en forma de un sólido de color blanco.

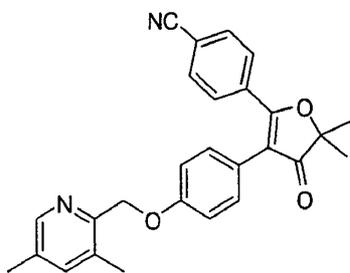
10 RMN H^1 : 500 MHz, DMSO- d_6 : δ 8,45 (s, 1H), 8,4 (s, 1H) 8,15 (d,1H), 7,55 (d, 2H), 7,25 (d, 1H), 7,15 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,25 (s, 2H) 3,8 (s, 3H), 1,25 (s, 6H). MS: [M + H] $^+$: m/z = 442,3. HPLC: (97,4%, Condición A).

Metanosulfonato de 4-(4-(imidazo[1,2-b]piridazin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2, 2-dimetilfuran-3(2H)-ona



15 Se añadió ácido metanosulfónico (34,8 mg, 0,36 mmoles) a una disolución del compuesto 4-(4-(imidazo[1,2-b]piridazin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (160 mg, 0,36 mmoles) en DCM (3 ml) y éter dietílico (15 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4h, después de lo cual la mezcla se filtró y los sólidos se lavaron con DCM al 20% en éter dietílico. Los sólidos se secaron a vacío para proporcionar metanosulfonato de 4-(4-(imidazo[1,2-b]piridazin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (110 mg, 56 %), en forma de un sólido de color blanco. RMN H^1 : 500 MHz, DMSO- d_6 : δ 8,45 (s, 1H), 8,4 (s, 1H) 8,15 (d,1H), 7,55 (d, 2H), 7,25 (d, 1H), 7,15 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,25 (s, 2H) 3,8 (s, 3H), 1,25 (s, 6H). HPLC: (98,5%, Condición A).

25 4-(3-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo

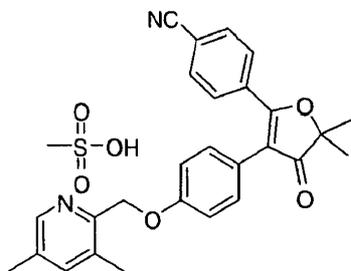


30 Se añadió 4-(3-(4-(3,5-dimetilpiridin-2-il)metoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (1,5 g, 4,9 mmoles) a una mezcla de carbonato (6,3 g, 19,6 mmoles) y DMF (100 mL) a RT en nitrógeno. La mezcla de reacción se agitó a RT durante 30 min después de lo cual se añadió 2-(clorometil)-3,5-dimetilpiridina (1,14 g, 7,3 mmoles). La mezcla se calentó a 80°C durante 4h (la reacción se verificó por medio de TLC). La mezcla de reacción se diluyó con agua y se extrajo con EtOAc; los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 22% en n-hexano y gel de sílice (malla 230-400) para proporcionar 4-(3-(4-((3,5-dimetilpiridin-2-

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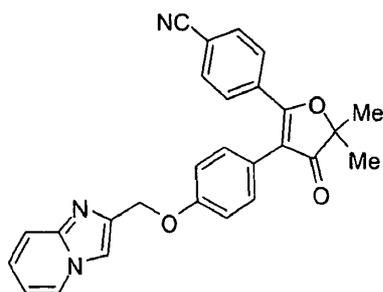
il)metoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il) (0,70 g, 35 %), en forma de un sólido de color amarillo. RMN H^1 , 200 MHz, $CDCl_3$: δ 7,45-6,8 (Ar, 11H), 4,9 (d, 1H), 4,6 (d, 1H), 3,75 (s, 3H), 3,2 (d, 2H) 3,1 (c, 1H), 2,5 (c, 1H) 0,95 (t, 6H). MS: $[M + H]^+$: $m/z = 425,2$. HPLC: (96,3%, Condición A).

5 Metanosulfonato de 4-(3-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo



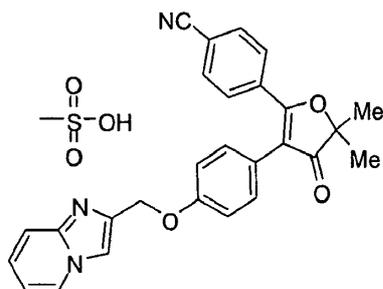
10 Se añadió ácido metanosulfónico (158 mg, 1,6 mmoles) a una disolución del compuesto 4-(3-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il) (700 mg, 1,6 mmoles) en DCM (0,5 ml) y éter dietílico (15 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4h después de lo cual, la mezcla se filtró y los sólidos se lavaron con DCM al 20% en éter dietílico y se secaron a vacío para proporcionar metanosulfonato de 4-(3-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (2,1 g, 75%), en forma de un sólido de color blanco. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,2 (d, 1H), 7,5 (t, 1H), 7,3-6,8 (Ar, 9H) 5,1 (s, 2H), 4,05 (s, 2H), 3,8 (s, 3H). HPLC: (97,1%, Condición A).

4-(3-(4-(Imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il) benzonitrilo



20 Se añadió 4-(3-(4-hidroxifenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (3,15 g, 10,3 mmoles) a una mezcla de carbonato de cesio (13,4 g, 41,3 mmoles) y DMF (100mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 30 min después de lo cual se añadió 2-(clorometil)imidazo[1,2-a]piridina (2,0 g, 12,3 mmoles). La mezcla se calentó a 80°C durante 4h (la reacción se verificó por medio de TLC). La mezcla de reacción se diluyó con agua y se extrajo con EtOAc, los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en n-hexano y gel de sílice (malla 230-400) para proporcionar 4-(3-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (2,7 g, 60%), en forma de un sólido de color blanquecino. RMN H^1 : 500 MHz, $DMSO-d_6$: δ 8,55 (d, 1H), 8,0 (s, 1H), 7,55 (Ar, 3H), 7,3-6,85 (Ar, 8H), 5,15 (s, 2H), 1,25 (s, 6H). MS: $[M + H]^+$: $m/z = 436,2$. HPLC: (97,3%, Condición A).

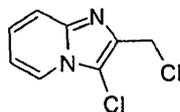
Metanosulfonato de 4-(3-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo



35 Se añadió ácido metanosulfónico (309 mg, 3,2 mmoles) a una disolución del compuesto 4-(3-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (1,4 g, 3,2 mmoles) en DCM (5 ml) y éter

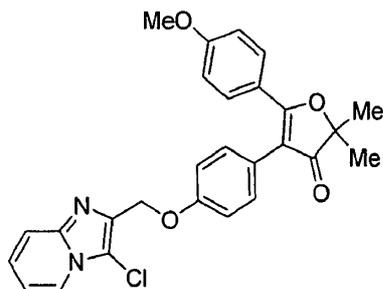
dietílico (30 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4h después de lo cual ésta se filtró y los sólidos se lavaron con DCM al 20% en éter dietílico y se secaron a vacío para proporcionar metanosulfonato de 4-(3-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzonitrilo (1,1 g, 64 %), en forma de un sólido de color blanco. RMN H^1 : 500 MHz, DMSO- d_6 : δ 8,55 (d, 1H), 8,0 (s, 1H), 7,55 (Ar, 3H), 7,3-6,85 (Ar, 8H), 5,15 (s, 2H) 2,15 (s, 3H), 1,25 (s, 6H). HPLC: (98,5%, Condición A).

3-Cloro-2-(clorometil)imidazo[1,2-a]piridina



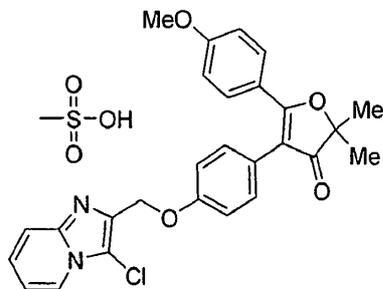
Se añadió N-clorosuccinimida (329 g, 2,46 mmoles) a una disolución de 2-(clorometil)imidazo[1,2-a]piridina (450 mg, 2,2 mmoles) en DCM (15 ml) a RT en una atmósfera de nitrógeno. Se continuó agitando durante 2h (la reacción se verificó por medio de TLC) después de lo cual la mezcla de reacción se diluyó con DCM y se lavó con agua y una disolución de salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 10% en n-hexano y gel de sílice (malla 230-400) para proporcionar 3-cloro-2-(clorometil)imidazo[1,2-a]piridina (400 mg, 76%), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,4 (d, 1H), 7,7 (d, 1H), 7,5 (t, 1H), 7,1 (t, 1H), 4,85 (s, 2H). MS: $[M + H]^+$: $m/z = 201,8$. HPLC: (98,3%, Condición A).

4-(4-((3-Cloroimidazo [1,2-a] piridin-2-il) metoxi) fenil)-5-(4-metoxifenil)-2, 2-dimetilfuran-3(2H)-ona



Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (200 mg, 0,64 mmoles) a una mezcla de carbonato de cesio (843 mg, 2,5 mmoles) y DMF (20mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 30 min, después de lo cual se añadió 3-cloro-2-(clorometil)imidazo[1,2-a]piridina (183 mg, 0,77 mmoles). La mezcla se calentó a 80°C durante 4 h (la reacción se verificó por medio de TLC) después de lo cual, la mezcla se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 18% en n-hexano y gel de sílice (malla 230-400) para proporcionar 4-(4-((3-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (250 mg, 81%), en forma de un sólido de color blanquecino. RMN H^1 :500 MHz, DMSO- d_6 : δ 8,4 (d, 1H), 7,7 (d,1H), 7,55 (Ar, 3H), 7,7-6,9 (Ar, 10H), 5,2 (s, 2H) 3,8 (s, 3H), 1,4 (s, 6H). MS: $[M + H]^+$: $m/z = 470,7$. HPLC: (97,2%, Condición A).

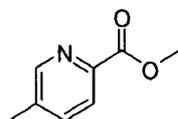
Metanosulfonato de 4-(4-((3-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



Se añadió ácido metanosulfónico (50,5 mg, 0,52 mmoles) a una disolución de 4-(4-((3-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (250 mg, 0,52 mmoles) en DCM (2,5 ml) y éter dietílico (25 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4h después de lo cual el compuesto se filtró, se lavó con DCM al 20% en éter dietílico y se secó a vacío para proporcionar metanosulfonato

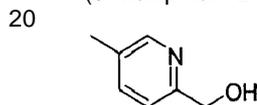
de 4-(4-((3-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (260 mg, 86%), en forma de un sólido de color blanco. RMN H^1 : 500 MHz, DMSO- d_6 : δ 8,55 (d, 1H), 8,0 (s, 1H), 7,65 (Ar, 3H), 7,3-6,85 (Ar, 7H), 5,2 (s, 2H), 3,85 (s, 3H), 2,15 (s, 3H), 1,25 (s, 6H). HPLC: (98,8%, Condición A).

5 5-Metilpicolinato de metilo



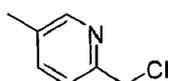
10 Se añadió 2-cloro-5-metilpiridina (10 g, 78 mmoles) a una disolución de metanol (75 ml) y acetonitrilo (75 ml) en una bomba de acero a RT haciendo burbujear nitrógeno seguido de la adición de trietilamina (11,8 g, 117 mmoles), BINAP (970 mg, 1,5 mmoles) y dicloruro de paladio - bisacetonitrilo (0,4 g, 1,5 mmoles). La mezcla se calentó a 100°C y esta temperatura se mantuvo durante la noche (la reacción se verificó por medio de TLC). La mezcla de reacción se filtró a través de un lecho de Celite® y lavando con acetato de etilo. El producto filtrado se lavó con agua y salmuera. La capa orgánica se concentró a presión reducida y se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo 10% en n-hexano y gel de sílice (malla 230-400) para proporcionar 5-metilpicolinato de metilo (6,5 g, 55%), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,6 (s, 1H), 8,0 (d, 1H), 7,65 (d, 1H), 4,05 (s, 3H), 2,4 (s, 3H). MS: $[M + H]^+$: $m/z = 151,9$.

20 (5-Metilpiridin-2-il)metanol



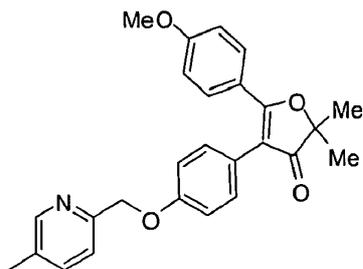
25 Se añadió borohidruro de sodio (4,5 g, 115, mmoles) a una disolución de 5-metilpicolinato de metilo (6,0 g, 39,5 mmoles) en THF (60 mL) y metanol (6 ml) a RT. La mezcla de reacción se agitó a RT durante 2h (la reacción se verificó por medio de TLC). La mezcla se concentró a presión reducida y el residuo se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. La capa orgánica se concentró a vacío para proporcionar (5-metilpiridin-2-il)metanol (3,5 g, 72,9%), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,5 (s, 1H), 7,7 (d, 1H), 7,15 (d, 1H), 5,0 (s, 3H), 3,4 (s, 3H). MS: $[M + H]^+$: $m/z = 124,0$.

30 2-(Clorometil)-5-metilpiridina



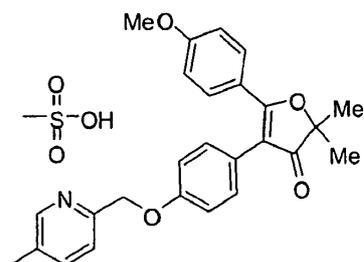
35 Se añadió cloruro de tionilo (30 ml) a (5-metilpiridin-2-il)metanol (3,0 g, 24,3 mmoles) a 20°C en nitrógeno. La mezcla de reacción se agitó a reflujo durante 3h (la reacción se verificó por medio de TLC). La mezcla de reacción se concentró a presión reducida después de lo cual se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 6% en n-hexano y gel de sílice (malla 230-400), para proporcionar 2-(clorometil)-5-metilpiridina (2,5 g, 73 %), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,4 (s, 1H), 7,5 (d, 1H), 7,3 (d, 1H), 4,6 (s, 2H), 2,3 (s, 3H). MS: $[M + H]^+$: $m/z = 142,2$.

45 5-(4-Metoxifenil)-2,2-dimetil-4-(4-((5-metilpiridin-2-il)metoxi)fenil)furan-3(2H)-ona



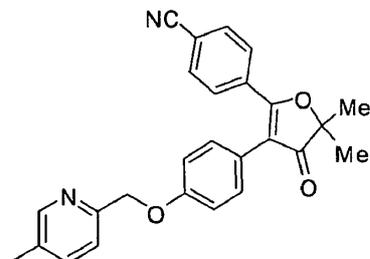
Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (2,0, 6,5 mmoles) a una mezcla de carbonato de cesio (10,5 g, 32,2 mmoles) y DMF (50mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 30 min, después de lo cual se añadió 2-(clorometil)-5-metilpiridina (1,36 g, 9,6 mmoles). La mezcla se calentó a 80°C durante 4 h (la reacción se verificó por medio de TLC). Se dejó que se enfriara la mezcla de reacción, se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en n-hexano y gel de sílice (malla 230-400), para proporcionar 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilpiridin-2-il)metoxi)fenil)furan-3(2H)-ona (2,0 g, 76,9%), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, DMSO- d_6 : δ 8,4 (s, 1H), 7,6 (d, 1H), 7,55 (d, 2H), 7,4 (d, 1H), 7,2 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,2 (s, 2H) 3,8 (s, 3H), 2,3 (s, 3H), 1,45 (s, 6H). MS: $[M + H]^+$: $m/z = 415,2$. HPLC: (97,5%, Condición A).

Metanosulfonato de 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilpiridin-2-il)metoxi)fenil)furan-3(2H)-ona



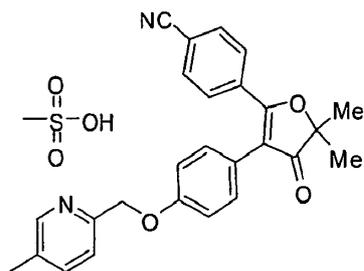
Se añadió ácido metanosulfónico (462 mg, 4,8 mmoles) a una disolución de 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilpiridin-2-il)metoxi)fenil)furan-3(2H)-ona (2,0 g, 4,8 mmoles) en DCM (5 ml) y éter dietílico (50 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4 h después de lo cual los sólidos se recogieron mediante filtración, se lavaron con DCM al 20% en éter dietílico y se secaron a vacío para proporcionar metanosulfonato de 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilpiridin-2-il)metoxi)fenil)furan-3(2H)-ona (2,0 g, 90,9%), en forma de un sólido de color blanco. RMN H^1 : 200 MHz, DMSO- d_6 : δ 8,5 (s, 1H), 7,6 (d, 1H), 7,55 (d, 2H), 7,4 (d, 1H), 7,2 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,2 (s, 2H) 3,8 (s, 3H), 2,35 (s, 3H), 2,3 (s, 3H), 1,45 (s, 6H). HPLC: (99,3%, Condición A).

4-(5,5-Dimetil-3-(4-((5-metilpiridin-2-il)metoxi)fenil)-4-oxo-4,5-dihidrofuran-2-il)benzocitrilo



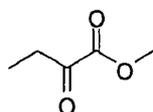
Se añadió 4-(3-(4-hidroxifenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzocitrilo (0,4 g, 1,3 mmoles) a una mezcla de carbonato de cesio (1,7 g, 5,2 mmoles) y DMF (20 mL) a RT en nitrógeno. La mezcla de reacción se agitó a RT durante 30 minutos después de lo cual se añadió 2-(clorometil)-5-metilpiridina (306 mg, 1,9 mmoles). La mezcla se calentó a 80°C durante 4 h (la reacción se verificó por medio de TLC). La mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 25% en n-hexano y gel de sílice (malla 230-400) para proporcionar 4-(5,5-dimetil-3-(4-((5-metilpiridin-2-il)metoxi)fenil)-4-oxo-4,5-dihidrofuran-2-il)benzocitrilo (160 mg, 30,1 %), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, DMSO- d_6 : δ 8,4 (s, 1H), 7,6 (d, 1H), 7,55 (d, 2H), 7,4 (d, 1H), 7,2 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,2 (s, 2H), 2,3 (s, 3H), 1,45 (s, 6H). MS: $[M + H]^+$: $m/z = 411,2$. HPLC: (97,3%, Condición A).

Metanosulfonato de 4-(5,5-dimetil-3-(4-((5-metilpiridin-2-il)metoxi)fenil)-4-oxo-4,5-dihidrofuran-2-il)benzocitrilo



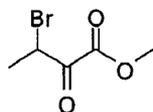
5 Se añadió ácido metanosulfónico (36 mg, 0,3 mmoles) a una disolución de 4-(5,5-dimetil-3-(4-((5-metilpiridin-2-il)metoxi)fenil)-4-oxo-4,5-dihidrofuran-2-il)benzocitrilo (150 mg, 0,3 mmoles) en DCM (5 ml) y éter dietílico (50 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4h después de lo cual los sólidos se recogieron mediante filtración, se lavaron con DCM al 20% en éter dietílico, se secaron a vacío para proporcionar metanosulfonato de 4-(5,5-dimetil-3-(4-((5-metilpiridin-2-il)metoxi)fenil)-4-oxo-4,5-dihidrofuran-2-il)benzocitrilo (120 mg, 67,0 %), en forma de un sólido de color blanco. RMN H^1 : 200 MHz, DMSO- d_6 : δ 8,5 (s, 1H), 7,6 (d, 1H), 7,55 (d, 2H), 7,4 (d, 1H), 7,2 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,2 (s, 2H), 2,35 (s, 3H), 2,3 (s, 3H), 1,45 (s, 6H). HPLC: (98,3%, Condición A).

2-Oxobutanoato de metilo



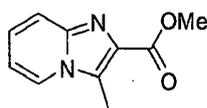
15 Se añadió cloruro de trimetilsililo (1,06 g, 9,8 mmoles) a una disolución agitada de ácido 2-oxobutanoico (10,0 g, 98,0 mmoles) en 2,2-dimetoxipropano (90 ml) y metanol (20 ml). La mezcla se agitó durante 18 horas a RT (la reacción se verificó por medio de TLC) después de lo cual la mezcla se concentró a presión reducida para proporcionar 2-oxobutanoato de metilo bruto (8,0 g) en forma de un líquido de color pardo. RMN H^1 : 200 MHz, $CDCl_3$: δ 3,85 (s, 3H), 2,9 (c, 2H), 1,15 (t, 1H), 6,8 (t, 1H), 4,75 (s, 2H).

3-Bromo-2-oxobutanoato de metilo



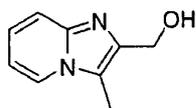
25 Se añadió bromuro de cobre (30,0 g, 137 mmoles) a una disolución agitada de 2-oxobutanoato de metilo (8,0 g, 68,9 mmoles) en acetato de etilo (150 ml) y cloroformo (100 ml). La mezcla se agitó durante 18 horas a reflujo (la reacción se verificó por medio de TLC). La mezcla se filtró y se lavó con acetato de etilo y los productos filtrados se concentraron a vacío para proporcionar 3-bromo-2-oxobutanoato de metilo bruto (6,5 g) en forma de un líquido incoloro. RMN H^1 : 200 MHz, $CDCl_3$: δ 5,2 (c, 1H), 3,9 (s, 3H), 1,8 (d, 3H).

3-Metilimidazo[1,2-a]piridino-2-carboxilato de metilo



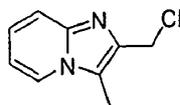
35 Se añadió 3-bromo-2-oxobutanoato de metilo (6,5 g, 34,3 mmoles) a una disolución agitada de 2-aminopiridina (4,0 g, 42,5 mmoles) en acetonitrilo (100 ml). La mezcla se calentó a reflujo durante 14 h (la reacción se verificó por medio de TLC). La mezcla se concentró a vacío y el residuo se diluyó con agua y el pH se llevó a 7,5 utilizando una disolución de bicarbonato de sodio. La mezcla se extrajo con EtOAc; los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 8% en n-hexano y gel de sílice (malla 230-400) para proporcionar 3-metilimidazo[1,2-a]piridino-2-carboxilato de metilo (2,0 g, 25,1%), en forma de un sólido de color amarillo pálido. RMN H^1 : 200 MHz, $CDCl_3$: δ 7,95 (d, 1H), 7,7 (d, 1H), 7,25 (t, 1H), 6,8 (t, 1H), 4,0 (s, 3H), 2,8 (s, 3H). MS: $[M+H]^+$: $m/z = 191,1$.

(3-Metilimidazo[1,2-a]piridin-2-il)metanol



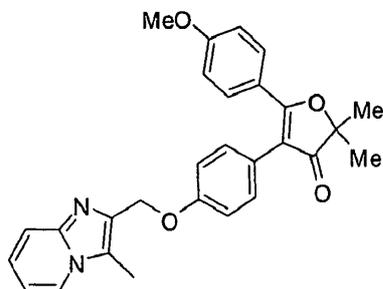
5 Se añadió borohidruro de sodio (1,5 g, 41,6 mmoles) a una disolución de 3-metilimidazo[1,2-a]piridino-2-carboxilato de metilo (2,0 g, 10,5 mmoles) en THF (50 mL) y metanol (2,5 ml) a RT. La mezcla de reacción se agitó a RT durante 2 h (la reacción se verificó por medio de TLC) después de lo cual la mezcla se concentró a presión reducida. El residuo se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida para proporcionar (3-metilimidazo[1,2-a]piridin-2-il)metanol (0,8 g, 47,05 %), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, $CDCl_3$: δ 7,45 (d, 1H), 7,6 (d, 1H), 7,2 (t, 1H), 6,8 (t, 1H), 4,85 (s, 2H), 2,45 (s, 3H). MS: $[M + H]^+$: $m/z = 162,9$.

2-(Clorometil)-3-metilimidazo[1,2-a]piridina



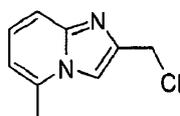
15 Se añadió cloruro de tionilo (10 ml) a (3-metilimidazo[1,2-a]piridin-2-il)metanol (0,8 g, 4,9 mmoles) a 20°C en una atmósfera de nitrógeno. La mezcla de reacción se agitó a reflujo durante 3h (la reacción se verificó por medio de TLC). La mezcla se concentró a presión reducida, el residuo se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 6% en n-hexano y gel de sílice (malla 230-400) para proporcionar 2-(cloroetil)-3-metilimidazo[1,2-a]piridina (400 mg, 45,4 %), en forma de un sólido de color blanquecino. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,15 (s, 1H), 7,6 (s, 1H), 7,55 (d, 1H), 7,15 (d, 1H), 4,75 (s, 2H). MS: $[M + H]^+$: $m/z = 181,3$.

25 5-(4-Metoxifenil)-2,2-dimetil-4-(4-((3-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona



30 Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (0,1 g, 0,32 mmoles) a una mezcla de carbonato de cesio (0,52 g, 1,62 mmoles) y DMF (20 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 30 min después de lo cual se añadió 2-(clorometil)-3-metilimidazo[1,2-a]piridina (87 mg, 0,48 mmoles). La mezcla se calentó a durante 4 h (la reacción se verificó por medio de TLC). La mezcla de reacción se diluyó con agua y se extrajo con EtOAc, los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en n-hexano y gel de sílice (malla 230-400) para proporcionar 5-(4-metoxifenil)-2,2-dimetil-4-(4-((3-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona (2,8 g, 77%), en forma de un sólido de color blanquecino. RMN H^1 , 500 MHz, $DMSO-d_6$: δ 8,25 (d, 1H), 7,45 (d, 3H), 7,25 (t, 1H), 7,15-6,95 (Ar, 7H), 5,2 (s, 2H), 3,85 (s, 3H), 2,45 (s, 3H), 1,45 (s, 6H). MS: $[M + H]^+$: $m/z = 455,3$. HPLC: (96,3%, Condición A).

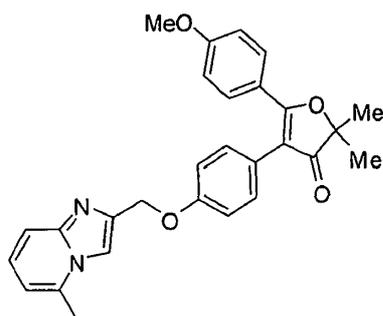
40 2-(Clorometil)-5-metilimidazo[1,2-a]piridina



45 Se añadió 1,3-dicloroacetona (17,6 g, 138,3 mmoles) a una disolución de 6-metilpiridin-2-amina (10 g, 92,5 mmoles) en acetonitrilo (200 ml). La mezcla se calentó a reflujo durante 14h (la reacción se verificó por medio de TLC). La

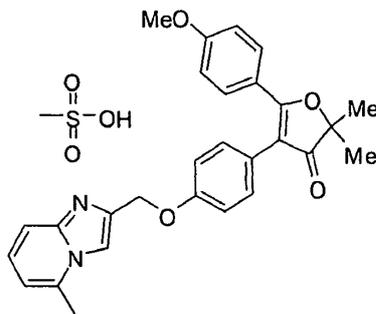
mezcla se concentró a presión reducida, el residuo se diluyó con agua, y el pH se ajustó a 7,5 con una disolución de bicarbonato de sodio. La mezcla se extrajo con EtOAc, los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 10% en n-hexano y gel de sílice (malla 230-400) para proporcionar 2-(clorometil)-5-metilimidazo[1,2-a]piridina (7,0 g, 70,7%), en forma de un sólido de color amarillo pálido. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,15 (s, 1H), 7,6 (dd, 2H), 7,1 (t, 1H), 6,8 (t, 1H), 4,95 (s, 2H), 2,6 (s, 3H). MS: $[M + H]^+$: m/z = 181,5.

5-(4-Metoxifenil)-2,2-dimetil-4-(4-((5-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona



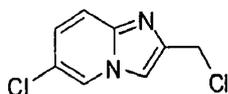
Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (250 mg, 0,8 mmoles) a una mezcla de carbonato de cesio (1,05 g, 3,22 mmoles) y DMF (20mL) a RT en nitrógeno. La mezcla de reacción se agitó a RT durante 30 minutos después de lo cual se añadió 2-(clorometil)-5-metilimidazo[1,2-a]piridina (218 mg, 1,2 mmoles). La mezcla se calentó a durante 4 h (la reacción se verificó por medio de TLC) después de lo cual la mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 15% en n-hexano y gel de sílice (malla 230-400) para proporcionar 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona (280 mg, 77,7%), en forma de un sólido de color amarillo claro. RMN H^1 : 500 MHz, $DMSO-d_6$: δ 7,95 (s, 1H), 7,6 (d, 2H), 7,4 (d, 1H), 7,25 (t, 1H), 7,2 (d, 3H), 7,15 (d, 2H), 7,0 (d, 2H), 6,8 (d, 1H), 5,2 (s, 2H) 3,85 (s, 3H), 2,6 (s, 3H), 1,25 (s, 6H). MS: $[M + H]^+$: m/z = 455,6. HPLC: (97,3%, Condición A).

Metanosulfonato de 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona



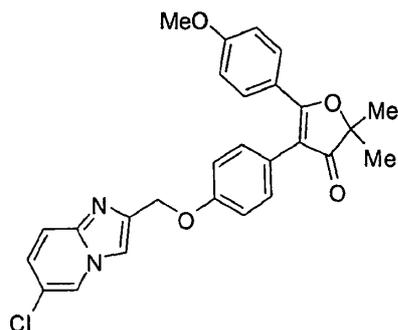
Se añadió ácido metanosulfónico (53,1 mg, 0,5 mmoles) a una disolución de 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona (250 g, 0,5 mmoles) en DCM (2,5 ml) y éter dietílico (50 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4 h después de lo cual, los sólidos se recogieron mediante filtración, se lavaron con DCM al 20% en éter dietílico, se secaron a vacío para proporcionar metanosulfonato de 5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona (240 mg, 82,7 %), en forma de un sólido de color blanco. RMN H^1 : 500 MHz, $DMSO-d_6$: δ 7,95 (s, 1H), 7,6 (d, 2H), 7,4 (d, 1H), 7,25 (t, 1H), 7,2 (d, 3H), 7,15 (d, 2H), 7,0 (d, 2H), 6,8 (d, 1H), 5,2 (s, 2H) 3,85 (s, 3H), 2,6 (s, 3H), 2,5 (s, 3H), 1,25 (s, 6H). HPLC: (98,4%, Condición A).

6-Cloro-2-(clorometil)imidazo[1,2-a]piridina



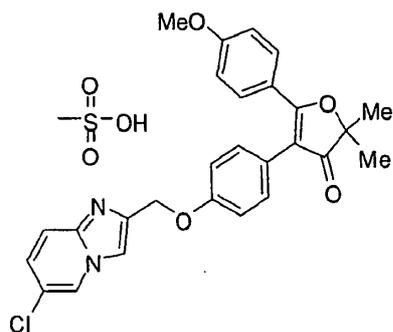
Se añadió 1,3-dicloroacetona (7,4 g, 58,3 mmoles) a una disolución de 5-cloropiridin-2-amina (5,0 g, 38,9 mmoles) en acetonitrilo (100 ml). La mezcla se calentó a reflujo durante 14 h (la reacción se verificó por medio de TLC). Una vez completada la reacción según se evaluó mediante TLC, la mezcla se concentró a presión reducida. El residuo se diluyó con agua y el pH se ajustó a 7,5 con una disolución de bicarbonato de sodio. La mezcla se extrajo con EtOAc, los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 10% en n-hexano y gel de sílice (malla 230-400) para proporcionar 6-cloro-2-(clorometil)imidazo[1,2-a]piridina (1,5 g, 30%), en forma de un sólido de color amarillo pálido. RMN H^1 : 200 MHz, $CDCl_3$: δ 8,0 (d, 1H), 7,6 (dd, 2H), 6,8 (d, 1H), 4,75 (s, 2H). MS: $[M + H]^+$: $m/z = 201,9$.

4-(4-((6-Cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona



Se añadió 4-(4-hidroxifenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (300 mg, 0,96 mmoles) a una mezcla de carbonato de cesio (1,05 g, 3,8 mmoles) y DMF (20 mL) a RT en nitrógeno. La mezcla de reacción se agitó a RT durante 30 minutos, después de lo cual se añadió 6-cloro-2-(clorometil)imidazo[1,2-a]piridina (201 mg, 1,4 mmoles). La mezcla se calentó a 80°C durante 4h (la reacción se verificó por medio de TLC). Una vez completada la reacción según se evaluó mediante TLC, la mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó por medio de cromatografía en columna instantánea utilizando acetato de etilo al 20% en n-hexano y gel de sílice (malla 230-400) para proporcionar 4-(4-((6-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (180 mg, 39,3 %), en forma de un sólido de color blanco. RMN H^1 , 500 MHz, $DMSO-d_6$: δ 8,85 (s, 1H), 8,0 (s, 1H), 7,6 (d, 3H), 7,3 (d, 1H), 7,15 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H), 5,15 (s, 2H) 3,8 (s, 3H), 1,4 (s, 6H). MS: $[M + H]^+$: $m/z = 475$. HPLC: (98,0%, Condición A).

Metanosulfonato de 4-(4-((6-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona

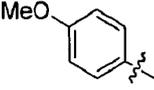
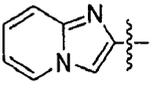
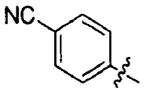
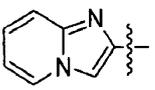
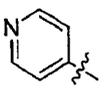
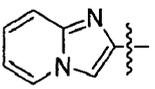
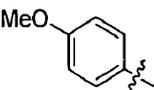
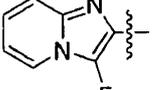
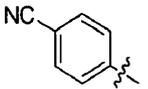
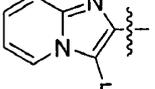
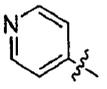
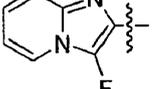
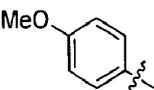
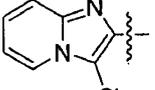
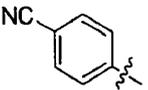
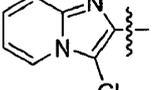
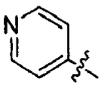
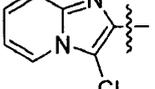
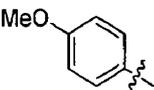
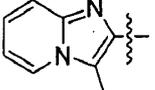


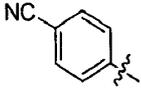
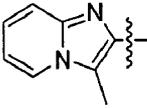
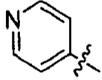
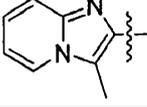
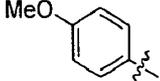
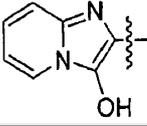
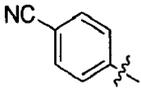
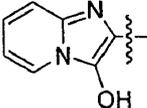
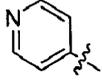
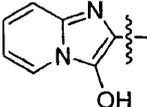
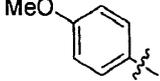
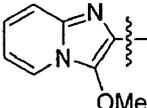
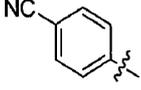
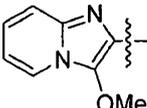
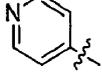
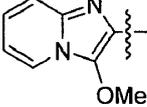
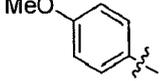
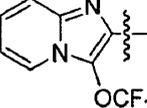
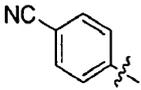
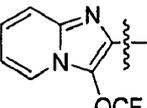
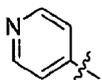
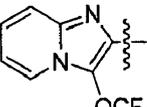
Se añadió ácido metanosulfónico (53,1 mg, 0,5 mmoles) a una disolución del compuesto 4-(4-((6-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (250 g, 0,5 mmoles) en DCM (2,5 ml) y éter dietílico (50 mL) a RT en una atmósfera de nitrógeno. La mezcla de reacción se agitó a RT durante 4h después de lo cual los sólidos se recogieron mediante filtración, se lavaron con DCM al 20% en éter dietílico y se secaron a vacío para proporcionar metanosulfonato de 4-(4-((6-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona (240 mg, 82 %), en forma de un sólido de color blanco. RMN H^1 : 500 MHz, $DMSO-d_6$: δ 8,8 (s, 1H), 8,3 (s, 1H), 8,0 (s, 1H), 7,6 (d, 2H), 7,4 (d, 1H), 7,15 (d, 2H), 7,1 (d, 2H), 7,0 (d, 2H) 5,35 (s, 2H), 3,8 (s, 3H), 2,3 (s, 3H), 1,4 (s, 6H). HPLC: (99,3%, Condición A).

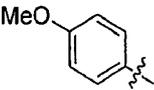
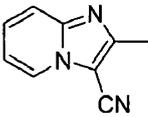
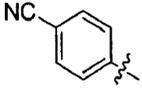
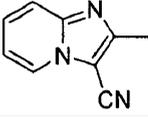
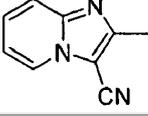
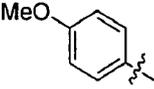
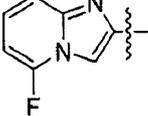
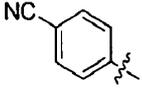
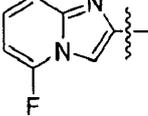
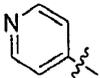
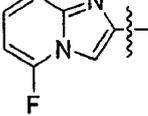
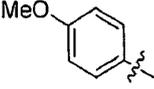
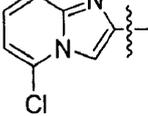
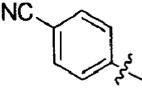
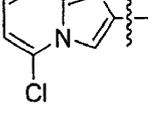
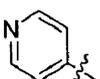
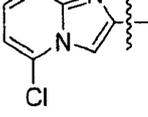
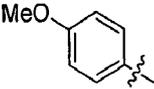
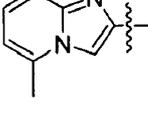
Tablas

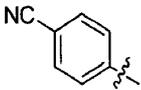
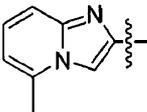
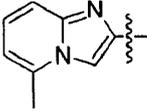
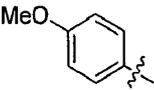
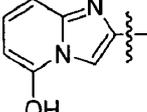
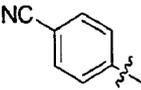
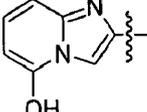
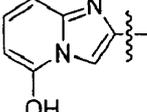
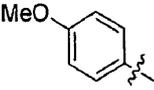
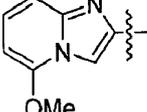
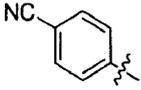
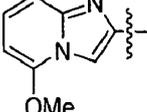
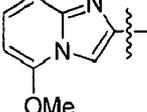
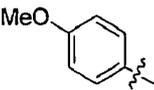
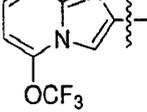
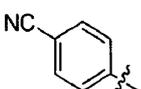
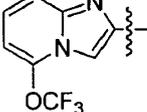
5 En las siguientes tablas, si un ejemplo específico contiene múltiples casos de R₂, estos se separarán por medio de comas en la tabla (p. ej. Me, Me o Et, Me). Si la columna de R₂ contiene un valor "--grupo--" p. ej. "--ciclopropilo--", en ese caso ambos valores de R₂ se toman juntos para constituir un anillo espiro.

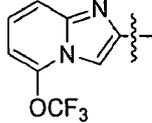
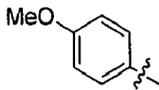
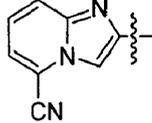
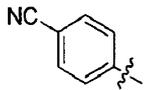
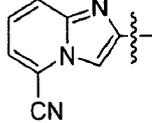
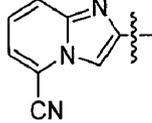
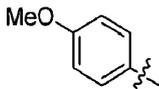
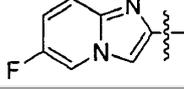
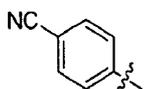
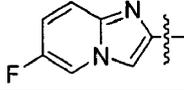
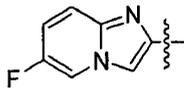
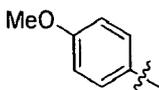
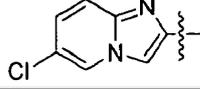
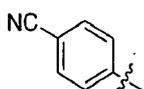
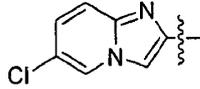
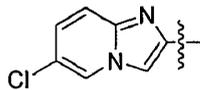
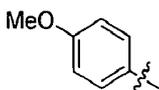
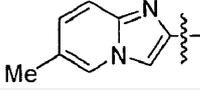
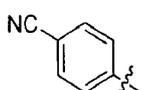
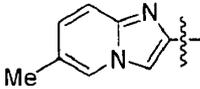
En un aspecto adicional los compuestos de la descripción se plasman con distintos ejemplos enumerados en la tabla de más abajo tomados de la Fórmula (I):

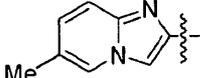
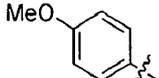
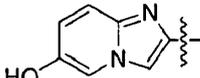
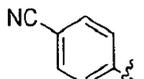
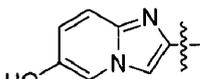
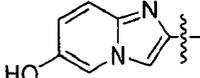
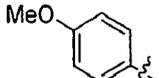
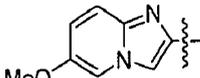
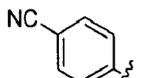
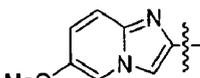
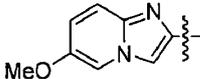
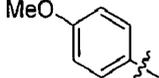
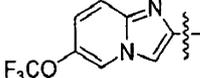
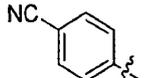
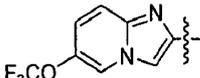
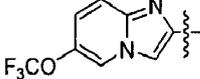
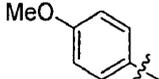
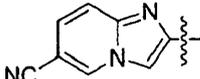
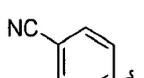
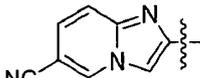
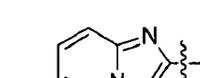
Núm. de Ejemplo	HET	X	Z	R ₂
1	A29			Me, Me
2	A29			Me, Me
3	A29			Me, Me
4	A29			Me, Me
5	A29			Me, Me
6	A29			Me, Me
7	A29			Me, Me
8	A29			Me, Me
9	A29			Me, Me
10	A29			Me, Me

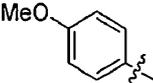
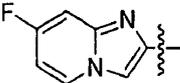
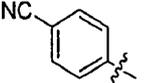
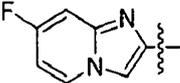
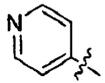
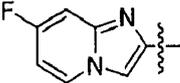
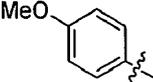
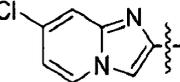
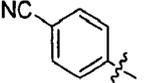
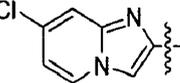
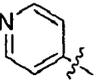
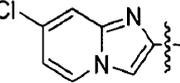
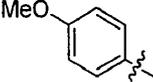
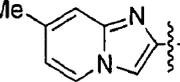
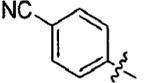
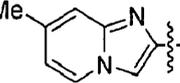
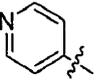
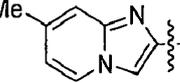
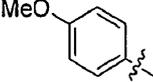
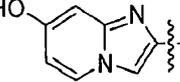
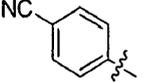
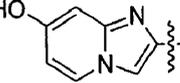
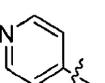
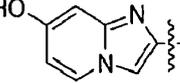
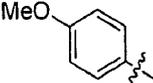
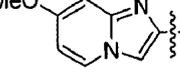
Núm. de Ejemplo	HET	X	Z	R ₂
11	A29			Me, Me
12	A29			Me, Me
13	A29			Me, Me
14	A29			Me, Me
15	A29			Me, Me
16	A29			Me, Me
17	A29			Me, Me
18	A29			Me, Me
19	A29			Me, Me
20	A29			Me, Me
21	A29			Me, Me

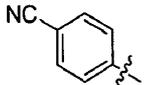
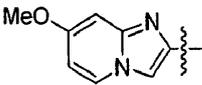
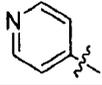
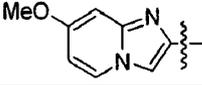
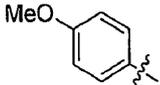
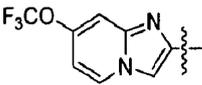
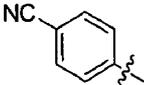
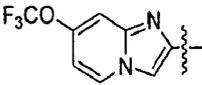
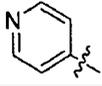
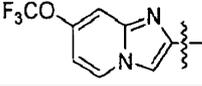
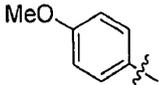
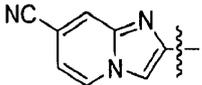
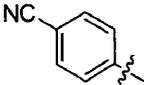
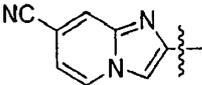
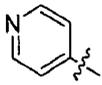
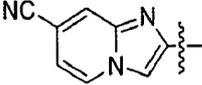
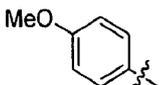
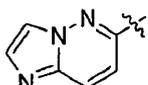
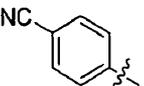
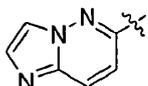
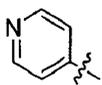
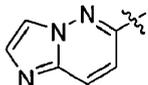
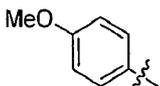
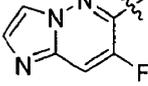
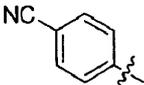
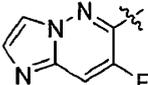
Núm. de Ejemplo	HET	X	Z	R ₂
22	A29			Me, Me
23	A29			Me, Me
24	A29			Me, Me
25	A29			Me, Me
26	A29			Me, Me
27	A29			Me, Me
28	A29			Me, Me
29	A29			Me, Me
30	A29			Me, Me
31	A29			Me, Me

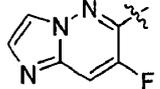
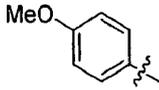
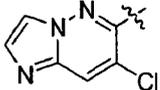
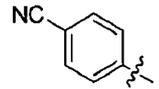
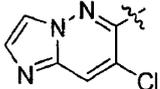
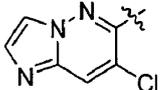
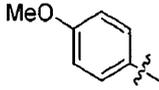
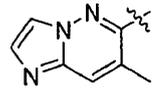
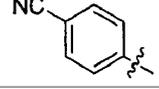
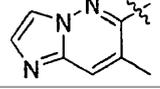
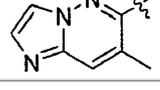
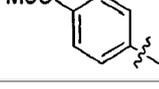
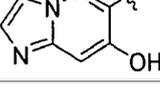
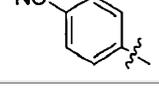
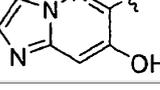
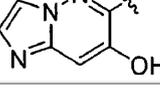
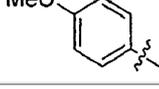
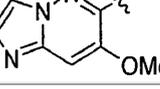
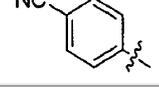
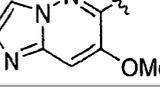
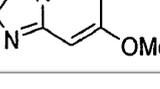
Núm. de Ejemplo	HET	X	Z	R ₂
32	A29			Me, Me
33	A29			Me, Me
34	A29			Me, Me
35	A29			Me, Me
36	A29			Me, Me
37	A29			Me, Me
38	A29			Me, Me
39	A29			Me, Me
40	A29			Me, Me
41	A29			Me, Me

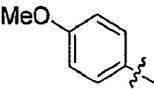
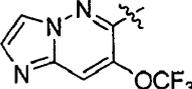
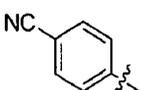
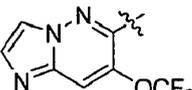
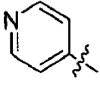
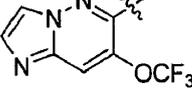
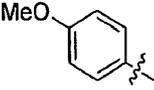
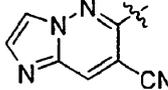
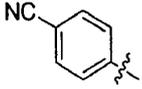
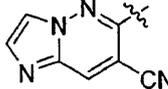
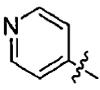
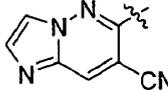
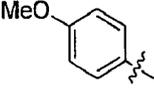
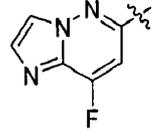
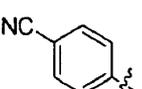
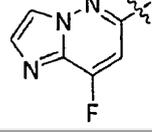
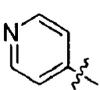
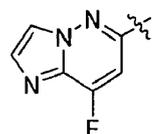
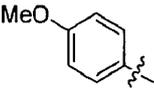
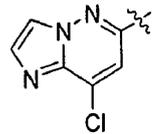
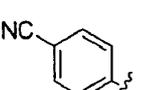
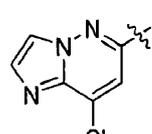
Núm. de Ejemplo	HET	X	Z	R ₂
42	A29			Me, Me
43	A29			Me, Me
44	A29			Me, Me
45	A29			Me, Me
46	A29			Me, Me
47	A29			Me, Me
48	A29			Me, Me
49	A29			Me, Me
50	A29			Me, Me
51	A29			Me, Me
52	A29			Me, Me
53	A29			Me, Me

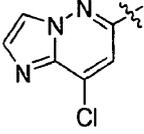
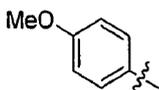
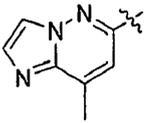
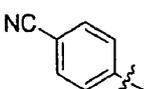
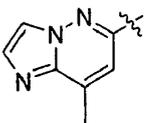
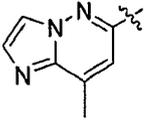
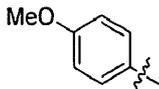
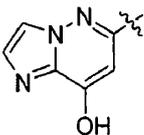
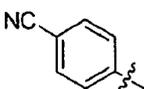
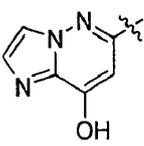
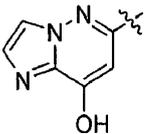
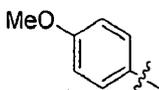
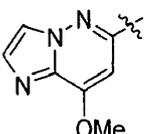
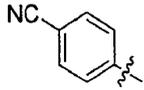
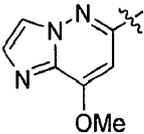
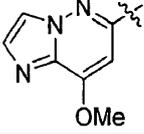
Núm. de Ejemplo	HET	X	Z	R ₂
54	A29			Me, Me
55	A29			Me, Me
56	A29			Me, Me
57	A29			Me, Me
58	A29			Me, Me
59	A29			Me, Me
60	A29			Me, Me
61	A29			Me, Me
62	A29			Me, Me
63	A29			Me, Me
64	A29			Me, Me
65	A29			Me, Me
66	A29			Me, Me

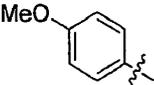
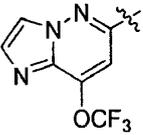
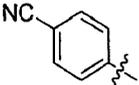
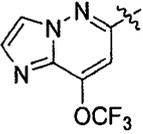
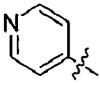
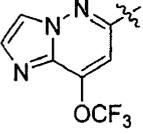
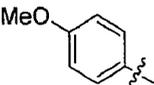
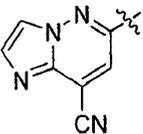
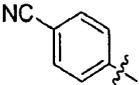
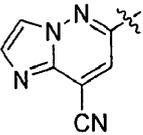
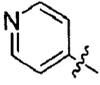
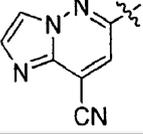
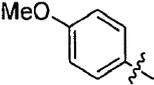
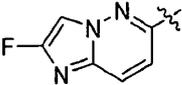
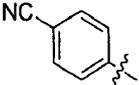
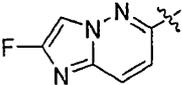
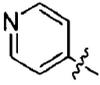
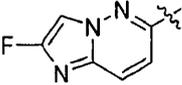
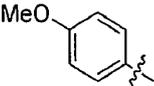
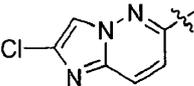
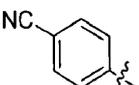
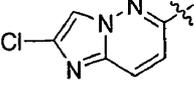
Núm. de Ejemplo	HET	X	Z	R ₂
67	A29			Me, Me
68	A29			Me, Me
69	A29			Me, Me
70	A29			Me, Me
71	A29			Me, Me
72	A29			Me, Me
73	A29			Me, Me
74	A29			Me, Me
75	A29			Me, Me
76	A29			Me, Me
77	A29			Me, Me
78	A29			Me, Me
79	A29			Me, Me

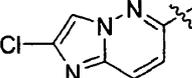
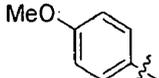
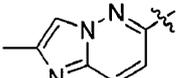
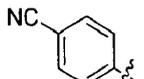
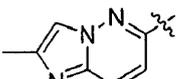
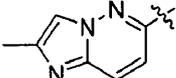
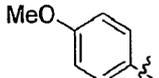
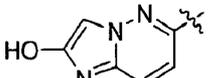
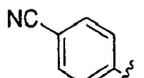
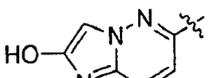
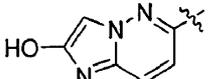
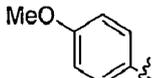
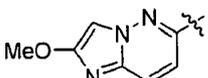
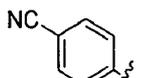
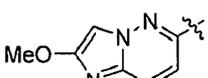
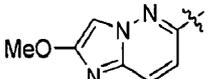
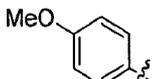
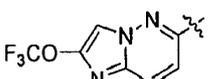
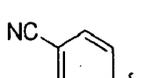
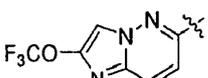
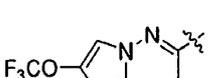
Núm. de Ejemplo	HET	X	Z	R ₂
80	A29			Me, Me
81	A29			Me, Me
82	A29			Me, Me
83	A29			Me, Me
84	A29			Me, Me
85	A29			Me, Me
86	A29			Me, Me
87	A29			Me, Me
88	A29			Me, Me
89	A29			Me, Me
90	A29			Me, Me
91	A29			Me, Me
92	A29			Me, Me

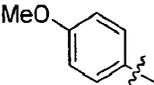
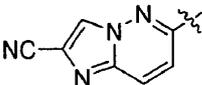
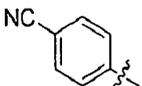
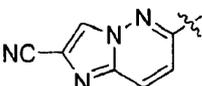
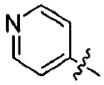
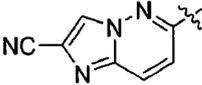
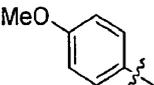
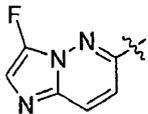
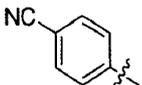
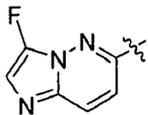
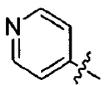
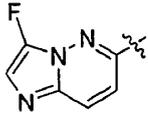
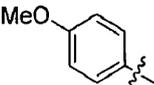
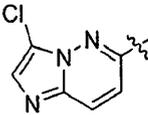
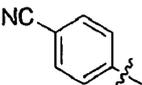
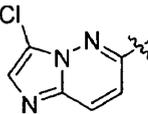
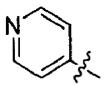
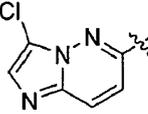
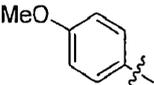
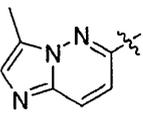
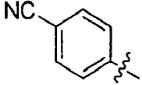
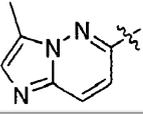
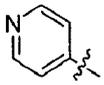
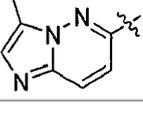
Núm. de Ejemplo	HET	X	Z	R ₂
93	A29			Me, Me
94	A29			Me, Me
95	A29			Me, Me
96	A29			Me, Me
97	A29			Me, Me
98	A29			Me, Me
99	A29			Me, Me
100	A29			Me, Me
101	A29			Me, Me
102	A29			Me, Me
103	A29			Me, Me
104	A29			Me, Me
105	A29			Me, Me

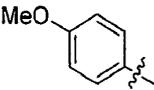
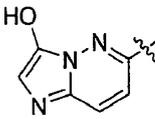
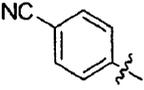
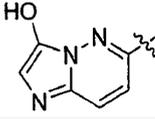
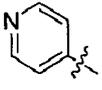
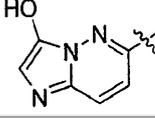
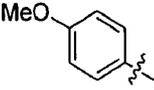
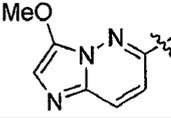
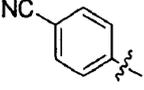
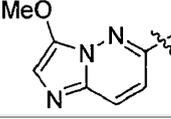
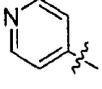
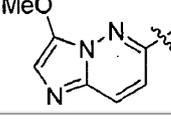
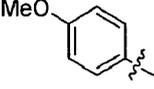
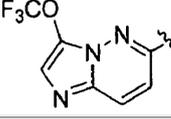
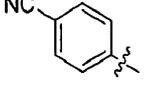
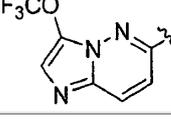
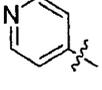
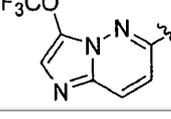
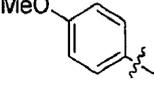
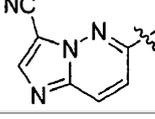
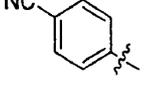
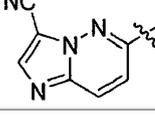
Núm. de Ejemplo	HET	X	Z	R ₂
106	A29			Me, Me
107	A29			Me, Me
108	A29			Me, Me
109	A29			Me, Me
110	A29			Me, Me
111	A29			Me, Me
121	A29			Me, Me
122	A29			Me, Me
123	A29			Me, Me
124	A29			Me, Me
125	A29			Me, Me

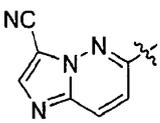
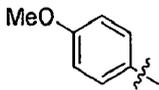
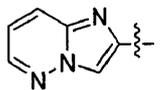
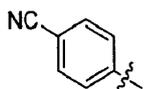
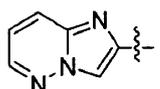
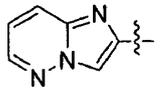
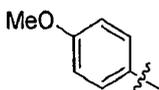
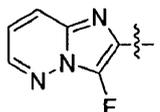
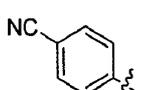
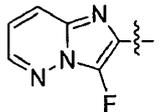
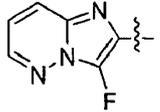
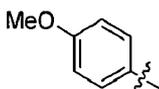
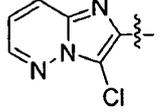
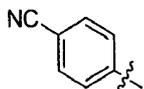
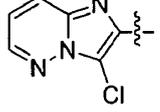
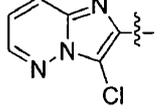
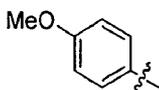
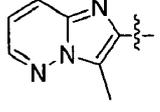
Núm. de Ejemplo	HET	X	Z	R ₂
126	A29			Me, Me
127	A29			Me, Me
128	A29			Me, Me
129	A29			Me, Me
130	A29			Me, Me
131	A29			Me, Me
132	A29			Me, Me
133	A29			Me, Me
134	A29			Me, Me
135	A29			Me, Me

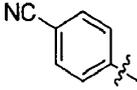
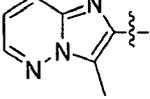
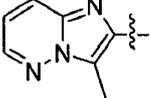
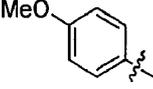
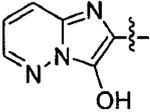
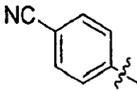
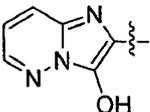
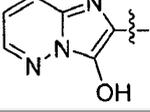
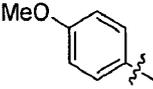
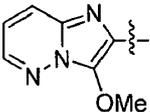
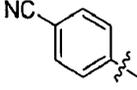
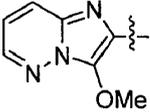
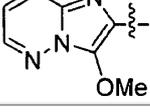
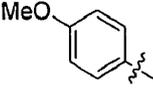
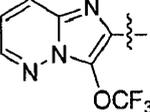
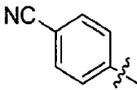
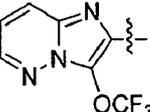
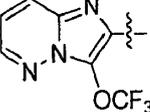
Núm. de Ejemplo	HET	X	Z	R ₂
136	A29			Me, Me
137	A29			Me, Me
138	A29			Me, Me
139	A29			Me, Me
140	A29			Me, Me
141	A29			Me, Me
142	A29			Me, Me
143	A29			Me, Me
144	A29			Me, Me
145	A29			Me, Me
146	A29			Me, Me

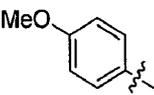
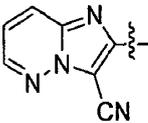
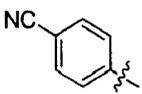
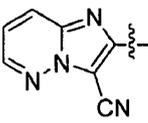
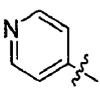
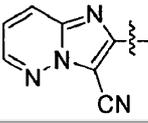
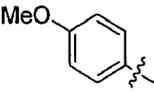
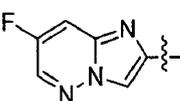
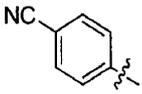
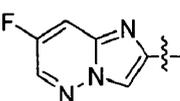
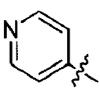
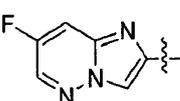
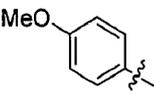
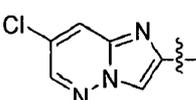
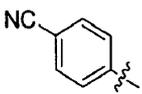
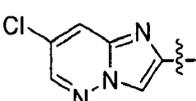
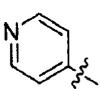
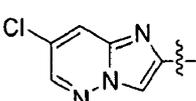
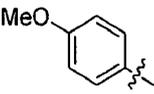
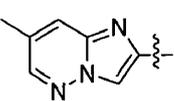
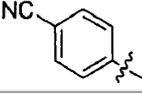
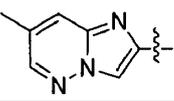
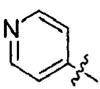
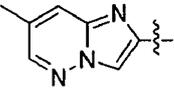
Núm. de Ejemplo	HET	X	Z	R ₂
147	A29			Me, Me
148	A29			Me, Me
149	A29			Me, Me
150	A29			Me, Me
151	A29			Me, Me
152	A29			Me, Me
153	A29			Me, Me
154	A29			Me, Me
155	A29			Me, Me
156	A29			Me, Me
157	A29			Me, Me
158	A29			Me, Me
159	A29			Me, Me

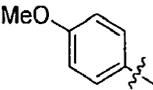
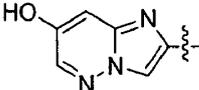
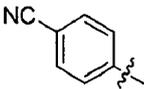
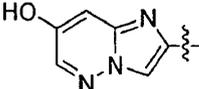
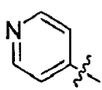
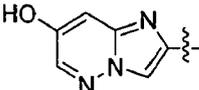
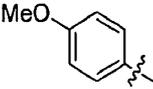
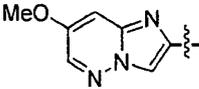
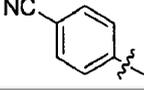
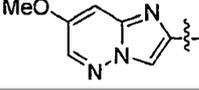
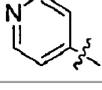
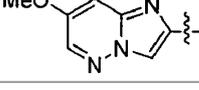
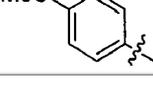
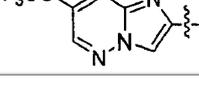
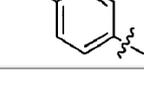
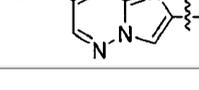
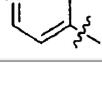
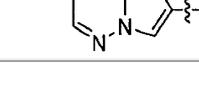
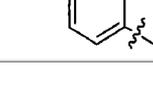
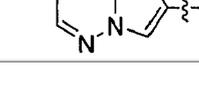
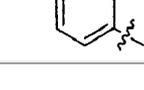
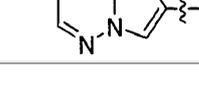
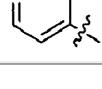
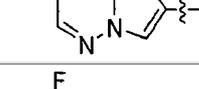
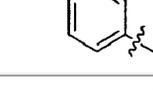
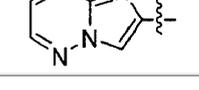
Núm. de Ejemplo	HET	X	Z	R ₂
160	A29			Me, Me
161	A29			Me, Me
162	A29			Me, Me
163	A29			Me, Me
164	A29			Me, Me
165	A29			Me, Me
166	A29			Me, Me
167	A29			Me, Me
168	A29			Me, Me
169	A29			Me, Me
170	A29			Me, Me
171	A29			Me, Me

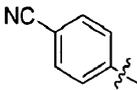
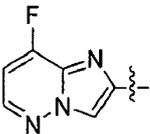
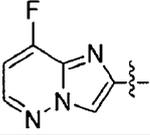
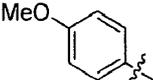
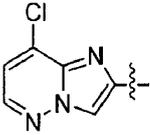
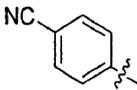
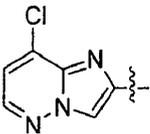
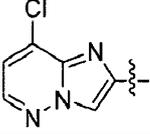
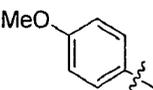
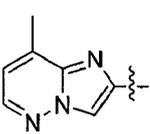
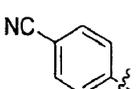
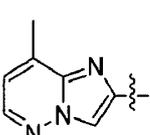
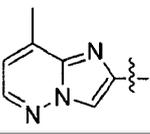
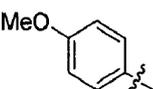
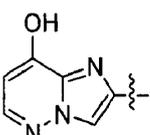
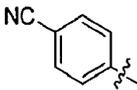
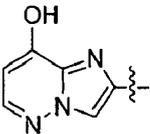
Núm. de Ejemplo	HET	X	Z	R ₂
172	A29			Me, Me
173	A29			Me, Me
174	A29			Me, Me
175	A29			Me, Me
176	A29			Me, Me
177	A29			Me, Me
178	A29			Me, Me
179	A29			Me, Me
180	A29			Me, Me
181	A29			Me, Me
182	A29			Me, Me

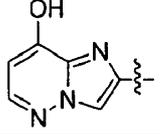
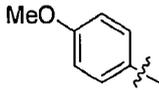
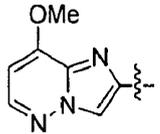
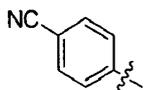
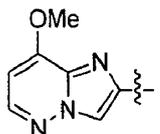
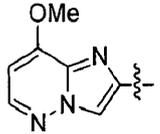
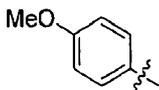
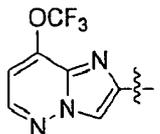
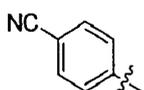
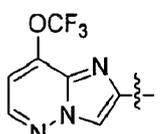
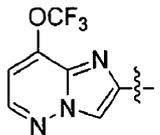
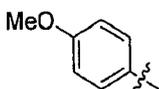
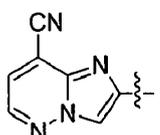
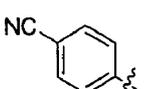
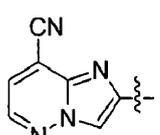
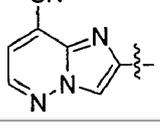
Núm. de Ejemplo	HET	X	Z	R ₂
183	A29			Me, Me
184	A29			Me, Me
185	A29			Me, Me
186	A29			Me, Me
187	A29			Me, Me
188	A29			Me, Me
189	A29			Me, Me
190	A29			Me, Me
191	A29			Me, Me
192	A29			Me, Me
193	A29			Me, Me

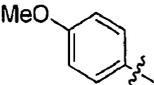
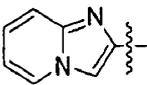
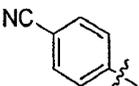
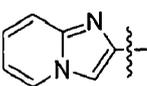
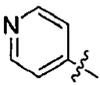
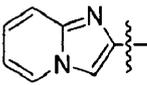
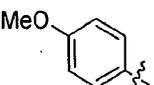
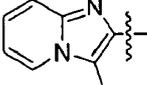
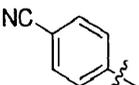
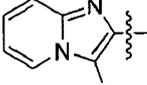
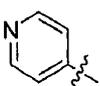
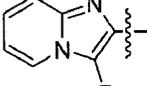
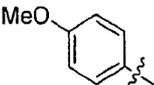
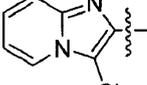
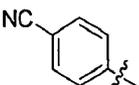
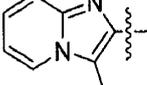
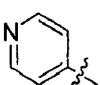
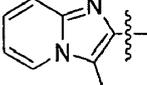
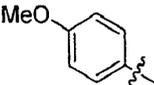
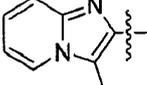
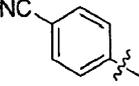
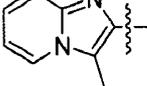
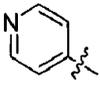
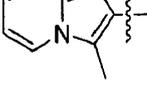
Núm. de Ejemplo	HET	X	Z	R ₂
194	A29			Me, Me
195	A29			Me, Me
196	A29			Me, Me
197	A29			Me, Me
198	A29			Me, Me
199	A29			Me, Me
200	A29			Me, Me
201	A29			Me, Me
202	A29			Me, Me
203	A29			Me, Me
204	A29			Me, Me

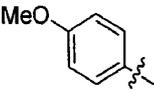
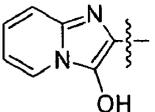
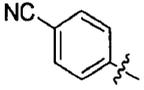
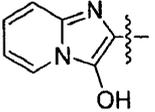
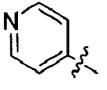
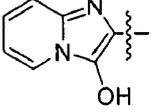
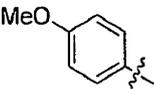
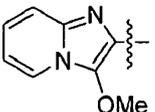
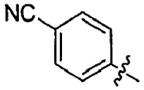
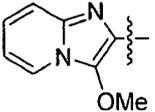
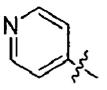
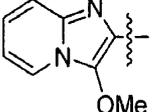
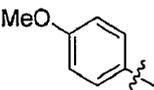
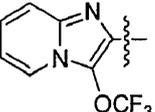
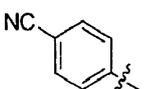
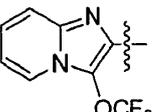
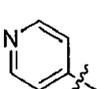
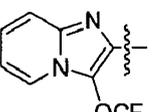
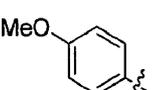
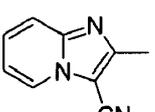
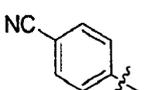
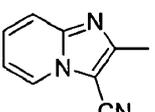
Núm. de Ejemplo	HET	X	Z	R ₂
205	A29			Me, Me
206	A29			Me, Me
207	A29			Me, Me
211	A29			Me, Me
212	A29			Me, Me
213	A29			Me, Me
214	A29			Me, Me
215	A29			Me, Me
216	A29			Me, Me
217	A29			Me, Me
218	A29			Me, Me
219	A29			Me, Me

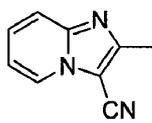
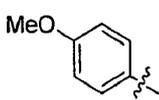
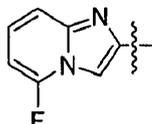
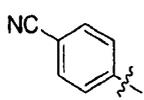
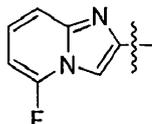
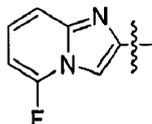
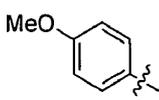
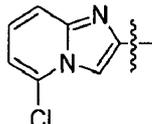
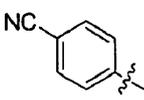
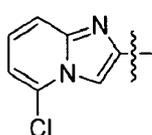
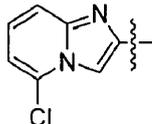
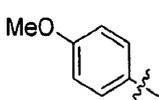
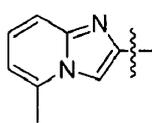
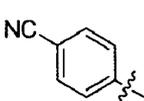
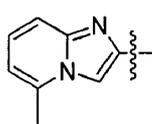
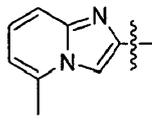
Núm. de Ejemplo	HET	X	Z	R ₂
220	A29			Me, Me
221	A29			Me, Me
222	A29			Me, Me
223	A29			Me, Me
224	A29			Me, Me
225	A29			Me, Me
226	A29			Me, Me
227	A29			Me, Me
228	A29			Me, Me
229	A29			Me, Me
230	A29			Me, Me
231	A29			Me, Me
232	A29			Me, Me

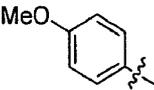
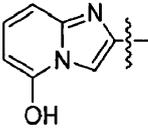
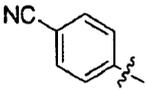
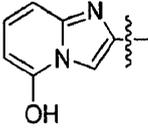
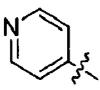
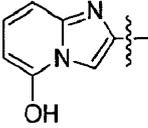
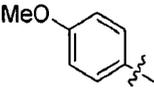
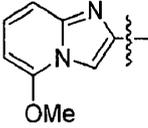
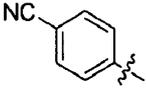
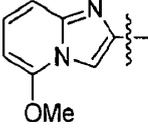
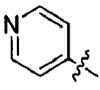
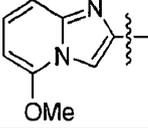
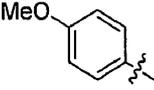
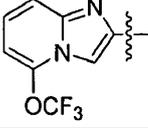
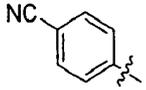
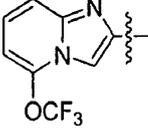
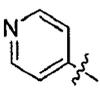
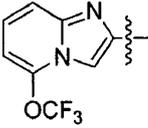
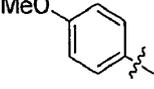
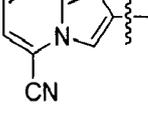
Núm. de Ejemplo	HET	X	Z	R ₂
233	A29			Me, Me
234	A29			Me, Me
235	A29			Me, Me
236	A29			Me, Me
237	A29			Me, Me
238	A29			Me, Me
239	A29			Me, Me
240	A29			Me, Me
241	A29			Me, Me
242	A29			Me, Me

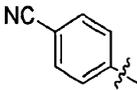
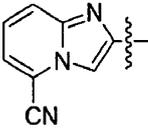
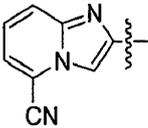
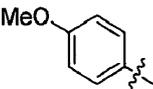
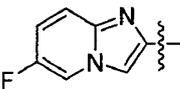
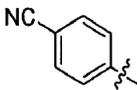
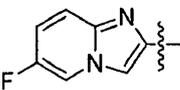
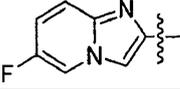
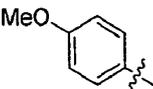
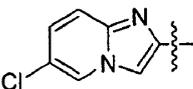
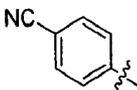
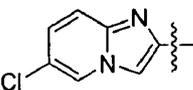
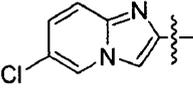
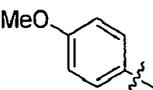
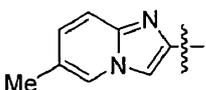
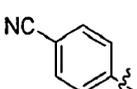
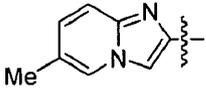
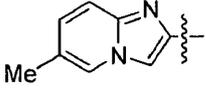
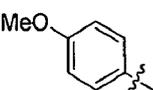
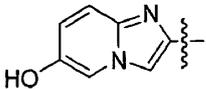
Núm. de Ejemplo	HET	X	Z	R ₂
243	A29			Me, Me
244	A29			Me, Me
245	A29			Me, Me
246	A29			Me, Me
247	A29			Me, Me
248	A29			Me, Me
249	A29			Me, Me
250	A29			Me, Me
251	A29			Me, Me
252	A29			Me, Me

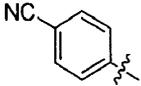
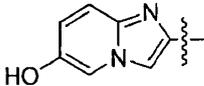
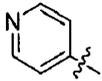
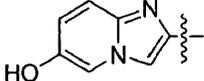
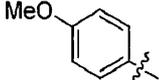
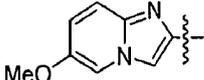
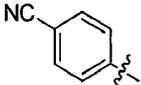
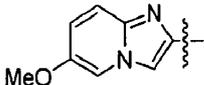
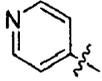
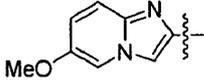
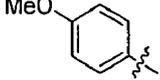
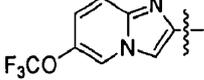
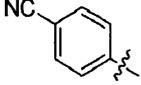
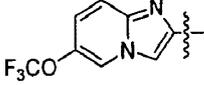
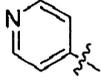
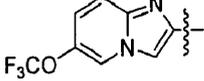
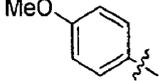
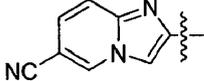
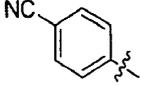
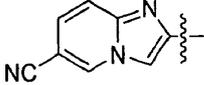
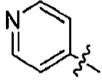
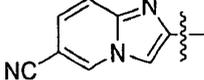
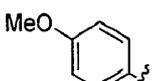
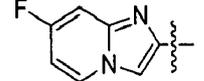
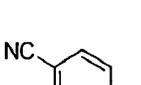
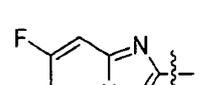
Núm. de Ejemplo	HET	X	Z	R ₂
253	A31			Me, Me
254	A31			Me, Me
255	A31			Me, Me
256	A31			Me, Me
257	A31			Me, Me
258	A31			Me, Me
259	A31			Me, Me
260	A31			Me, Me
261	A31			Me, Me
262	A31			Me, Me
263	A31			Me, Me
264	A31			Me, Me

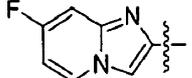
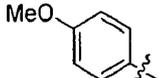
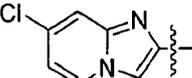
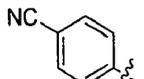
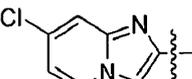
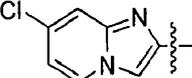
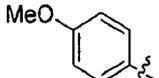
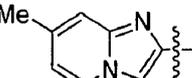
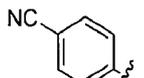
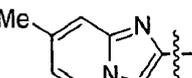
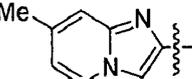
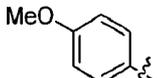
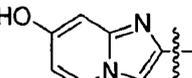
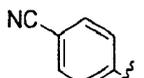
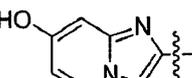
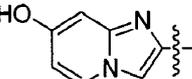
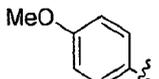
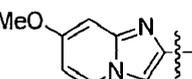
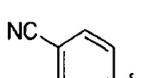
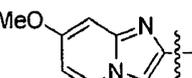
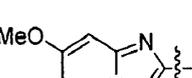
Núm. de Ejemplo	HET	X	Z	R ₂
265	A31			Me, Me
266	A31			Me, Me
267	A31			Me, Me
268	A31			Me, Me
269	A31			Me, Me
270	A31			Me, Me
271	A31			Me, Me
272	A31			Me, Me
273	A31			Me, Me
274	A31			Me, Me
275	A31			Me, Me

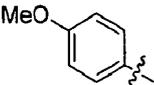
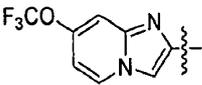
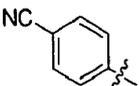
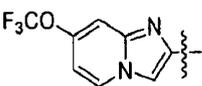
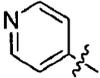
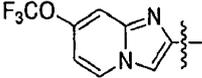
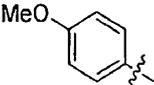
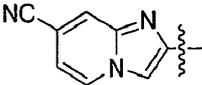
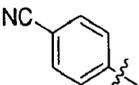
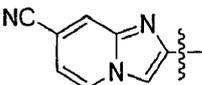
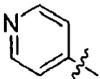
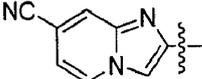
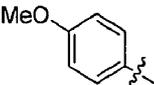
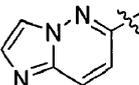
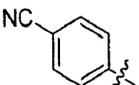
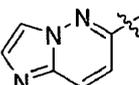
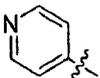
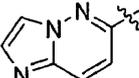
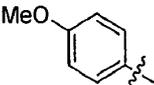
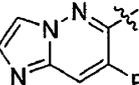
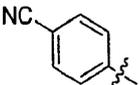
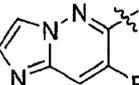
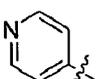
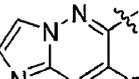
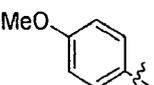
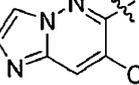
Núm. de Ejemplo	HET	X	Z	R ₂
276	A31			Me, Me
277	A31			Me, Me
278	A31			Me, Me
279	A31			Me, Me
280	A31			Me, Me
281	A31			Me, Me
282	A31			Me, Me
283	A31			Me, Me
284	A31			Me, Me
285	A31			Me, Me

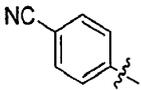
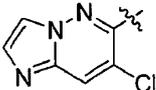
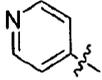
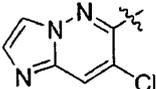
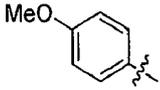
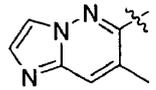
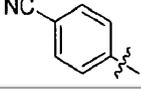
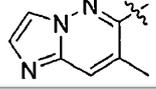
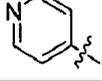
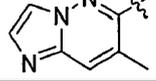
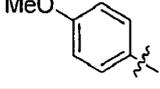
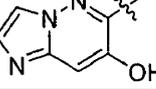
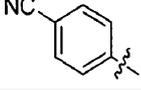
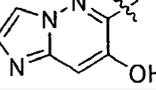
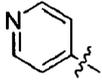
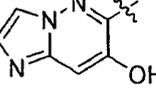
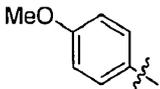
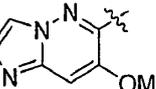
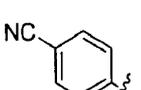
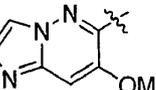
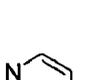
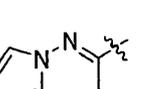
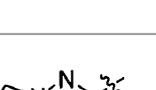
Núm. de Ejemplo	HET	X	Z	R ₂
286	A31			Me, Me
287	A31			Me, Me
288	A31			Me, Me
289	A31			Me, Me
290	A31			Me, Me
291	A31			Me, Me
292	A31			Me, Me
293	A31			Me, Me
294	A31			Me, Me
295	A31			Me, Me

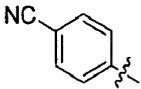
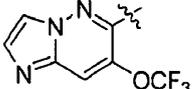
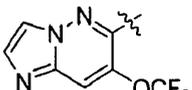
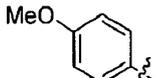
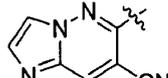
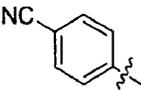
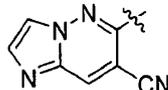
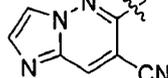
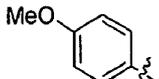
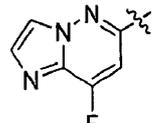
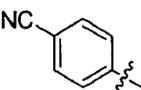
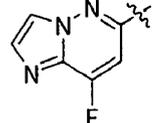
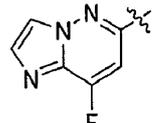
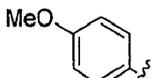
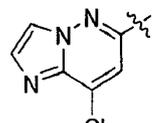
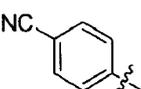
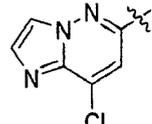
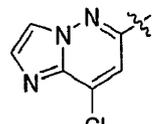
Núm. de Ejemplo	HET	X	Z	R ₂
296	A31			Me, Me
297	A31			Me, Me
298	A31			Me, Me
299	A31			Me, Me
300	A31			Me, Me
301	A31			Me, Me
302	A31			Me, Me
303	A31			Me, Me
304	A31			Me, Me
305	A31			Me, Me
306	A31			Me, Me
307	A31			Me, Me

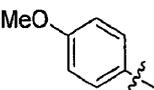
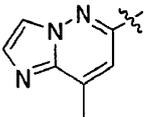
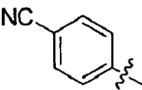
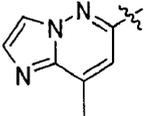
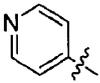
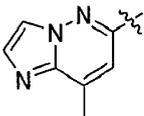
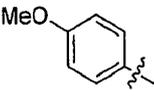
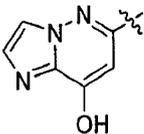
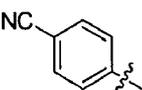
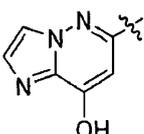
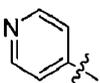
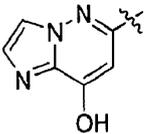
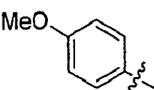
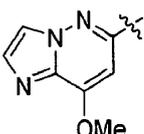
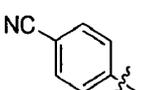
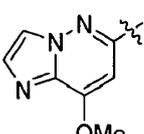
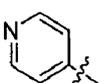
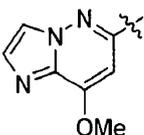
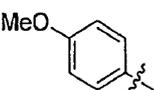
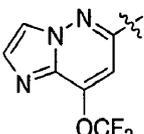
Núm. de Ejemplo	HET	X	Z	R ₂
308	A31			Me, Me
309	A31			Me, Me
310	A31			Me, Me
311	A31			Me, Me
312	A31			Me, Me
313	A31			Me, Me
314	A31			Me, Me
315	A31			Me, Me
316	A31			Me, Me
317	A31			Me, Me
318	A31			Me, Me
319	A31			Me, Me
320	A31			Me, Me

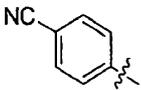
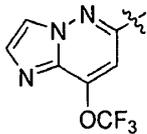
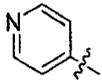
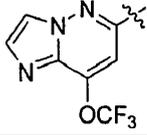
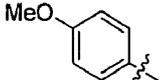
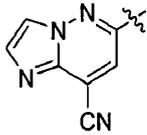
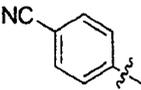
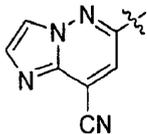
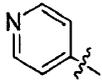
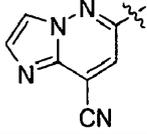
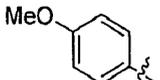
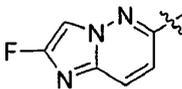
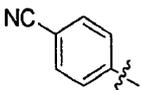
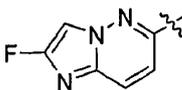
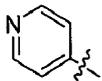
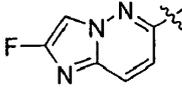
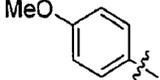
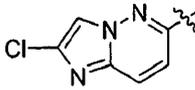
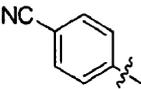
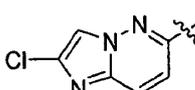
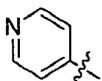
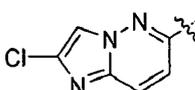
Núm. de Ejemplo	HET	X	Z	R ₂
321	A31			Me, Me
322	A31			Me, Me
323	A31			Me, Me
324	A31			Me, Me
325	A31			Me, Me
326	A31			Me, Me
327	A31			Me, Me
328	A31			Me, Me
329	A31			Me, Me
330	A31			Me, Me
331	A31			Me, Me
332	A31			Me, Me
333	A31			Me, Me

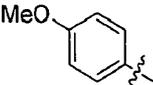
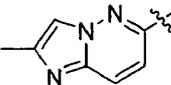
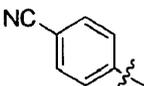
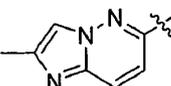
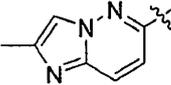
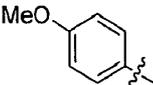
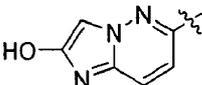
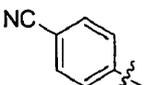
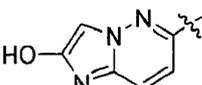
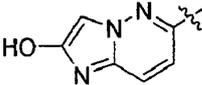
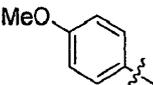
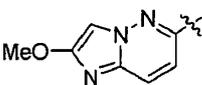
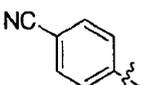
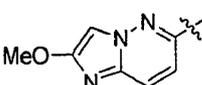
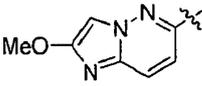
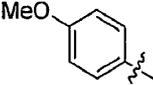
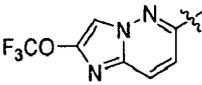
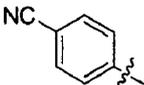
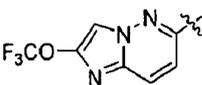
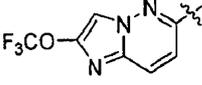
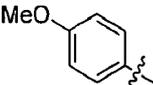
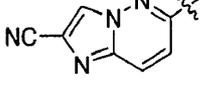
Núm. de Ejemplo	HET	X	Z	R ₂
334	A31			Me, Me
335	A31			Me, Me
336	A31			Me, Me
337	A31			Me, Me
338	A31			Me, Me
339	A31			Me, Me
340	A31			Me, Me
341	A31			Me, Me
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343	A31			Me, Me
344	A31			Me, Me
345	A31			Me, Me
346	A31			Me, Me

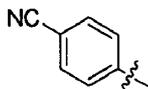
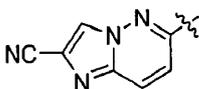
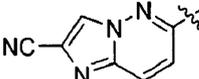
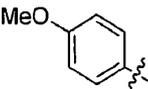
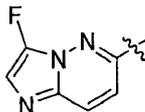
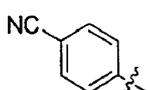
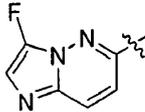
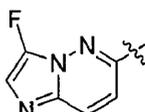
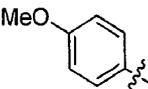
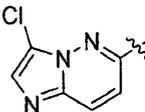
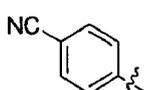
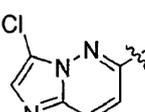
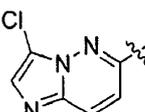
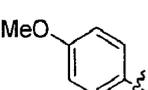
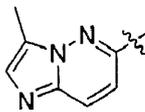
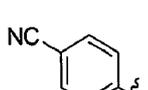
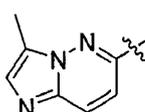
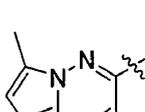
Núm. de Ejemplo	HET	X	Z	R ₂
347	A31			Me, Me
348	A31			Me, Me
349	A31			Me, Me
350	A31			Me, Me
351	A31			Me, Me
352	A31			Me, Me
353	A31			Me, Me
354	A31			Me, Me
355	A31			Me, Me
356	A31			Me, Me
357	A31			Me, Me
358	A31			Me, Me

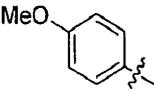
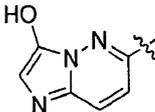
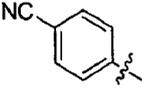
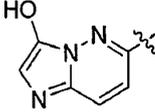
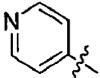
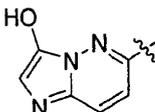
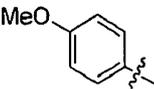
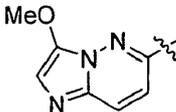
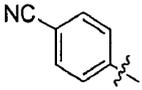
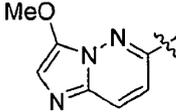
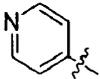
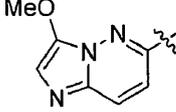
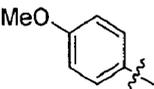
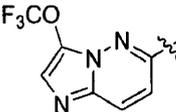
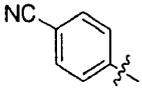
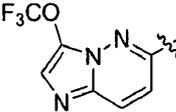
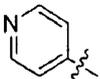
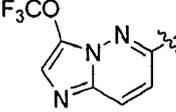
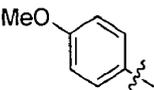
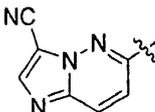
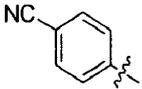
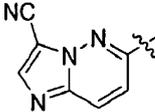
Núm. de Ejemplo	HET	X	Z	R ₂
359	A31			Me, Me
360	A31			Me, Me
361	A31			Me, Me
362	A31			Me, Me
363	A31			Me, Me
364	A31			Me, Me
365	A31			Me, Me
366	A31			Me, Me
367	A31			Me, Me
368	A31			Me, Me
369	A31			Me, Me

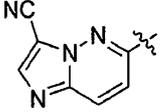
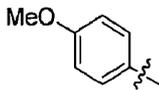
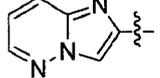
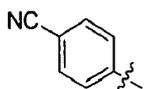
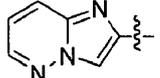
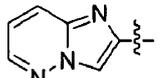
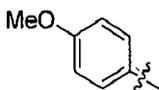
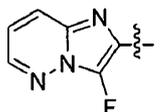
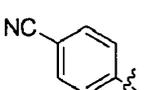
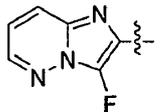
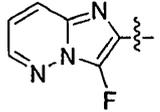
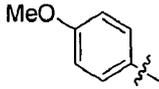
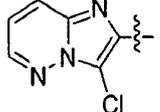
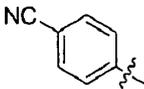
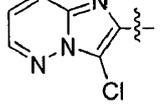
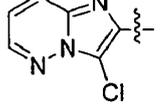
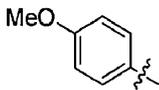
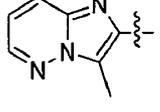
Núm. de Ejemplo	HET	X	Z	R ₂
370	A31			Me, Me
371	A31			Me, Me
372	A31			Me, Me
373	A31			Me, Me
374	A31			Me, Me
375	A31			Me, Me
376	A31			Me, Me
377	A31			Me, Me
378	A31			Me, Me
379	A31			Me, Me

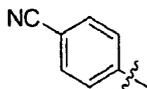
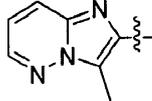
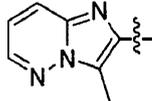
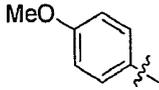
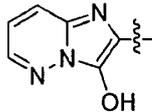
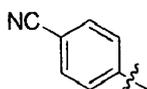
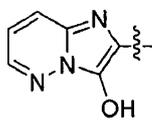
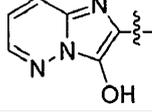
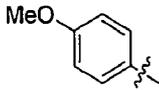
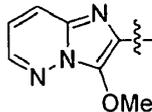
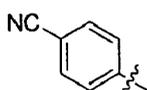
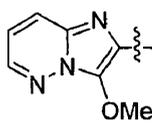
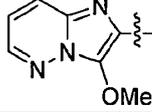
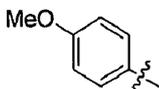
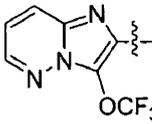
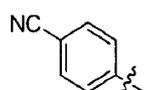
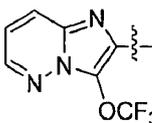
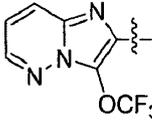
Núm. de Ejemplo	HET	X	Z	R ₂
380	A31			Me, Me
381	A31			Me, Me
382	A31			Me, Me
383	A31			Me, Me
384	A31			Me, Me
385	A31			Me, Me
386	A31			Me, Me
387	A31			Me, Me
388	A31			Me, Me
389	A31			Me, Me
390	A31			Me, Me

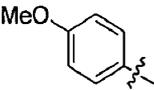
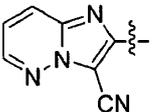
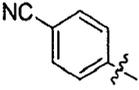
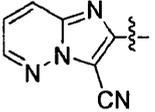
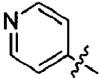
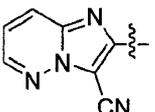
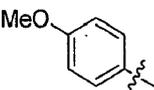
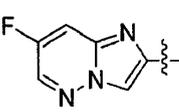
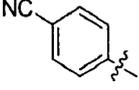
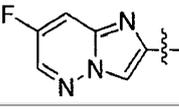
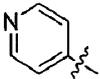
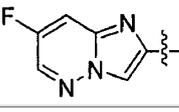
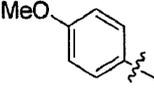
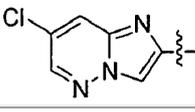
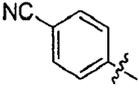
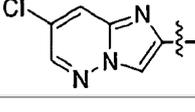
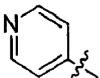
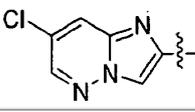
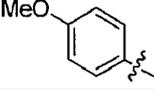
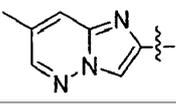
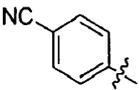
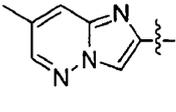
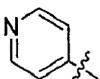
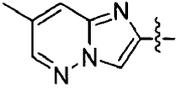
Núm. de Ejemplo	HET	X	Z	R ₂
391	A31			Me, Me
392	A31			Me, Me
393	A31			Me, Me
394	A31			Me, Me
395	A31			Me, Me
396	A31			Me, Me
397	A31			Me, Me
398	A31			Me, Me
399	A31			Me, Me
400	A31			Me, Me
401	A31			Me, Me
402	A31			Me, Me
403	A31			Me, Me

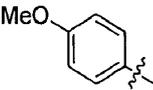
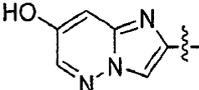
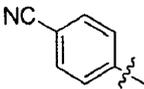
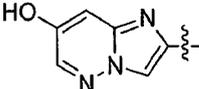
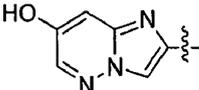
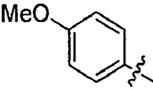
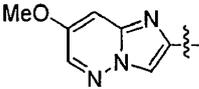
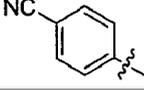
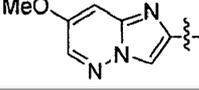
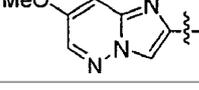
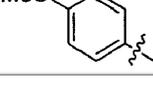
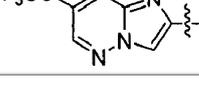
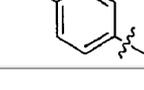
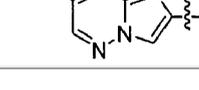
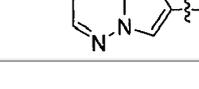
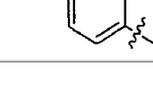
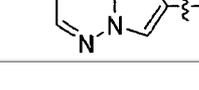
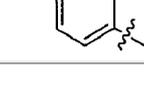
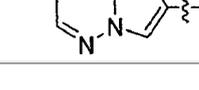
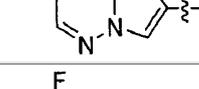
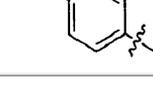
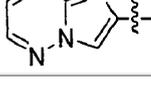
Núm. de Ejemplo	HET	X	Z	R ₂
404	A31			Me, Me
405	A31			Me, Me
406	A31			Me, Me
407	A31			Me, Me
408	A31			Me, Me
409	A31			Me, Me
410	A31			Me, Me
411	A31			Me, Me
412	A31			Me, Me
413	A31			Me, Me
414	A31			Me, Me

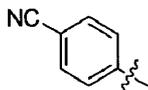
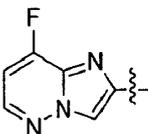
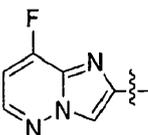
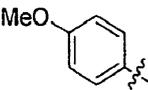
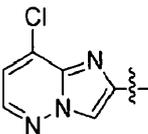
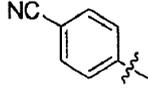
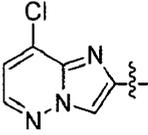
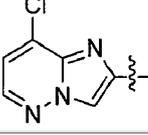
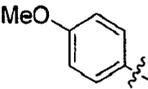
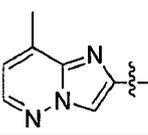
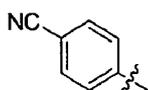
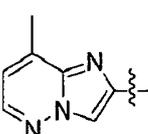
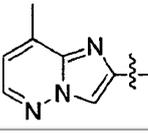
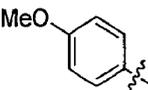
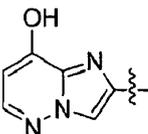
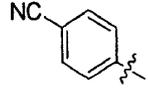
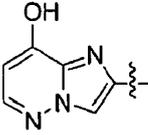
Núm. de Ejemplo	HET	X	Z	R ₂
415	A31			Me, Me
416	A31			Me, Me
417	A31			Me, Me
418	A31			Me, Me
419	A31			Me, Me
420	A31			Me, Me
421	A31			Me, Me
422	A31			Me, Me
423	A31			Me, Me
424	A31			Me, Me
425	A31			Me, Me

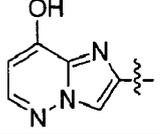
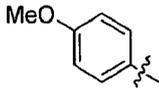
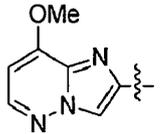
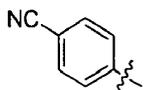
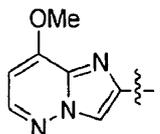
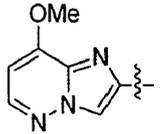
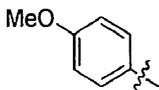
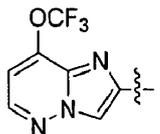
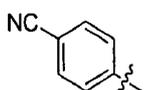
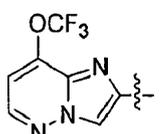
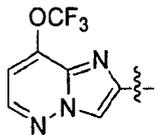
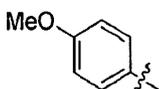
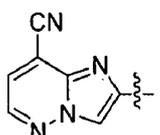
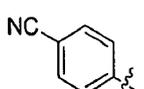
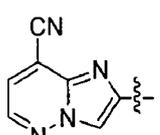
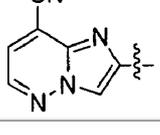
Núm. de Ejemplo	HET	X	Z	R ₂
426	A31			Me, Me
427	A31			Me, Me
428	A31			Me, Me
429	A31			Me, Me
430	A31			Me, Me
431	A31			Me, Me
432	A31			Me, Me
433	A31			Me, Me
434	A31			Me, Me
435	A31			Me, Me
436	A31			Me, Me

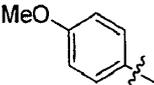
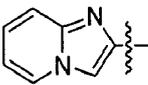
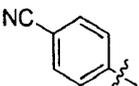
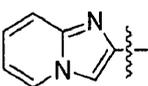
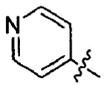
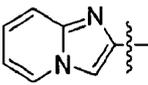
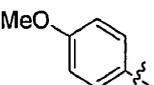
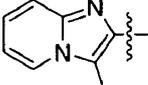
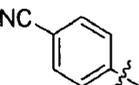
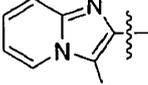
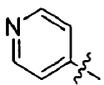
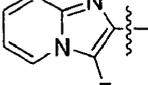
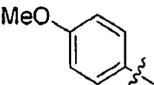
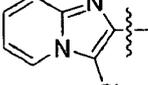
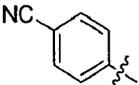
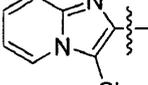
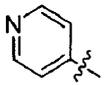
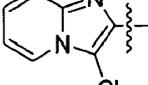
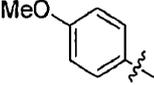
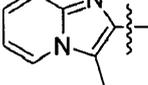
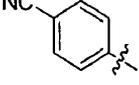
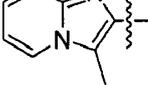
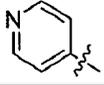
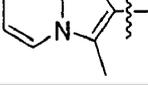
Núm. de Ejemplo	HET	X	Z	R ₂
437	A31			Me, Me
438	A31			Me, Me
439	A31			Me, Me
440	A31			Me, Me
441	A31			Me, Me
442	A31			Me, Me
443	A31			Me, Me
444	A31			Me, Me
445	A31			Me, Me
446	A31			Me, Me
447	A31			Me, Me

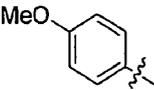
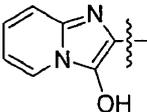
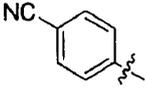
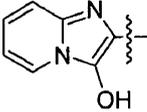
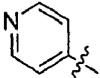
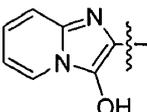
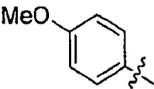
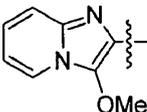
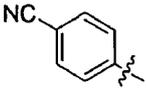
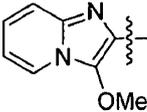
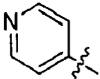
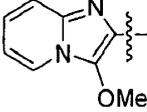
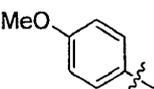
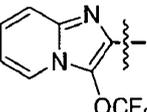
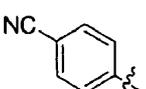
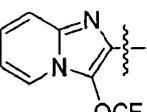
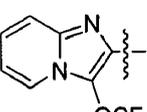
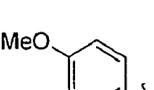
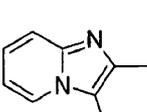
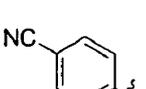
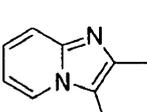
Núm. de Ejemplo	HET	X	Z	R ₂
448	A31			Me, Me
449	A31			Me, Me
450	A31			Me, Me
451	A31			Me, Me
452	A31			Me, Me
453	A31			Me, Me
454	A31			Me, Me
455	A31			Me, Me
456	A31			Me, Me
457	A31			Me, Me
458	A31			Me, Me
459	A31			Me, Me

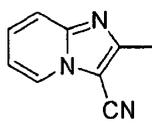
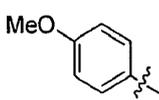
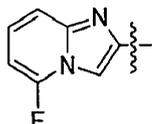
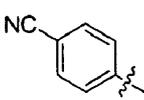
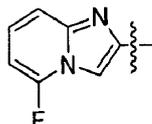
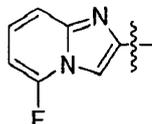
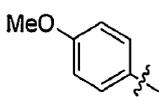
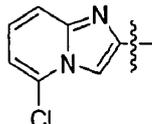
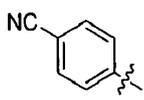
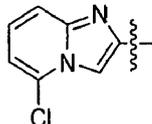
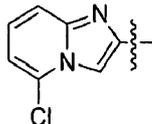
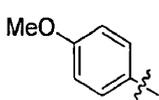
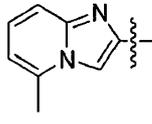
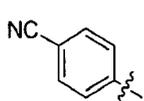
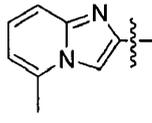
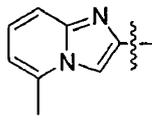
Núm. de Ejemplo	HET	X	Z	R ₂
460	A31			Me, Me
461	A31			Me, Me
462	A31			Me, Me
463	A31			Me, Me
464	A31			Me, Me
465	A31			Me, Me
466	A31			Me, Me
467	A31			Me, Me
468	A31			Me, Me
469	A31			Me, Me
470	A31			Me, Me
471	A31			Me, Me
472	A31			Me, Me

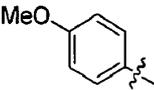
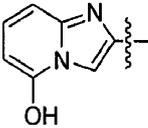
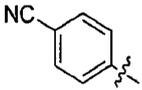
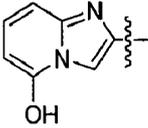
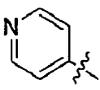
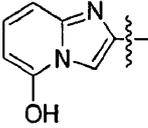
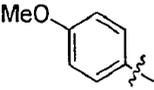
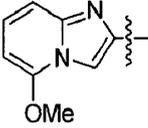
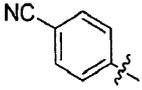
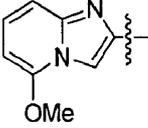
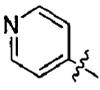
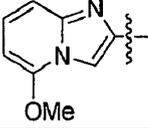
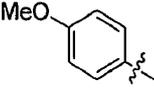
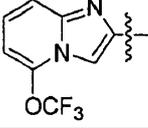
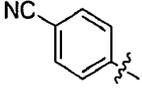
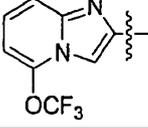
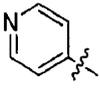
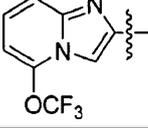
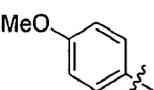
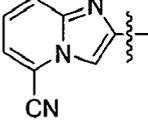
Núm. de Ejemplo	HET	X	Z	R ₂
473	A31			Me, Me
474	A31			Me, Me
475	A31			Me, Me
476	A31			Me, Me
477	A31			Me, Me
478	A31			Me, Me
479	A31			Me, Me
480	A31			Me, Me
481	A31			Me, Me
482	A31			Me, Me

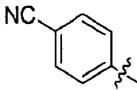
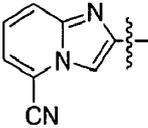
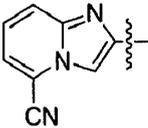
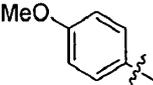
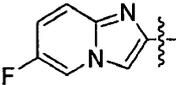
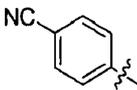
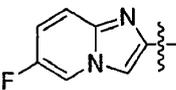
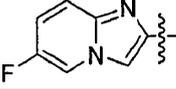
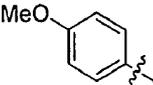
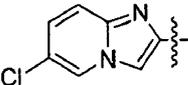
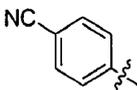
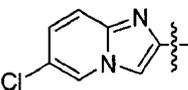
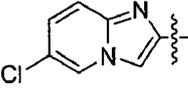
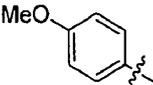
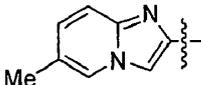
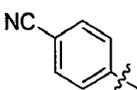
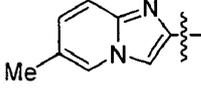
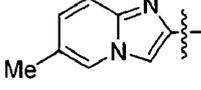
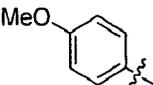
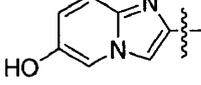
Núm. de Ejemplo	HET	X	Z	R ₂
483	A31			Me, Me
484	A31			Me, Me
485	A31			Me, Me
486	A31			Me, Me
487	A31			Me, Me
488	A31			Me, Me
489	A31			Me, Me
490	A31			Me, Me
491	A31			Me, Me
492	A31			Me, Me

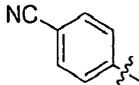
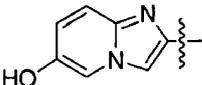
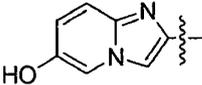
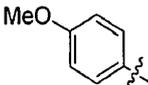
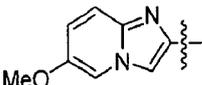
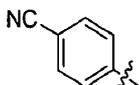
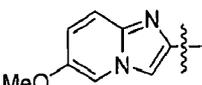
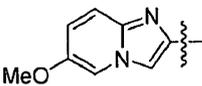
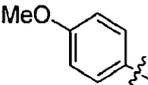
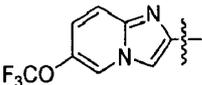
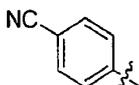
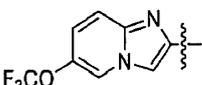
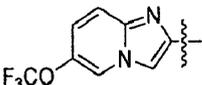
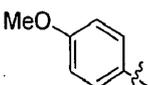
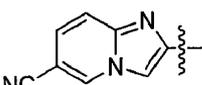
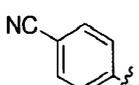
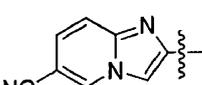
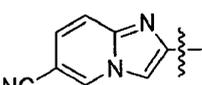
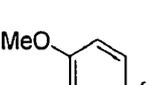
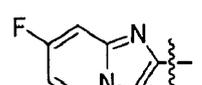
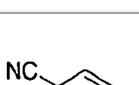
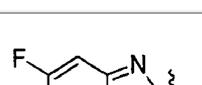
Núm. de Ejemplo	HET	X	Z	R ₂
493	A29			-ciclopropilo-
494	A29			--ciclopropilo--
495	A29			-ciclopropilo-
496	A29			--ciclopropilo--
497	A29			--ciclopropilo-
498	A29			-ciclopropilo-
499	A29			--ciclopropilo--
500	A29			-ciclopropilo-
501	A29			-ciclopropilo-
502	A29			-ciclopropilo-
503	A29			-ciclopropilo-
504	A29			-ciclopropilo-

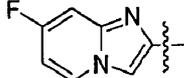
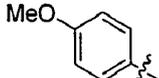
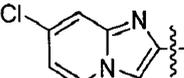
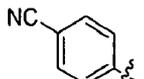
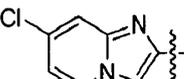
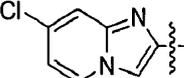
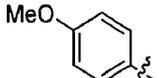
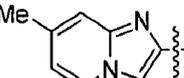
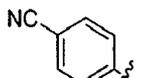
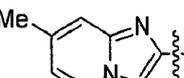
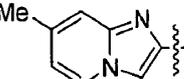
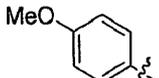
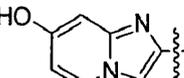
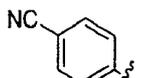
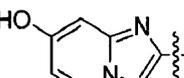
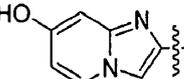
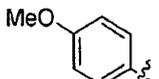
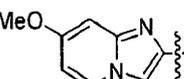
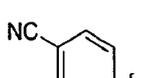
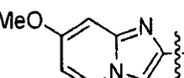
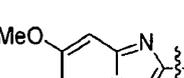
Núm. de Ejemplo	HET	X	Z	R ₂
505	A29			-ciclopropilo-
506	A29			-ciclopropilo-
507	A29			-ciclopropilo-
508	A29			-ciclopropilo--
509	A29			-ciclopropilo-
510	A29			-ciclopropilo--
511	A29			-ciclopropilo--
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513	A29			-ciclopropilo-
514	A29			--ciclopropilo-
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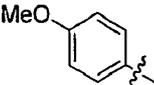
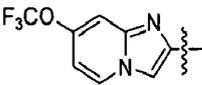
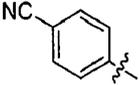
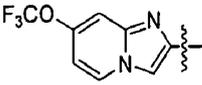
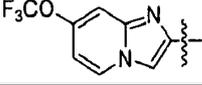
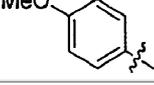
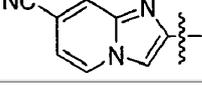
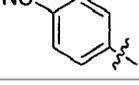
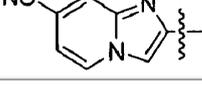
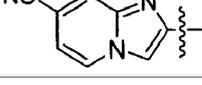
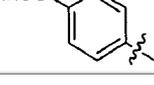
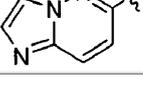
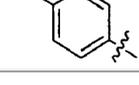
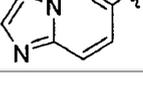
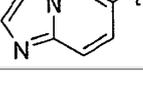
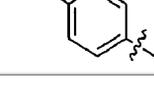
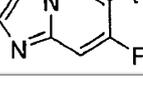
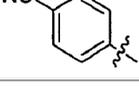
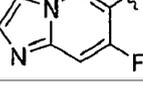
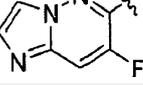
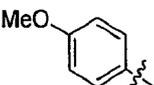
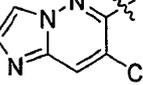
Núm. de Ejemplo	HET	X	Z	R ₂
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520	A29			-ciclopropilo-
521	A29			-ciclopropilo-
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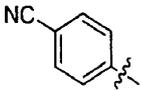
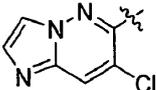
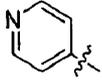
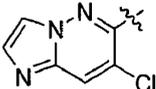
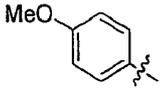
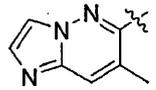
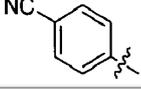
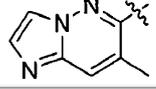
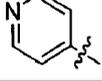
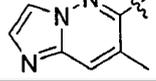
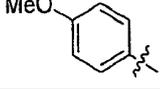
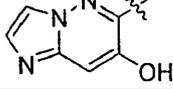
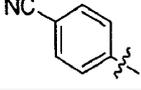
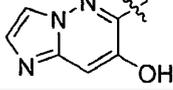
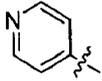
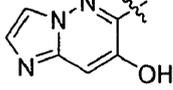
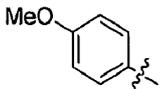
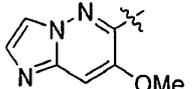
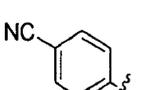
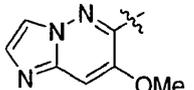
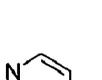
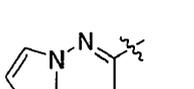
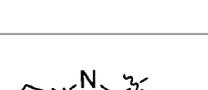
Núm. de Ejemplo	HET	X	Z	R ₂
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531	A29			--ciclopropilo-
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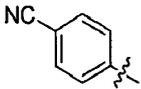
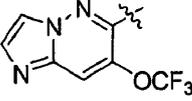
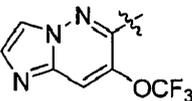
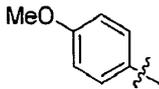
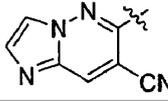
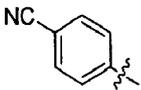
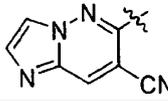
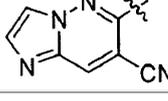
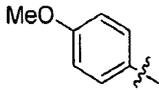
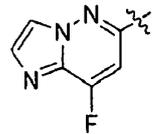
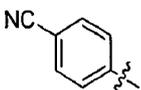
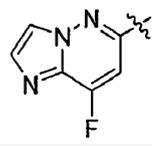
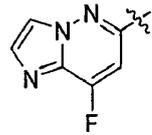
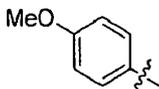
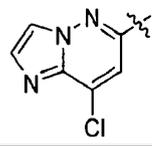
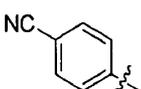
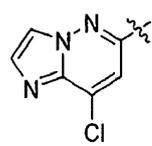
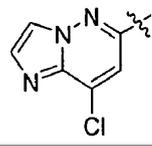
Núm. de Ejemplo	HET	X	Z	R ₂
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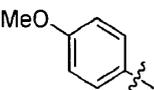
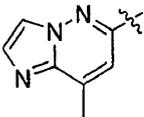
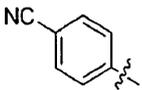
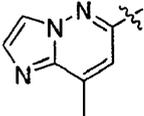
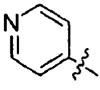
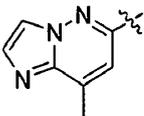
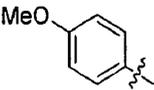
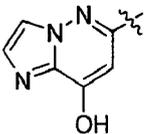
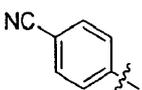
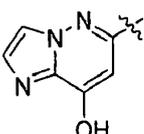
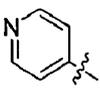
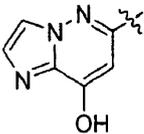
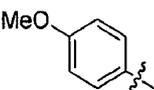
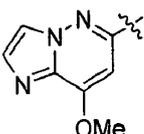
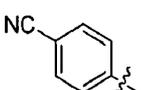
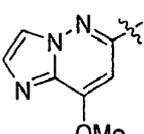
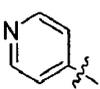
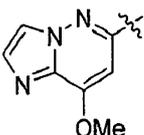
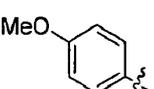
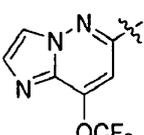
Núm. de Ejemplo	HET	X	Z	R ₂
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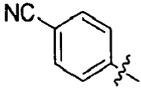
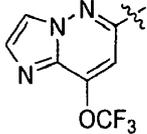
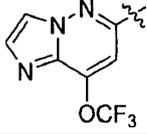
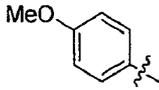
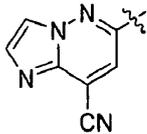
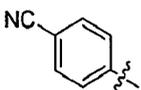
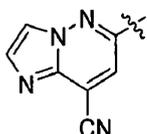
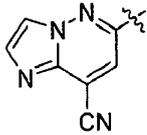
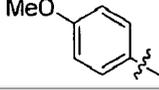
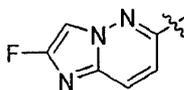
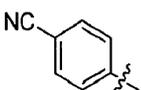
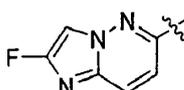
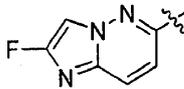
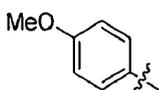
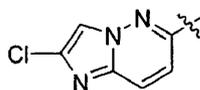
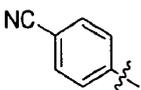
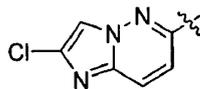
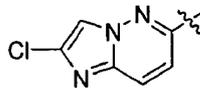
Núm. de Ejemplo	HET	X	Z	R ₂
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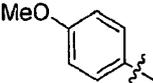
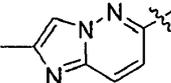
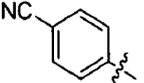
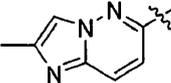
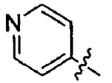
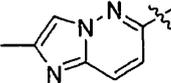
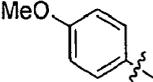
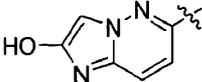
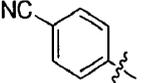
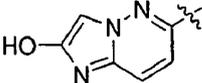
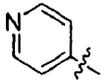
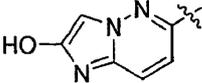
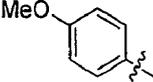
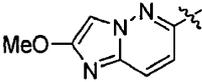
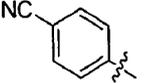
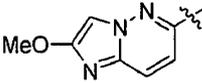
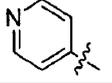
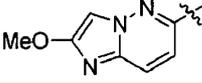
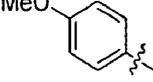
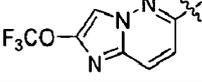
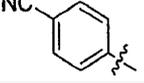
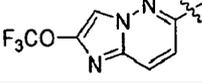
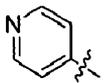
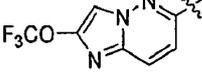
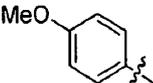
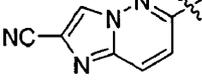
Núm. de Ejemplo	HET	X	Z	R ₂
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578	A29			-ciclopropilo-
579	A29			-ciclopropilo-
580	A29			-ciclopropilo-
581	A29			-ciclopropilo--
582	A29			-ciclopropilo--
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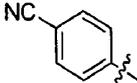
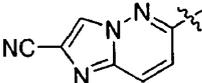
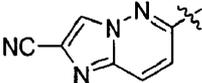
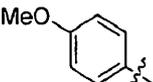
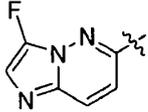
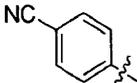
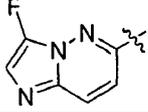
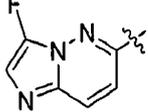
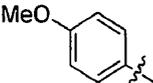
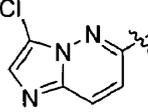
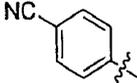
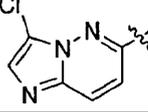
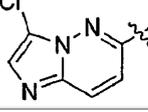
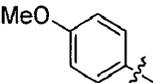
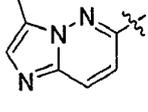
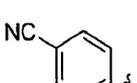
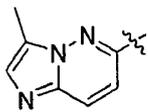
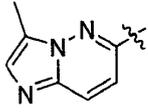
Núm. de Ejemplo	HET	X	Z	R ₂
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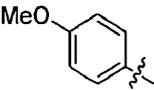
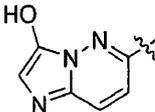
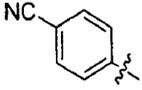
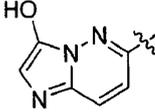
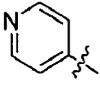
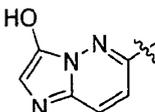
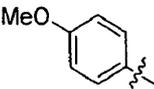
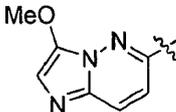
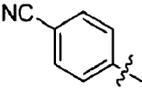
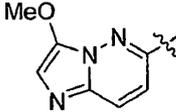
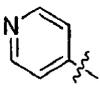
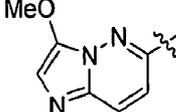
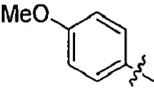
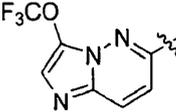
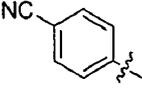
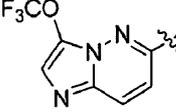
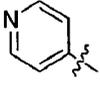
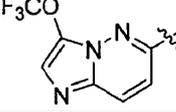
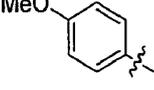
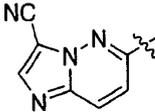
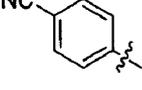
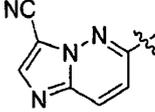
Núm. de Ejemplo	HET	X	Z	R ₂
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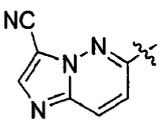
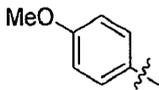
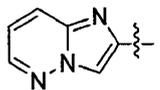
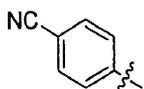
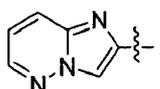
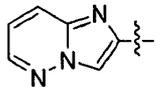
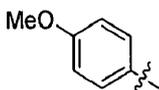
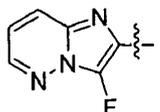
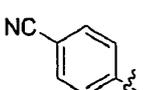
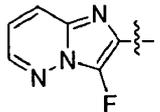
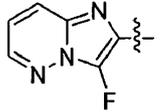
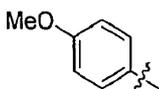
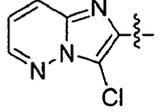
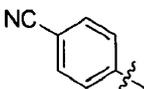
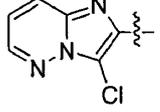
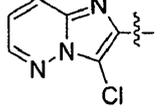
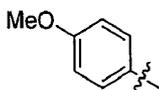
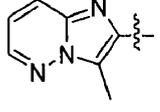
Núm. de Ejemplo	HET	X	Z	R ₂
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615	A29			--ciclopropilo-
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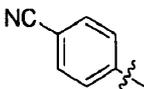
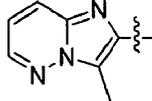
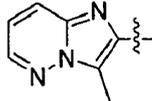
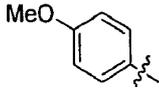
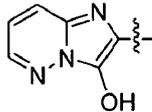
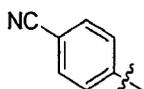
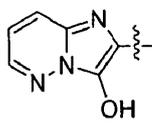
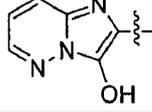
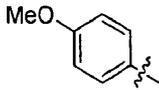
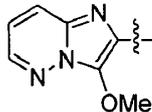
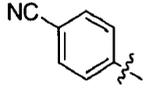
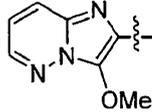
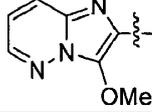
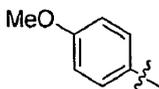
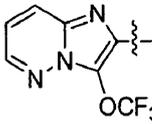
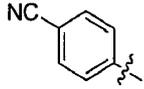
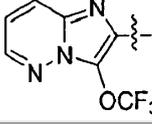
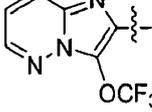
Núm. de Ejemplo	HET	X	Z	R ₂
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626	A29			--ciclopropilo-
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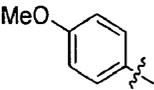
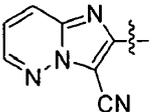
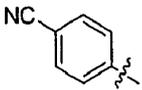
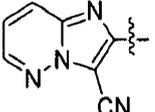
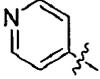
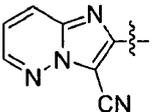
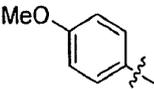
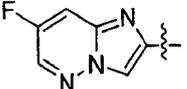
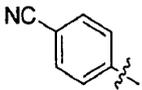
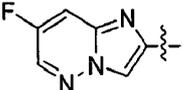
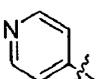
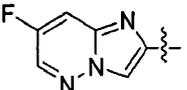
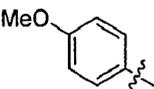
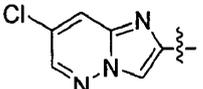
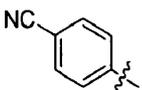
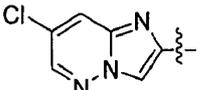
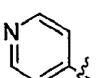
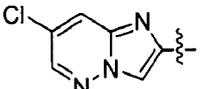
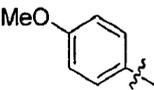
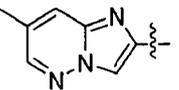
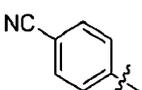
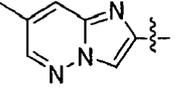
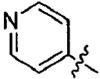
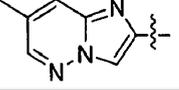
Núm. de Ejemplo	HET	X	Z	R ₂
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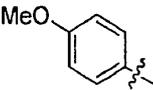
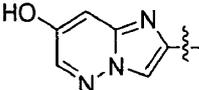
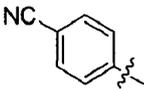
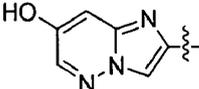
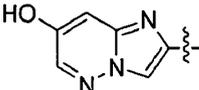
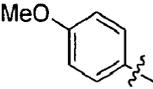
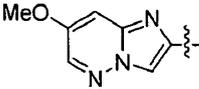
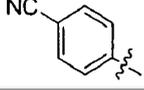
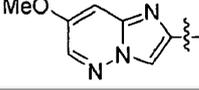
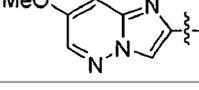
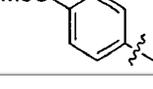
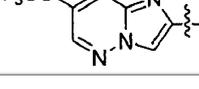
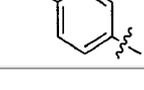
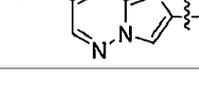
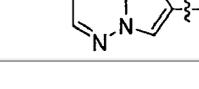
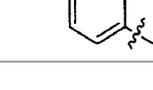
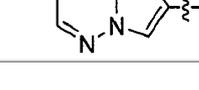
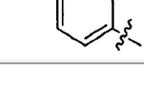
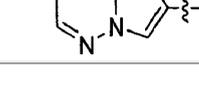
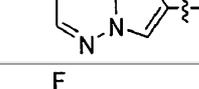
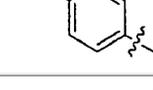
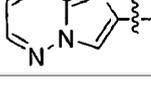
Núm. de Ejemplo	HET	X	Z	R ₂
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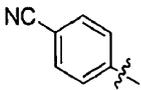
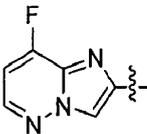
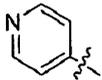
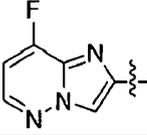
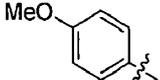
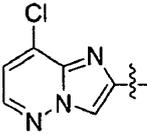
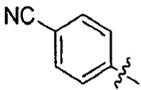
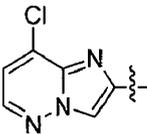
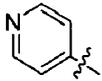
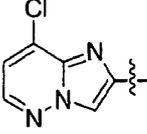
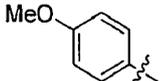
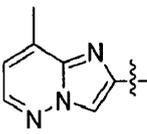
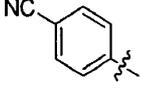
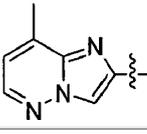
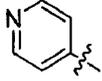
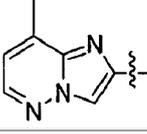
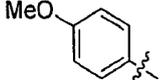
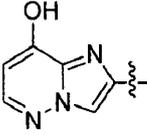
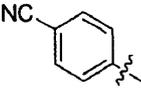
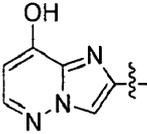
Núm. de Ejemplo	HET	X	Z	R ₂
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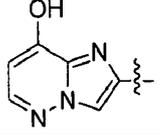
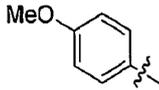
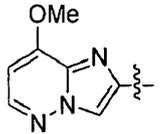
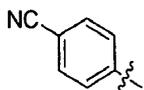
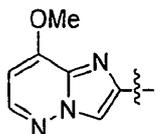
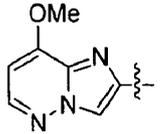
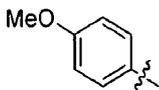
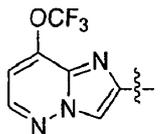
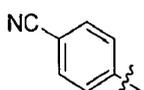
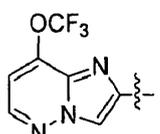
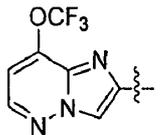
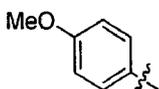
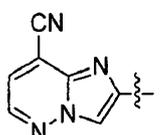
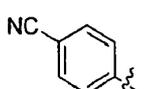
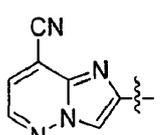
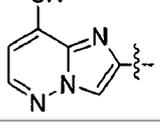
Núm. de Ejemplo	HET	X	Z	R ₂
666	A29			-ciclopropilo-
667	A29			-ciclopropilo-
668	A29			-ciclopropilo-
669	A29			--ciclopropilo-
670	A29			-ciclopropilo-
671	A29			-ciclopropilo-
672	A29			-ciclopropilo-
673	A29			-ciclopropilo-
674	A29			-ciclopropilo-
675	A29			--ciclopropilo-
676	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
677	A29			-ciclopropilo-
678	A29			-ciclopropilo-
679	A29			-ciclopropilo-
680	A29			--ciclopropilo-
681	A29			--ciclopropilo-
682	A29			--ciclopropilo-
683	A29			--ciclopropilo-
684	A29			-ciclopropilo-
685	A29			-ciclopropilo-
686	A29			-ciclopropilo-
687	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
688	A29			--ciclopropilo--
689	A29			-ciclopropilo-
690	A29			-ciclopropilo-
691	A29			-ciclopropilo-
692	A29			--ciclopropilo-
693	A29			-ciclopropilo-
694	A29			-ciclopropilo-
695	A29			-ciclopropilo-
696	A29			--ciclopropilo-
697	A29			--ciclopropilo-
698	A29			-ciclopropilo--
699	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
700	A29			--ciclopropilo--
701	A29			--ciclopropilo-
702	A29			-ciclopropilo-
703	A29			-ciclopropilo-
704	A29			--ciclopropilo--
705	A29			-ciclopropilo--
706	A29			-ciclopropilo-
707	A29			-ciclopropilo--
708	A29			-ciclopropilo-
709	A29			-ciclopropilo-
710	A29			-ciclopropilo-
711	A29			--ciclopropilo--
712	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
713	A29			-ciclopropilo-
714	A29			-ciclopropilo-
715	A29			-ciclopropilo-
716	A29			-ciclopropilo-
717	A29			-ciclopropilo-
718	A29			--ciclopropilo-
719	A29			-ciclopropilo-
720	A29			-ciclopropilo-
721	A29			-ciclopropilo-
722	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
723	A29			--ciclopropilo-
724	A29			--ciclopropilo--
725	A29			-ciclopropilo-
726	A29			-ciclopropilo-
727	A29			-ciclopropilo-
728	A29			-ciclopropilo-
729	A29			-ciclopropilo-
730	A29			-ciclopropilo-
731	A29			-ciclopropilo-
732	A29			-ciclopropilo-

Dosificación y Administración

La presente descripción incluye una composición farmacéutica para el tratamiento de un sujeto que tiene un trastorno neurológico que comprende una cantidad terapéuticamente eficaz de un compuesto de Fórmula (I), un derivado o una sal farmacéuticamente aceptable del mismo, y un excipiente, portador o diluyente farmacéuticamente aceptable.

Las composiciones farmacéuticas se pueden administrar en una variedad de formas de dosificación incluyendo, pero no limitadas a, una forma de dosificación sólida o una forma de dosificación líquida, una forma de dosificación oral, una forma de dosificación parenteral, una forma de dosificación intranasal, un supositorio, una gragea, un trocisco, bucal, una forma de liberación controlada, una forma de dosificación de liberación pulsada, una forma de dosificación de liberación inmediata, una disolución intravenosa, una suspensión o combinaciones de las mismas. La dosificación puede ser una forma de dosificación oral que es una forma de dosificación de liberación controlada. La forma de dosificación oral puede ser un comprimido o un comprimido de forma ovalada. Los compuestos se pueden administrar, por ejemplo, por medio de las rutas oral o parenteral, incluyendo la administración intravenosa, intramuscular, intraperitoneal, subcutánea, transdérmica, por las vías respiratorias (aerosol), rectal, vaginal y tópica (incluyendo bucal y sublingual). En una realización, los compuestos o composiciones farmacéuticas que comprenden los compuestos se liberan en un sitio deseado, tal como el cerebro, por medio de inyección continua a través de una derivación.

En otra realización, el compuesto se puede administrar parenteralmente, por ejemplo mediante administración intravenosa (IV). Las formulaciones para su administración comprenderán comúnmente una disolución del compuesto de Fórmula (I) disuelto en un portador farmacéuticamente aceptable. Entre los vehículos y disolventes aceptables que se pueden emplear se pueden mencionar el agua y la solución de Ringer, un cloruro de sodio isotónico. Además, se pueden emplear convencionalmente aceites fijados estériles como medio disolvente o suspensor. Para este fin se puede emplear cualquier aceite fijado blando incluyendo mono- y diglicéridos sintéticos. Además, en la preparación de inyectables se pueden utilizar del mismo modo ácidos grasos tales como ácido oleico. Estas disoluciones son estériles y generalmente están libres de materia no deseable. Estas formulaciones se pueden esterilizar por medio de técnicas de esterilización bien conocidas, convencionales. Las formulaciones pueden contener sustancias auxiliares farmacéuticamente aceptables según se requiera para que se aproximen a condiciones fisiológicas tales como agentes para el ajuste del pH y tamponadores, agentes para el ajuste de la toxicidad, p. ej., acetato de sodio, cloruro de sodio, cloruro de potasio, cloruro de calcio, lactato de sodio y similares. La concentración del compuesto de Fórmula (I) en estas formulaciones puede variar ampliamente, y se seleccionará principalmente basándose en los volúmenes de líquido, las viscosidades, el peso corporal, y similares, de acuerdo con el modo concreto de administración seleccionado y las necesidades del paciente. Para la administración IV, la formulación puede ser una preparación inyectable estéril, tal como una suspensión acuosa u oleaginosa inyectable estéril. Esta suspensión se puede formular de acuerdo con la técnica conocida utilizando agentes dispersantes o humectantes y agentes suspensores adecuados. La preparación inyectable estéril puede ser también una disolución o suspensión inyectable estéril en un diluyente o disolvente parenteralmente aceptable no tóxico, tal como una disolución de 1,3-butanodiol.

En una realización, un compuesto de Fórmula (I) se puede administrar por medio de su introducción en el sistema nervioso central del sujeto, p. ej., en el fluido cerebroespinal del sujeto. Las formulaciones para su administración comprenderán comúnmente una disolución del compuesto de Fórmula (I) disuelto en un portador farmacéuticamente aceptable. En ciertos aspectos, el compuesto de Fórmula (I) se introduce intratecalmente, p. ej., en un ventrículo cerebral, la zona lumbar, o la cisterna magna. En otro aspecto, el compuesto de Fórmula (I) se introduce intraocularmente, para poner en contacto de ese modo las células de los ganglios retinales.

Las formulaciones farmacéuticamente aceptables se pueden suspender fácilmente en vehículos acuosos e introducir a través de agujas hipodérmicas convencionales o utilizando bombas de infusión. Antes de su introducción, las formulaciones se pueden esterilizar, preferiblemente, con radiación gamma o esterilización con haces de electrones.

En una realización, la composición farmacéutica que comprende un compuesto de Fórmula (I) se administra en un sujeto intratecalmente. Según se utiliza en la presente memoria, se pretende que el término "administración intratecal" incluya la liberación de una composición farmacéutica que comprende un compuesto de Fórmula (I) directamente al fluido cerebroespinal de un sujeto, por medio de técnicas que incluyen inyección cerebroventricular a través de un trépano o punción cisternal o lumbar o similares (descritas por Lazorthes et al. en *Advances in Drug Delivery Systems and Applications in Neurosurgery*, 143-192 y Omay et al., *Cancer Drug Delivery*, 1: 169-179). Se pretende que el término "región lumbar" incluya la zona entre la tercera y cuarta vértebras lumbares (parte baja de la espalda). Se pretende que el término "cisterna magna" incluya la zona en la que finaliza el cráneo y comienza la columna vertebral en la parte de posterior de la cabeza. Se pretende que el término "ventrículo cerebral" incluya las cavidades del cerebro que son continuas con el canal central de la columna vertebral. La administración de un compuesto de Fórmula (I) a cualquiera de los sitios anteriormente mencionados se puede lograr por medio de inyección directa de la composición farmacéutica que comprende el compuesto de Fórmula (I) o por medio del uso de bombas de infusión. Para su inyección, las composiciones farmacéuticas se pueden formular en disoluciones

líquidas, preferiblemente en tampones fisiológicamente compatibles tales como solución de Hank o solución de Ringer. Además, las composiciones farmacéuticas se pueden formular en forma sólida y volver a disolver o suspender inmediatamente antes de su uso. También están incluidas las formas liofilizadas. La inyección puede ser, por ejemplo, en forma de una inyección en embolada o infusión continua (p. ej., utilizando bombas de infusión) de la composición farmacéutica.

En una realización, la composición farmacéutica que comprende un compuesto de Fórmula (I) se administra por medio de inyección cerebroventricular lateral al cerebro de un sujeto. La inyección se puede realizar, por ejemplo, a través de un orificio circular realizado en el cráneo del sujeto. En otra realización, el agente terapéutico encapsulado se administra a través de una derivación insertada quirúrgicamente en el ventrículo cerebral de un sujeto. Por ejemplo, la inyección se puede realizar en los ventrículos laterales, que son más grandes, incluso aunque también se puede realizar la inyección en el tercer y cuarto ventrículos más pequeños.

En otra realización más, la composición farmacéutica se administra por medio de inyección en la cisterna magna, o la zona lumbar de un sujeto.

Para su administración oral, los compuestos serán proporcionados generalmente en formas de dosificación unitarias tales como un comprimido, píldora, gragea, pastilla o cápsula; en forma de polvo o gránulos; o en forma de una solución, suspensión, líquido, gel, jarabe, pasta líquida, etc. acuosos adecuados para la ingestión por el paciente. Los comprimidos para uso oral pueden incluir los ingredientes activos mezclados con excipientes farmacéuticamente aceptables tales como diluyentes inertes, agentes disgregantes, agentes aglutinantes, agentes lubricantes, agentes edulcorantes, agentes aromatizantes, agentes colorantes y conservantes. Los diluyentes inertes adecuados incluyen carbonato de sodio y calcio, fosfato de sodio y calcio, y lactosa, mientras que el almidón de maíz y el ácido algínico son agentes disgregantes adecuados. Los agentes aglutinantes pueden incluir almidón y gelatina, mientras que el agente lubricante, si estuviera presente, será generalmente estearato de magnesio, ácido esteárico o talco. Si se desea, los comprimidos pueden estar recubiertos con un material tal como monoestearato de glicerilo o diestearato de glicerilo, para retrasar la absorción en el tracto gastrointestinal.

Las preparaciones farmacéuticas para uso oral se pueden obtener a través de una combinación de un compuesto de Fórmula (I) con un excipiente sólido, triturando opcionalmente la mezcla resultante, y procesando la mezcla de gránulos, después de añadir compuestos adicionales adecuados, si se desea, para obtener comprimidos o núcleos de grageas. Los excipientes sólidos adecuados además de los mencionados previamente son cargas de carbohidrato o proteína que incluyen, pero no están limitadas a, azúcares, incluyendo lactosa, sacarosa, manitol, o sorbitol; almidón de maíz, trigo, arroz, patata, u otras plantas; celulosa tal como metilcelulosa, hidroxipropilmetilcelulosa o carboximetilcelulosa sódica; y gomas incluyendo goma arábiga y tragacanto; así como proteínas tales como gelatina y colágeno. Si se desea, se pueden añadir agentes disgregantes o estabilizadores, tales como polivinilpirrolidona entrecruzada, agar, ácido algínico, o una de sus sales, tal como alginato de sodio.

Las cápsulas para uso oral incluyen cápsulas de gelatina dura en las que el ingrediente activo se mezcla con un diluyente sólido, y cápsulas de gelatina blanda en donde los ingredientes activos se mezclan con agua o un aceite tal como aceite de cacahuete, parafina líquida o aceite de oliva.

Los núcleos para grageas se proporcionan con recubrimientos adecuados. Para este fin, se pueden utilizar disoluciones de azúcar concentradas, que pueden contener opcionalmente goma arábiga, talco, polivinilpirrolidona, gel carboxipol, polietilenglicol, y/o dióxido de titanio, disoluciones de laca, y disolventes orgánicos o mezclas de disolventes adecuados. Se pueden añadir colorantes o pigmentos a los recubrimientos de comprimidos o grageas para su identificación o para caracterizar diferentes combinaciones de dosis de compuesto activo.

Para la administración transmucosa (p. ej., bucal, rectal, nasal, ocular, etc.), se utilizan en la formulación penetrantes apropiados para penetrar la barrera. Tales penetrantes son conocidos generalmente en la técnica.

Las formulaciones para su administración rectal se pueden presentar en forma de supositorio con una base adecuada que comprende por ejemplo manteca de cacao o un salicilato. Las formulaciones adecuadas para su administración vaginal se pueden presentar en forma de pesarios, tampones, cremas, geles, pastas, espumas o formulaciones para pulverización que contienen además del ingrediente activo portadores tales que se sabe que son apropiados en la técnica. Para su uso intramuscular, intraperitoneal, subcutáneo e intravenoso, los compuestos serán proporcionados generalmente en disoluciones o suspensiones acuosas estériles, tamponadas a un pH e isotonicidad apropiados. Los vehículos acuosos apropiados incluyen solución de Ringer y cloruro de sodio isotónico. Las suspensiones acuosas pueden incluir agentes suspensores tales como derivados de celulosa, alginato de sodio, polivinilpirrolidona y goma de tragacanto, y un agente humectante tal como lecitina. Los conservantes adecuados para las suspensiones acuosa incluyen p-hidroxibenzoato de etilo y n-propilo.

Los supositorios para la administración rectal del fármaco se pueden preparar mezclando el fármaco con un excipiente no irritante adecuado que es sólido a temperaturas normales pero líquido a las temperaturas del recto y por lo tanto se fundirá en el recto para liberar el fármaco. Tales materiales son manteca de cacao y polietilenglicoles.

Los compuestos se pueden liberar transdérmicamente, por medio de una ruta tópica, formular en forma de barras aplicadoras, soluciones, suspensiones, emulsiones, geles, cremas, pomadas, pastas, jaleas, pinturas, polvos, o aerosoles.

5 Los compuestos también se pueden presentar en forma de formulaciones acuosas o de liposomas. Las suspensiones acuosas pueden contener un compuesto de Formula (I) mezclado con excipientes adecuados para la fabricación de suspensiones acuosas. Tales excipientes incluyen un agente suspensor, carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma de tragacanto y goma acacia, y agentes dispersantes o humectantes tales como un fosfátido de origen natural (p. ej., lecitina), un producto de condensación de un óxido de alquileo con un ácido graso (p. ej., estearato de polioxietileno), un producto de condensación de óxido de etileno con un alcohol alifático de cadena larga (p. ej., heptadecaetilen oxacetanol), un producto de condensación de óxido de etileno con un éster parcial derivado de un ácido graso y un hexitol (p. ej., monooleato de polioxietilensorbitol), o un producto de condensación de óxido de etileno con un éster parcial derivado de un ácido graso y un anhídrido de hexitol (p. ej., monooleato de polioxietilensorbitán). La suspensión acuosas puede contener también uno o más conservantes tales como p-hidroxibenzoato de etilo o n-propilo, uno o más agentes colorantes, uno o más agentes aromatizantes y uno o más agentes edulcorantes, tales como sacarosa, aspartamo o sacarina. Se puede ajustar la osmolaridad de las formulaciones.

20 Las suspensiones oleosas se pueden formular suspendiendo un compuesto de Formula (I) en un aceite a vegetal, tal como aceite de araquis, aceite de oliva, aceite de sésamo o aceite de coco, o en un aceite mineral tal como parafina líquida; o una mezcla de estos. Las suspensiones oleosas pueden contener un agente espesante, tal como cera de abejas, parafina dura o alcohol cetílico. Se pueden añadir agentes edulcorantes para proporcionar una preparación oral agradable, tal como glicerol, sorbitol o sacarosa. Estas formulaciones se pueden conservar mediante la adición de un antioxidante tal como ácido ascórbico. Para un ejemplo de un vehículos oleoso inyectable, véase Minto, J. Pharmacol. Exp. Ther. 281:93-102, 1997. Las formulaciones farmacéuticas también pueden estar en forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal o un aceite mineral, descrito anteriormente, o una mezcla de estos. Los agentes emulsionantes adecuados incluyen gomas de origen natural, tales como goma de acacia y goma de tragacanto, fosfátidos de origen natural, tales como lecitina de soja, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, tales como mono-oleato de sorbitán, y productos de condensación de estos ésteres parciales con óxido de etileno, tales como monooleato de polioxietilensorbitán. La emulsión también puede contener agentes edulcorantes y agentes aromatizantes, como en la formulación de jarabes y elixires. Tales formulaciones pueden contener también un emoliente, un conservante, o un agente colorante.

35 Además de las formulaciones descritas previamente, los compuestos se pueden formular también en forma de una preparación de depósito. Tales formulaciones de acción prolongada se pueden administrar mediante implantación o liberación transcutánea (p. ej., subcutáneamente o intramuscularmente), inyección intramuscular o un parche transdérmico. De este modo, por ejemplo, los compuestos se pueden formular con sustancias poliméricas o hidrófobas adecuadas (p. ej., en forma de una emulsión en un aceite aceptable) o resinas de intercambio iónico, o en forma de derivados escasamente solubles, por ejemplo, en forma de una sal escasamente soluble.

45 Las composiciones farmacéuticas pueden comprender también portadores o excipientes en fase sólida o de gel adecuados. Los ejemplos de tales portadores o excipientes incluyen pero no están limitados a carbonato de calcio, fosfato de calcio, diversos azúcares, almidones, derivados de celulosa, gelatina, y polímeros tales como polietilenglicoles.

50 Para su administración mediante inhalación, los compuestos se liberan convenientemente en forma de un presentación de pulverización en aerosol a partir de envases presurizados o un nebulizador, con el uso de un propelente adecuado, p. ej., diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas adecuado. En el caso de los aerosoles presurizados la unidad de dosificación se puede determinar proporcionando una válvula para liberar una cantidad medida. Se pueden formular cápsulas y cartuchos p. ej., de gelatina para su uso en un inhalador o insuflador que contienen una mezcla de polvo del compuesto y una base de polvo adecuada tal como lactosa o almidón.

55 En general una dosis adecuada se encontrará en el intervalo de 0,01 a 100 mg por kilogramo de peso corporal del receptor por día, preferiblemente en el intervalo de 0,1 a 10 mg por kilogramo de peso corporal por día. La dosis deseada se presenta preferiblemente una vez al día, pero se puede administrar en forma de dos, tres, cuatro, cinco, seis o más sub-dosis administradas a intervalos apropiados a lo largo del día.

60 Los compuestos se pueden administrar en forma del único agente activo, o combinado con otros agentes terapéuticos conocidos para que sean beneficiosos en el tratamiento de los trastornos neurológicos. En cualquier caso, el médico a cargo de la administración puede proporcionar un método de tratamiento que sea profiláctico o terapéutico mediante el ajuste de la cantidad y el momento de la administración del fármaco basándose en las observaciones de uno o más síntomas (p. ej., función motora o cognitiva medida por medio de escalas o

evaluaciones clínicas convencionales) del trastorno que esté siendo tratado. Los detalles sobre las técnicas para la formulación y administración están bien descritos en la bibliografía científica y de patentes, véase, p. ej., la última edición de Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. Después de formular una composición farmacéutica en un portador aceptable, se puede colocar en un recipiente apropiado y etiquetar para el tratamiento de una afección indicada. Para la administración de los compuestos de Fórmula (I), tal etiquetado podría incluir, p. ej., instrucciones relativas a la cantidad, frecuencia y método de administración.

Ejemplos Biológicos

10 Métodos *in vivo*

Sujetos: Se utilizaron ratones C₅₇BL/6J macho (Charles River; 20-25 g) para todos los ensayos excepto para la inhibición prepulso (PPI) en la que se utilizaron ratones DBA/2N macho (Charles River, 20-25 g). Para todos los estudios, los animales se alojaron en un número de cinco/jaula en un ciclo de luz/oscuridad de 12 h con alimento y agua disponibles ad libitum.

Respuesta de evitación condicionada: La prueba se realizó en cajas de evitación asequibles comercialmente (Kinder Scientific, Poway CA). Las cajas se dividieron en dos compartimentos separados por un arco. Cada lado de la cámara tenía un suelo de parrilla electrónica que estaba equipado para administrar choques a la pata y una luz en el techo. El entrenamiento consistió en emparejamientos repetidos de la luz (estímulo condicionado) seguido de un choque (estímulo no condicionado). Para cada prueba la luz se presentó durante 5 seg. seguido de un choque de 0,5 mA que podría terminar si el ratón cruzara la cámara o al cabo de 10 segundos. El intervalo entre pruebas se ajustó a 20 segundos. Cada sesión de entrenamiento y de ensayo consistió en un período de habituación de cuatro minutos seguido de 30 pruebas. El número de evitaciones (el ratón cruzó al otro lado durante la presentación de la luz), escapes (el ratón cruzó al otro lado durante la presentación del choque) y fracasos (el ratón no cruzó durante el período de prueba completo) se registraron en un ordenador. Para la inclusión en el estudio un animal tenía que alcanzar un criterio de al menos 80% de evitaciones durante dos sesiones de ensayo consecutivas.

PPI: Los ratones se colocaron individualmente en las cámaras de ensayo (StartleMonitor, Kinder Scientific, Poway CA). A los animales se les proporcionó un período de aclimatación de cinco minutos a las cámaras de ensayo con el nivel de ruido de fondo ajustado a 65 decibelios (dB) que permaneció durante la sesión completa. Después de la aclimatación, se presentaron cuatro pruebas sucesivas de pulsos de 120 dB durante 40 mseg., sin embargo estas pruebas no se incluyeron en los análisis de datos. Los ratones se sometieron a continuación de cinco tipos diferentes de pruebas en orden aleatorio: pulso solo (120 dB durante 40 mseg.), sin estímulo y tres pruebas de prepulso diferente + pulso con el prepulso ajustado a 67, 69 o 74 dB durante 20 mseg. seguido 100 mseg. después de un pulso de 120 dB durante 40 mseg. Cada animal recibió 12 pruebas para cada condición para un total de 60 pruebas con un intervalo entre prueba promedio de 15 sec. El porcentaje de PPI se calculó de acuerdo con la siguiente fórmula: $(1 - (\text{respuesta de sobresalto a prepulso} + \text{pulso}) / \text{respuesta de sobresalto a pulso solo}) \times 100$.

Hiperactividad inducida por MK-801: Al cabo de una aclimatación de 30 min a la sala de ensayo, los ratones se colocaron individualmente en jaulas de ensayo durante un período de habituación de 30 min. Después de la habituación a las jaulas de ensayo, se registró la actividad del punto de partida durante 60 min. Los ratones se retiraron brevemente a continuación y se les administró el compuesto de ensayo y se volvieron a colocar inmediatamente en la jaula de ensayo. Cinco minutos antes del período de ensayo los ratones se volvieron a retirar brevemente de las jaulas de ensayo y se les administró MK-801 (0,3 mg/kg, i.p. en solución salina al 0,9%) y a continuación se volvieron a colocar inmediatamente en las jaulas de ensayo y se registró el nivel de actividad durante 1 hora. El nivel de actividad se midió como la distancia recorrida en centímetros (programa de seguimiento Ethovision, Noldus Inc. Wageningen, Netherlands).

Catalepsia: Los ratones se colocaron sobre una rejilla de malla de alambre colocada a un ángulo de 60 grados con sus cabezas hacia arriba y se registró la latencia para moverse o cambiar de postura. A los animales se les facilitaron tres pruebas por punto temporal con un corte de 30 seg. por prueba.

Análisis de los datos: Se utilizó un ANOVA de una vía o de dos vías para evaluar las diferencias totales entre los tratamientos y una prueba post-hoc de Tukey o una prueba t de Student para evaluar las diferencias entre los grupos de tratamiento para el ANOVA de una vía y se utilizó una prueba de Bonferroni para el ANOVA de dos vías. El criterio para la significación estadística se ajustó a $p \leq 0,05$.

60 Métodos *in vitro*

Actividad enzimática de hPDE10A1: Se incubaron muestras diluidas seriadamente de 50 µl de enzima PDE10A1 con 50 µl de [³H]-AMPc durante 20 minutos (a 37°C). Las reacciones se llevaron a cabo en placas de pocillos profundos de 1 ml Greiner 96 Masterblock. La enzima se diluyó en Tris HCl 20 mM de pH 7,4 y el [³H]-AMPc se diluyó en MgCl₂ 10 mM, Tris-HCl 40 mM de pH 7,4. La reacción se terminó mediante la desnaturalización de la enzima PDE (a 70°C)

5 después de lo cual el [³H]-5'-AMP se convirtió en [³H]-adenosina añadiendo 25 µl de nucleotidasa de veneno de serpiente e incubando durante 10 minutos (a 37°C). La adenosina, al ser neutra, se separó del AMPc o AMP cargados mediante la adición de 200 µl de resina Dowex. Las muestras se sacudieron durante 20 minutos, después se centrifugaron durante 3 minutos a 2.500 r.p.m. Se retiraron 50 µl de sobrenadante y se añadieron a 200 µl de MicroScint-20 en placas de color blanco (Greiner 96-well Optiplat) y se sacudieron durante 30 minutos antes de la lectura en Perkin Elmer TopCount Scintillation Counter.

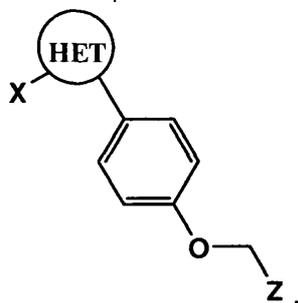
10 Inhibición de la enzima hPDE10A1: Para verificar el perfil de inhibición se añadieron 11 µl de inhibidor diluido seriadamente a 50 µl de [³H]-AMPc y 50 µl de PDE10A1 humana diluida y el análisis se llevó a cabo como en el análisis de la actividad enzimática. Los datos se analizaron utilizando Prism software (GraphPad Inc). Los compuestos representativos de esta descripción se muestran en la tabla de más abajo. Un compuesto con el valor "A" tuvo un valor de CI₅₀ menor o igual a 10 nM. Un compuesto con el valor "B" tuvo un valor de CI₅₀ mayor de 10 nM y menor de 50 nM:

Nombre	Banda CI ₅₀ hPDE10A1
4-(4-((3,5-dimetilpiridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona	A
4-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona	A
4-(4-(imidazo[1,2-b]piridazin-6-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona	B
4-(4-((6-cloroimidazo[1,2-b]piridazin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona	B
4-(4-(imidazo[1,2-b]piridazin-2-ilmetoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona	A
4-(3-(4-(imidazo[1,2-a]piridin-2-ilmetoxi)fenil)-5,5-dimetil-4-oxo-4,5-dihidrofuran-2-il)benzotrilo	A
4-(4-((3-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona	A
5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilpiridin-2-il)metoxi)fenil)furan-3(2H)-ona	A
4-(5,5-dimetil-3-(4-((5-metilpiridin-2-il)metoxi)fenil)-4-oxo-4,5-dihidrofuran-2-il)benzotrilo	A
4-(4-((6-cloroimidazo[1,2-a]piridin-2-il)metoxi)fenil)-5-(4-metoxifenil)-2,2-dimetilfuran-3(2H)-ona	A
5-(4-metoxifenil)-2,2-dimetil-4-(4-((3-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona	B
5-(4-metoxifenil)-2,2-dimetil-4-(4-((5-metilimidazo[1,2-a]piridin-2-il)metoxi)fenil)furan-3(2H)-ona	A

15

REIVINDICACIONES

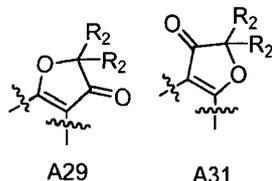
1. Un compuesto de Fórmula (I)



(I)

5 o una de sus sales farmacéuticamente aceptables, en donde:

HET es un anillo heterocíclico que tiene la fórmula A29 o A31



A29

A31

en donde el radical más a la izquierda está conectado al grupo X en la Fórmula (I);

10 X es arilo sustituido opcionalmente o heteroarilo sustituido opcionalmente, en donde los sustituyentes se seleccionan del grupo que consiste en alquilo C₁-C₄, cicloalquilo C₃-C₆, cicloalquil(C₃-C₆)oxi, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro;

15 Z es imidazo[1,2-a]piridin-2-ilo, imidazo[1,2-b]piridazin-2-ilo o imidazo[1,2-b]piridazin-6-ilo, cada uno de los cuales puede estar sustituido opcionalmente, en donde los sustituyentes se seleccionan del grupo que consiste en alquilo C₁-C₄, cicloalquilo C₃-C₆, cicloalcoxi C₃-C₆, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro; y

20 cada R₂ es independientemente alquilo C₁-C₄ sustituido opcionalmente con flúor, o dos grupos R₂ tomados junto con el carbono al que están anclados forman un anillo de cicloalquilo de 3 miembros;

y en donde:

- alquilo indica un hidrocarburo C₁-C₈ alifático saturado o insaturado lineal o ramificado que puede estar sustituido opcionalmente con hasta 3 átomos de flúor y, si se especifica, sustituido con otros grupos;

25 - arilo es un grupo fenilo o naftilo;

- heteroarilo es un tetrazol, 1,2,3,4-oxatriazol, 1,2,3,5-oxatriazol, un sistema anular aromático mono o bicíclico, o un sistema anular heterobicíclico con un anillo aromático que tiene de 5 a 10 átomos anulares seleccionados independientemente entre C, N, O y S, siempre que no más de 3 átomos anulares en cualquier anillo sencillo sean distintos de C; y

30 - cicloalquilo es un hidrocarburo no aromático cíclico C₃-C₇ que puede contener un solo enlace doble y está sustituido opcionalmente e independientemente con hasta tres grupos seleccionados entre alquilo, alcoxi, hidroxilo y oxo.

2. El compuesto de la reivindicación 1, en donde HET es A29.

35 3. El compuesto de una cualquiera de las reivindicaciones 1-2, en donde X es un heteroarilo sustituido opcionalmente.

4. El compuesto de una cualquiera de las reivindicaciones 1-3, en donde X es:

40 (a) un anillo de heteroarilo monocíclico sustituido opcionalmente que tiene cinco átomos anulares seleccionados entre C, O, S y N siempre que el número total de heteroátomos anulares sea menor o igual a cuatro y no más de uno de los heteroátomos anulares sea oxígeno o azufre, en donde los sustituyentes se seleccionan del grupo que consiste en alquilo C₁-C₄, cicloalquilo, cicloalquiloxi, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro; o

45 (b) un anillo de heteroarilo monocíclico que tiene seis átomos anulares seleccionados entre C y N siempre que no más de tres átomos anulares sean N, en donde el anillo aromático está opcionalmente e independientemente

sustituido con hasta dos sustituyentes seleccionados del grupo que consiste en alquilo C₁-C₄, cicloalquilo, cicloalquiloxi, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro.

5 5. El compuesto de la reivindicación 4, en donde X es un anillo de heteroarilo monocíclico sustituido opcionalmente que tiene cinco átomos anulares seleccionados entre C, O, S y N siempre que el número total de heteroátomos anulares sea menor o igual a cuatro y no más de uno de los heteroátomos anulares sea oxígeno o azufre, en donde el anillo de heteroarilo está sustituido opcionalmente e independientemente con hasta dos sustituyentes seleccionados del grupo que consiste en alquilo C₁-C₄, cicloalquilo C₃-C₆, cicloalquiloxi C₃-C₆, alcoxi C₁-C₄, CF₃,
10 carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro.

15 6. El compuesto de la reivindicación 5, en donde X se selecciona del grupo que consiste en 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo, 1H-pirrolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, isotiazolilo, isoxazolilo, oxazolilo, tiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tetrazolilo, 1,2,3,4-oxatriazolilo, 1,2,3,5-oxatriazolilo, 1,2,3,4-tiatriazolilo y 1,2,3,5-tiatriazolilo sustituidos opcionalmente.

20 7. El compuesto de la reivindicación 6, en donde X es un anillo de heteroarilo monocíclico que tiene seis átomos seleccionados entre C y N siempre que no más de tres átomos anulares sean N, en donde el anillo de heteroarilo está sustituido opcionalmente e independientemente con hasta dos sustituyentes seleccionados del grupo que consiste en alquilo C₁-C₄, cicloalquilo C₃-C₆, cicloalcoxi C₃-C₆, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno,
25 ciano, alquilsulfonilo y nitro.

8. El compuesto de la reivindicación 7, en donde X es 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo, piridinilo, pirazinilo, piridazinilo o pirimidinilo sustituidos opcionalmente.

30 9. El compuesto de la reivindicación 8, en donde X es 4-piridinilo sustituido opcionalmente con un sustituyente seleccionado del grupo que consiste en alquilo C₁-C₄, ciclopropilo, ciclopropiloxi, ciclopropilmetilo, alcoxi C₁-C₄, CF₃, amino, alquilamino, dialquilamino, tioalquilo, halógeno, alquilsulfonilo y ciano.

35 10. El compuesto de una cualquiera de las reivindicaciones 1-2, en donde X es un grupo fenilo sustituido opcionalmente, en donde los sustituyentes se seleccionan del grupo que consiste en alquilo C₁-C₄, cicloalquilo C₃-C₆, cicloalcoxi C₃-C₆, alcoxi C₁-C₄, CF₃, carboxi, alcoxialquilo, cicloalquilalcoxi C₁-C₄, amino, alquilamino, dialquilamino, amido, alquilamido, dialquilamido, tioalquilo, halógeno, ciano, alquilsulfonilo y nitro.

40 11. El compuesto de una cualquiera de las reivindicaciones 1-10, en donde Z está sustituido con hasta tres sustituyentes seleccionados independientemente del grupo que consiste en alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalcoxi C₃-C₆, halógeno, alquilsulfonilo y ciano.

45 12. El compuesto de una cualquiera de las reivindicaciones 1-10, en donde Z es imidazo[1,2-a]piridin-2-il sustituido con hasta 2 sustituyentes seleccionados independientemente del grupo que consiste en alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalcoxi C₃-C₆, halógeno, alquilsulfonilo y ciano.

50 13. El compuesto de una cualquiera de las reivindicaciones 1-10, en donde Z es imidazo[1,2-b]piridazin-2-il sustituido con hasta 2 sustituyentes seleccionados independientemente del grupo que consiste en alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalcoxi C₃-C₆, halógeno, alquilsulfonilo y ciano.

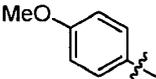
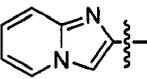
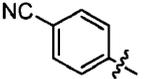
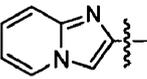
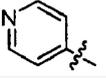
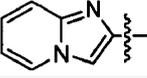
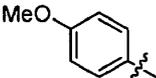
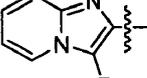
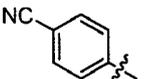
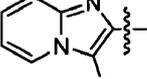
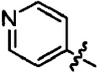
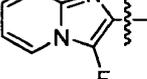
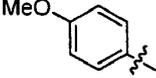
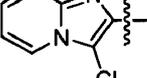
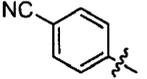
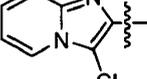
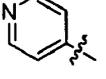
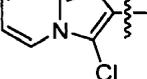
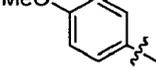
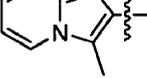
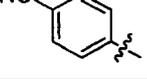
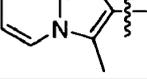
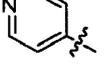
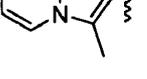
14. El compuesto de una cualquiera de las reivindicaciones 1-10, en donde Z es imidazo[1,2-b]piridazin-6-il sustituido con hasta 2 sustituyentes seleccionados independientemente del grupo que consiste en alquilo C₁-C₄, alcoxi C₁-C₄, cicloalquilo C₃-C₆, cicloalcoxi C₃-C₆, halógeno, alquilsulfonilo y ciano.

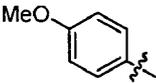
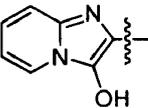
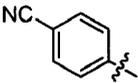
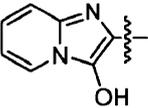
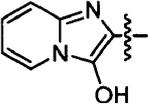
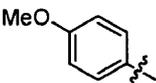
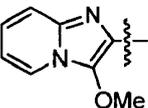
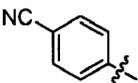
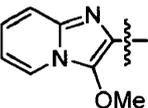
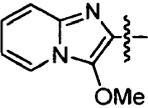
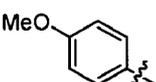
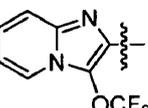
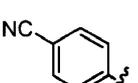
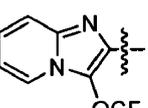
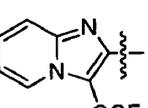
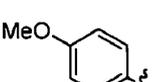
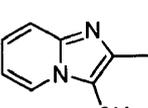
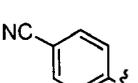
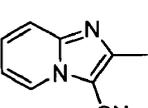
55 15. El compuesto de una cualquiera de las reivindicaciones 1-14, en donde Z no está sustituido.

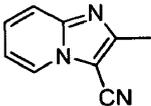
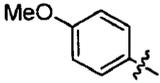
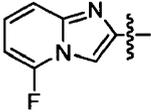
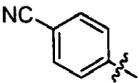
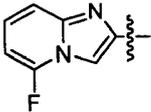
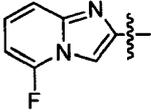
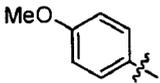
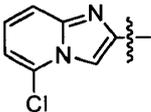
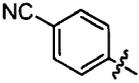
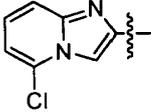
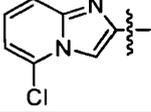
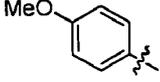
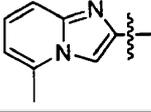
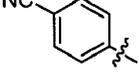
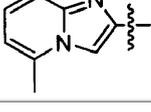
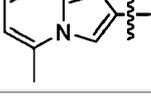
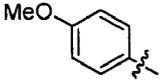
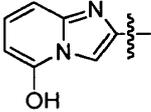
16. El compuesto de una cualquiera de las reivindicaciones 1-15, en donde R₂ es alquilo C₁-C₄.

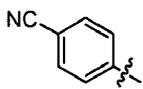
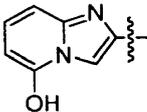
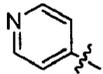
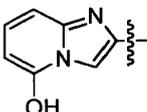
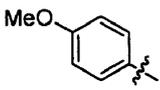
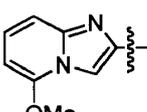
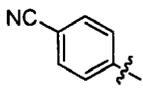
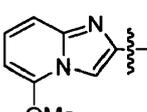
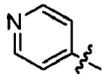
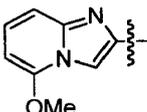
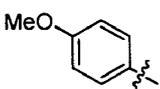
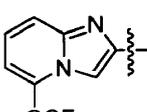
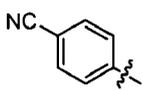
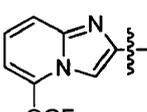
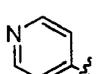
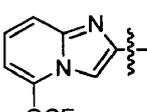
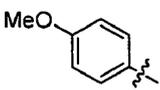
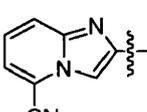
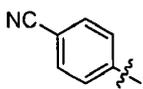
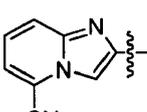
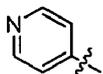
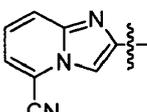
60 17. El compuesto de cualquiera de las reivindicaciones anteriores, en donde los sustituyentes se seleccionan independientemente del grupo que consiste en alquilo C₁-C₄, alcoxi C₁-C₄, CF₃, carboxi, ciano, amino y halógeno.

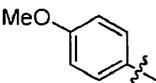
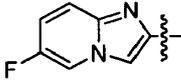
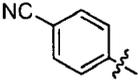
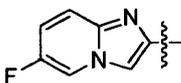
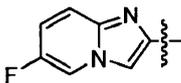
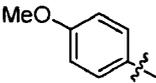
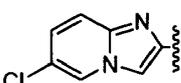
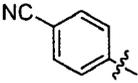
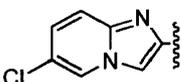
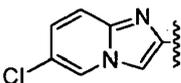
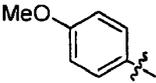
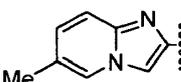
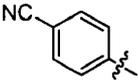
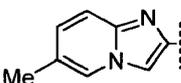
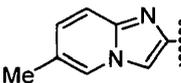
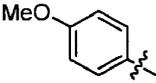
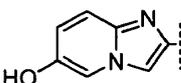
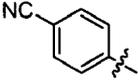
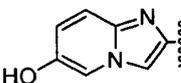
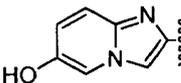
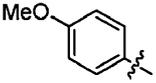
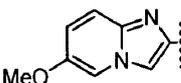
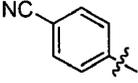
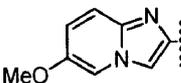
18. Una compuesto de acuerdo con la reivindicación 1, seleccionado entre uno cualquiera de los compuestos definidos como Ejemplos 1-185 y 187-732 en la Tabla de más abajo o una de sus sales farmacéuticamente aceptables:

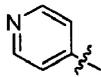
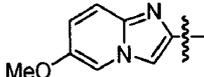
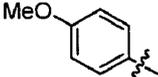
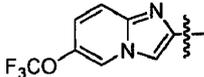
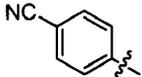
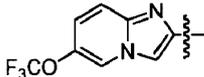
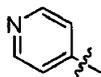
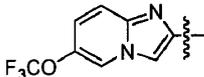
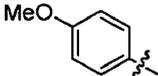
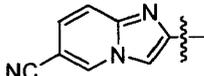
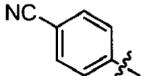
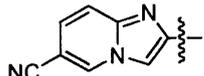
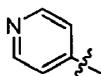
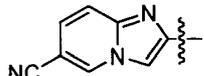
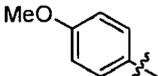
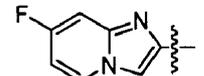
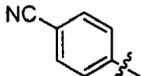
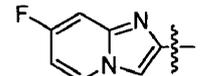
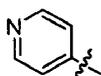
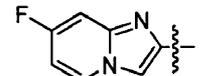
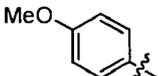
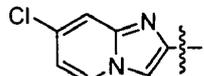
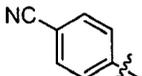
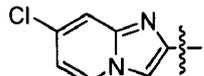
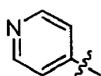
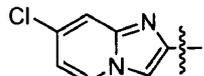
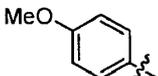
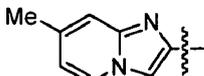
Núm. de Ejemplo	HET	X	Z	R ₂
1	A29			Me, Me
2	A29			Me, Me
3	A29			Me, Me
4	A29			Me, Me
5	A29			Me, Me
6	A29			Me, Me
7	A29			Me, Me
8	A29			Me, Me
9	A29			Me, Me
10	A29			Me, Me
11	A29			Me, Me
12	A29			Me, Me

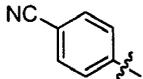
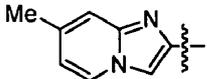
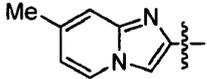
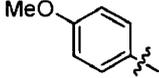
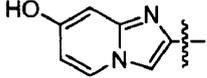
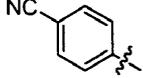
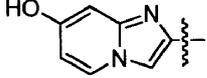
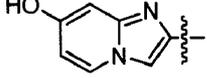
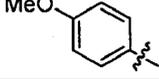
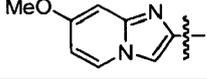
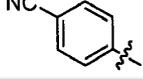
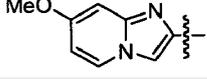
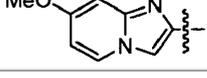
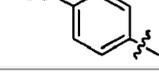
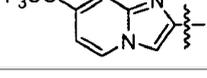
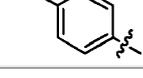
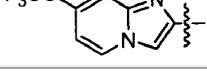
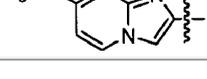
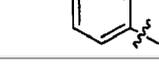
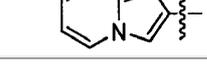
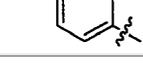
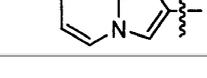
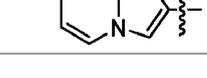
Núm. de Ejemplo	HET	X	Z	R ₂
13	A29			Me, Me
14	A29			Me, Me
15	A29			Me, Me
16	A29			Me, Me
17	A29			Me, Me
18	A29			Me, Me
19	A29			Me, Me
20	A29			Me, Me
21	A29			Me, Me
22	A29			Me, Me
23	A29			Me, Me

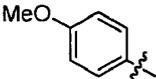
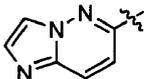
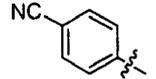
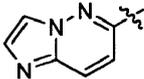
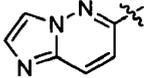
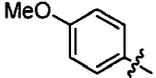
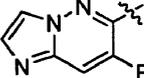
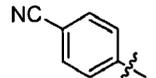
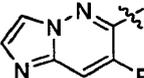
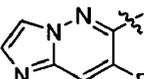
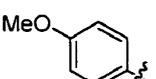
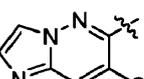
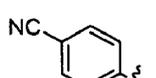
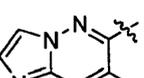
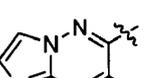
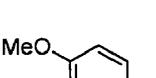
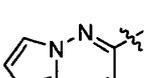
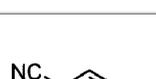
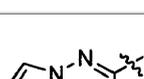
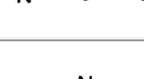
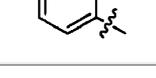
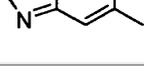
Núm. de Ejemplo	HET	X	Z	R ₂
24	A29			Me, Me
25	A29			Me, Me
26	A29			Me, Me
27	A29			Me, Me
28	A29			Me, Me
29	A29			Me, Me
30	A29			Me, Me
31	A29			Me, Me
32	A29			Me, Me
33	A29			Me, Me
34	A29			Me, Me

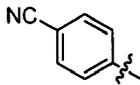
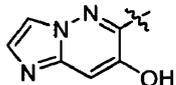
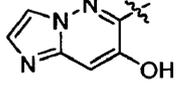
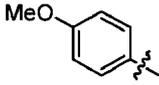
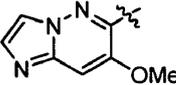
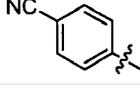
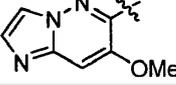
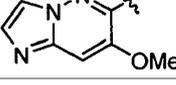
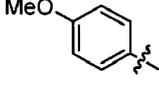
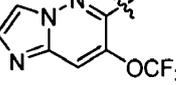
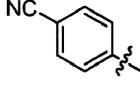
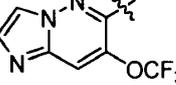
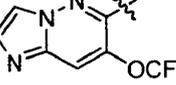
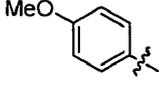
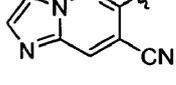
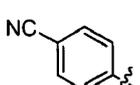
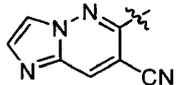
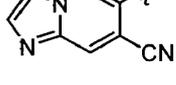
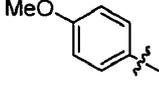
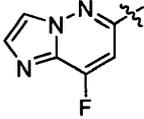
Núm. de Ejemplo	HET	X	Z	R ₂
35	A29			Me, Me
36	A29			Me, Me
37	A29			Me, Me
38	A29			Me, Me
39	A29			Me, Me
40	A29			Me, Me
41	A29			Me, Me
42	A29			Me, Me
43	A29			Me, Me
44	A29			Me, Me
45	A29			Me, Me

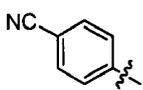
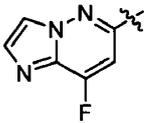
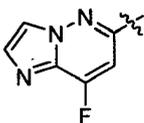
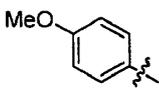
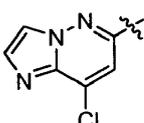
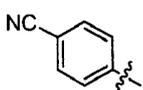
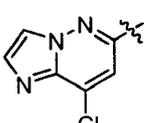
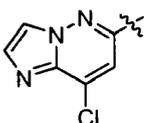
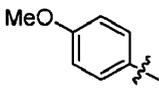
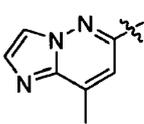
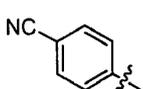
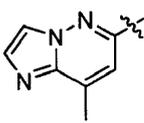
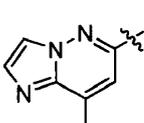
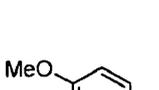
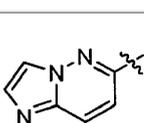
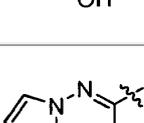
Núm. de Ejemplo	HET	X	Z	R ₂
46	A29			Me, Me
47	A29			Me, Me
48	A29			Me, Me
49	A29			Me, Me
50	A29			Me, Me
51	A29			Me, Me
52	A29			Me, Me
53	A29			Me, Me
54	A29			Me, Me
55	A29			Me, Me
56	A29			Me, Me
57	A29			Me, Me
58	A29			Me, Me
59	A29			Me, Me

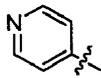
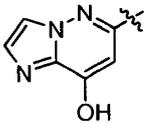
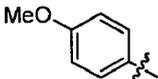
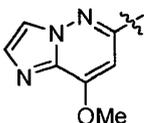
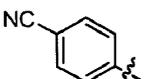
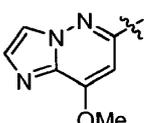
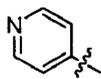
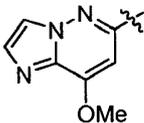
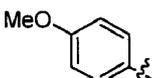
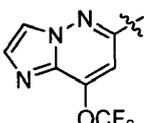
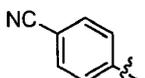
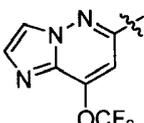
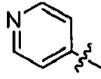
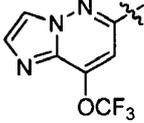
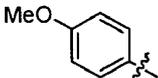
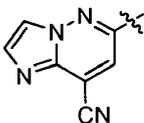
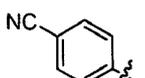
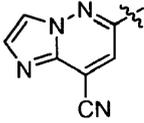
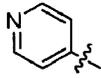
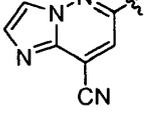
Núm. de Ejemplo	HET	X	Z	R ₂
60	A29			Me, Me
61	A29			Me, Me
62	A29			Me, Me
63	A29			Me, Me
64	A29			Me, Me
65	A29			Me, Me
66	A29			Me, Me
67	A29			Me, Me
68	A29			Me, Me
69	A29			Me, Me
70	A29			Me, Me
71	A29			Me, Me
72	A29			Me, Me
73	A29			Me, Me

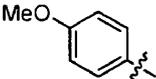
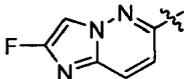
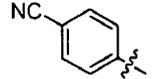
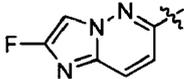
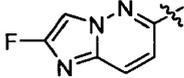
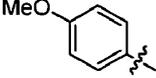
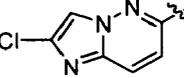
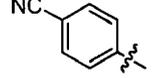
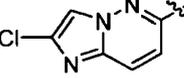
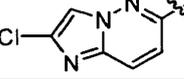
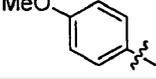
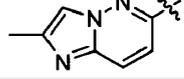
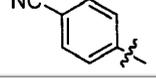
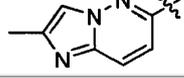
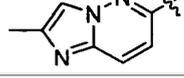
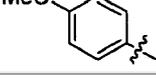
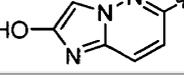
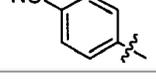
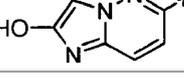
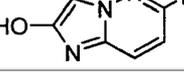
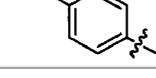
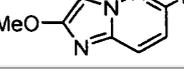
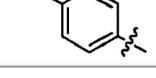
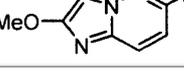
Núm. de Ejemplo	HET	X	Z	R ₂
74	A29			Me, Me
75	A29			Me, Me
76	A29			Me, Me
77	A29			Me, Me
78	A29			Me, Me
79	A29			Me, Me
80	A29			Me, Me
81	A29			Me, Me
82	A29			Me, Me
83	A29			Me, Me
84	A29			Me, Me
85	A29			Me, Me
86	A29			Me, Me
87	A29			Me, Me

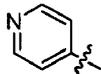
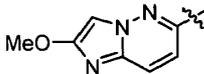
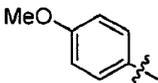
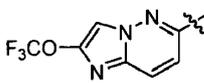
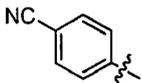
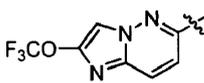
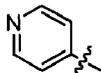
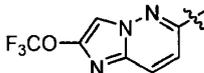
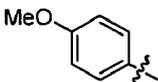
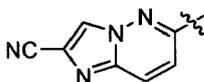
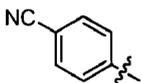
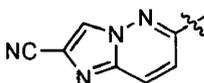
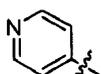
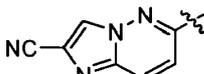
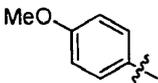
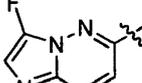
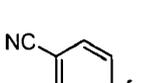
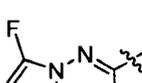
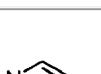
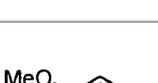
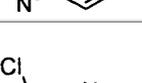
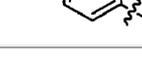
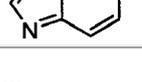
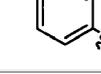
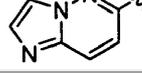
Núm. de Ejemplo	HET	X	Z	R ₂
88	A29			Me, Me
89	A29			Me, Me
90	A29			Me, Me
91	A29			Me, Me
92	A29			Me, Me
93	A29			Me, Me
94	A29			Me, Me
95	A29			Me, Me
96	A29			Me, Me
97	A29			Me, Me
98	A29			Me, Me
99	A29			Me, Me
100	A29			Me, Me

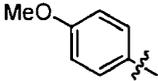
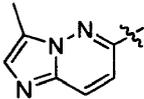
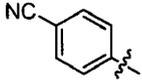
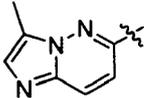
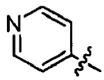
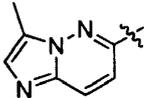
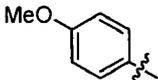
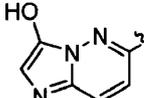
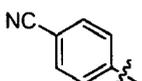
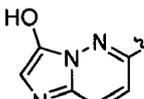
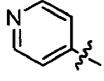
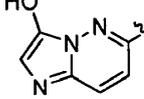
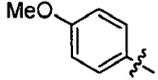
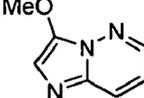
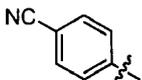
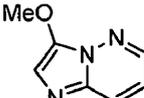
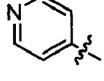
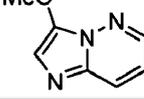
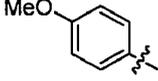
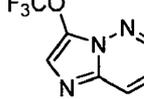
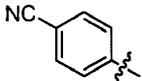
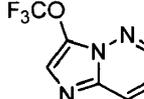
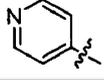
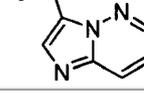
Núm. de Ejemplo	HET	X	Z	R ₂
101	A29			Me, Me
102	A29			Me, Me
103	A29			Me, Me
104	A29			Me, Me
105	A29			Me, Me
106	A29			Me, Me
107	A29			Me, Me
108	A29			Me, Me
109	A29			Me, Me
110	A29			Me, Me
111	A29			Me, Me
121	A29			Me, Me

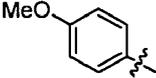
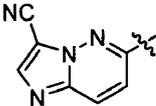
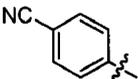
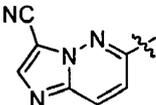
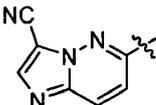
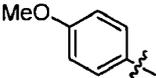
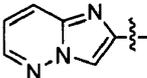
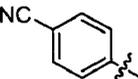
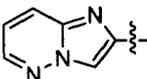
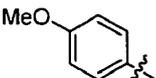
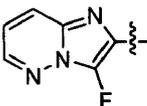
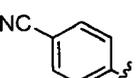
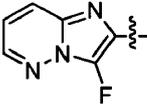
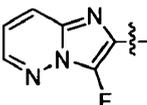
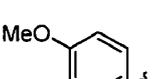
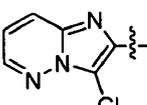
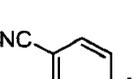
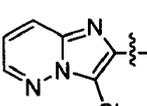
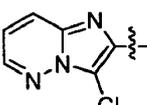
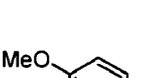
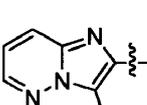
Núm. de Ejemplo	HET	X	Z	R ₂
122	A29			Me, Me
123	A29			Me, Me
124	A29			Me, Me
125	A29			Me, Me
126	A29			Me, Me
127	A29			Me, Me
128	A29			Me, Me
129	A29			Me, Me
130	A29			Me, Me
131	A29			Me, Me

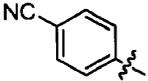
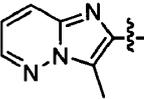
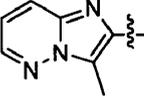
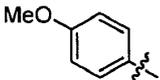
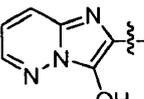
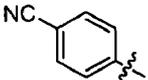
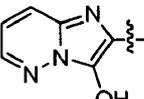
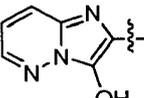
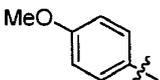
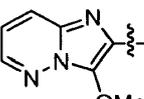
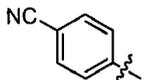
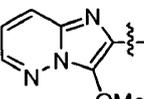
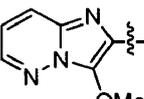
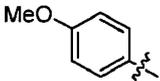
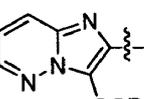
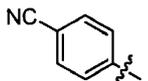
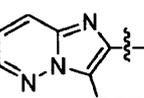
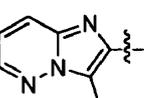
Núm. de Ejemplo	HET	X	Z	R ₂
132	A29			Me, Me
133	A29			Me, Me
134	A29			Me, Me
135	A29			Me, Me
136	A29			Me, Me
137	A29			Me, Me
138	A29			Me, Me
139	A29			Me, Me
140	A29			Me, Me
141	A29			Me, Me

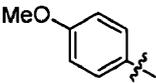
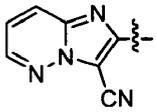
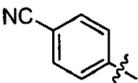
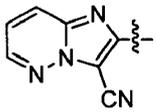
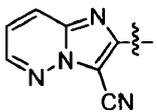
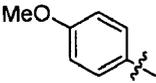
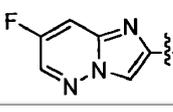
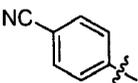
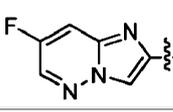
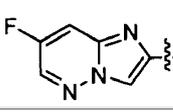
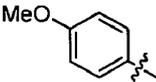
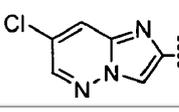
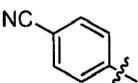
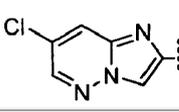
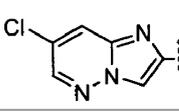
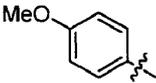
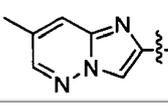
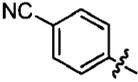
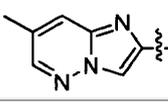
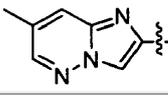
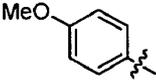
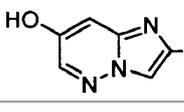
Núm. de Ejemplo	HET	X	Z	R ₂
142	A29			Me, Me
143	A29			Me, Me
144	A29			Me, Me
145	A29			Me, Me
146	A29			Me, Me
147	A29			Me, Me
148	A29			Me, Me
149	A29			Me, Me
150	A29			Me, Me
151	A29			Me, Me
152	A29			Me, Me
153	A29			Me, Me
154	A29			Me, Me
155	A29			Me, Me

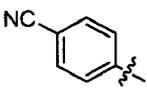
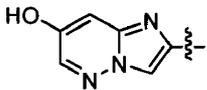
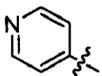
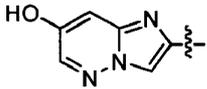
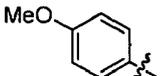
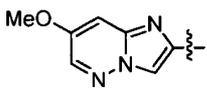
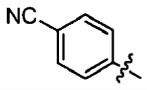
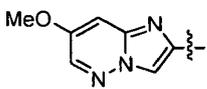
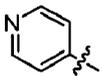
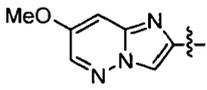
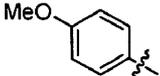
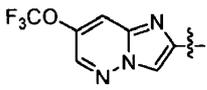
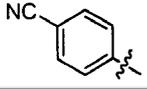
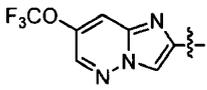
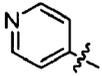
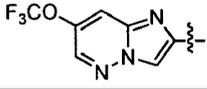
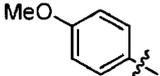
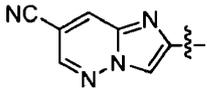
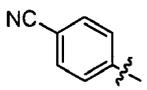
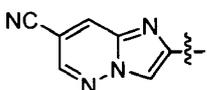
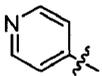
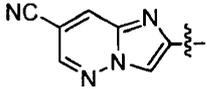
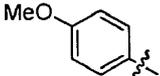
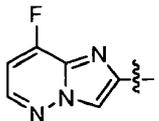
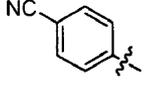
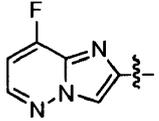
Núm. de Ejemplo	HET	X	Z	R ₂
156	A29			Me, Me
157	A29			Me, Me
158	A29			Me, Me
159	A29			Me, Me
160	A29			Me, Me
161	A29			Me, Me
162	A29			Me, Me
163	A29			Me, Me
164	A29			Me, Me
165	A29			Me, Me
166	A29			Me, Me
167	A29			Me, Me
168	A29			Me, Me

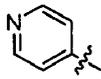
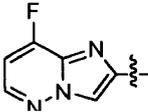
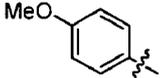
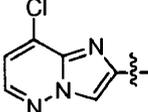
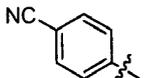
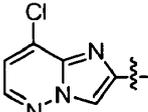
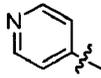
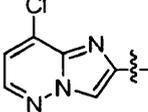
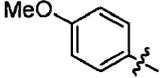
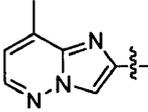
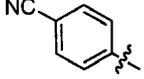
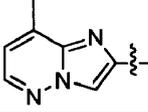
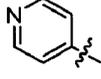
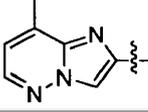
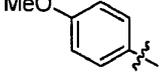
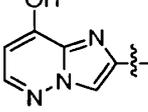
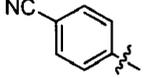
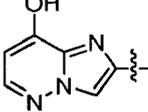
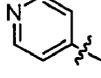
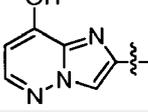
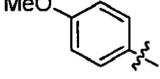
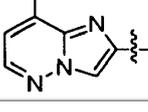
Núm. de Ejemplo	HET	X	Z	R ₂
169	A29			Me, Me
170	A29			Me, Me
171	A29			Me, Me
172	A29			Me, Me
173	A29			Me, Me
174	A29			Me, Me
175	A29			Me, Me
176	A29			Me, Me
177	A29			Me, Me
178	A29			Me, Me
179	A29			Me, Me
180	A29			Me, Me

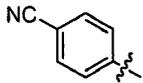
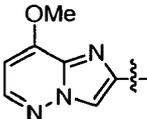
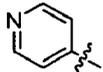
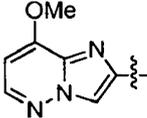
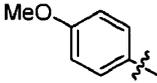
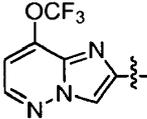
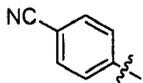
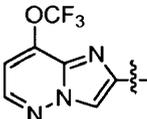
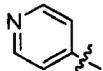
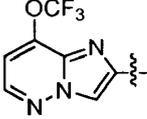
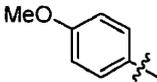
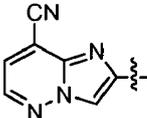
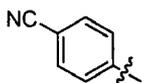
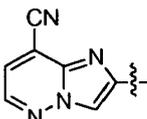
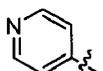
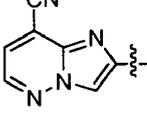
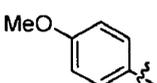
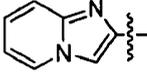
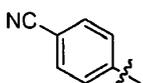
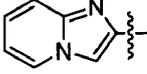
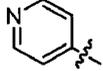
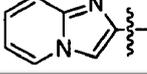
Núm. de Ejemplo	HET	X	Z	R ₂
181	A29			Me, Me
182	A29			Me, Me
183	A29			Me, Me
184	A29			Me, Me
185	A29			Me, Me
187	A29			Me, Me
188	A29			Me, Me
189	A29			Me, Me
190	A29			Me, Me
191	A29			Me, Me
192	A29			Me, Me
193	A29			Me, Me

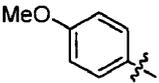
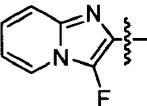
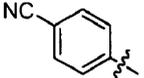
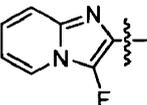
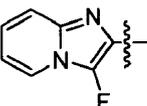
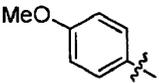
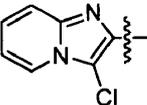
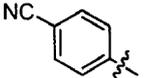
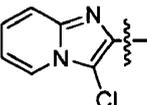
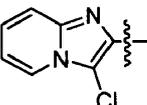
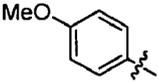
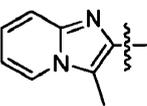
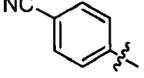
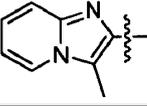
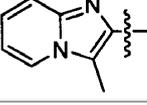
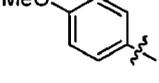
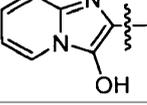
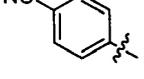
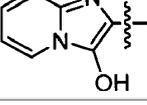
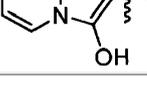
Núm. de Ejemplo	HET	X	Z	R ₂
194	A29			Me, Me
195	A29			Me, Me
196	A29			Me, Me
197	A29			Me, Me
198	A29			Me, Me
199	A29			Me, Me
200	A29			Me, Me
201	A29			Me, Me
202	A29			Me, Me
203	A29			Me, Me
204	A29			Me, Me

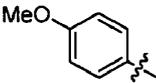
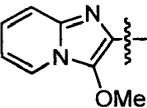
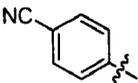
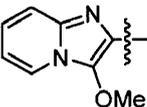
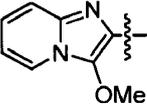
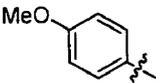
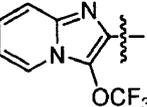
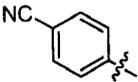
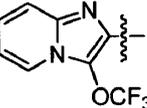
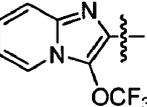
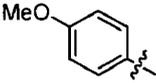
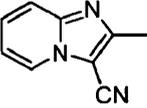
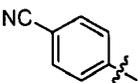
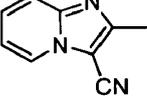
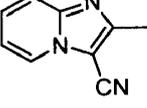
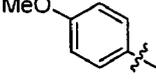
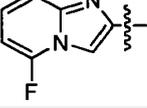
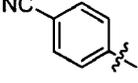
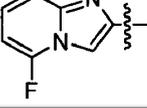
Núm. de Ejemplo	HET	X	Z	R ₂
205	A29			Me, Me
206	A29			Me, Me
207	A29			Me, Me
211	A29			Me, Me
212	A29			Me, Me
213	A29			Me, Me
214	A29			Me, Me
215	A29			Me, Me
216	A29			Me, Me
217	A29			Me, Me
218	A29			Me, Me
219	A29			Me, Me
220	A29			Me, Me

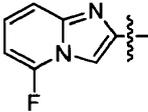
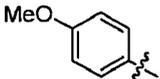
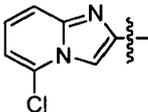
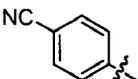
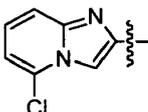
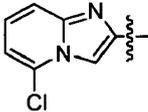
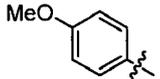
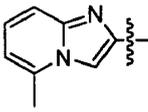
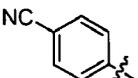
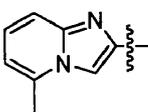
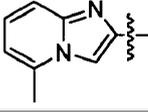
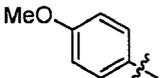
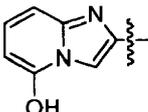
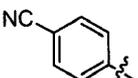
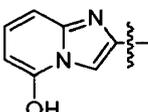
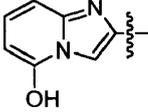
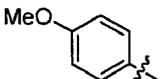
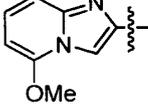
Núm. de Ejemplo	HET	X	Z	R ₂
221	A29			Me, Me
222	A29			Me, Me
223	A29			Me, Me
224	A29			Me, Me
225	A29			Me, Me
226	A29			Me, Me
227	A29			Me, Me
228	A29			Me, Me
229	A29			Me, Me
230	A29			Me, Me
231	A29			Me, Me
232	A29			Me, Me
233	A29			Me, Me

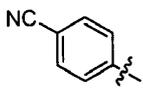
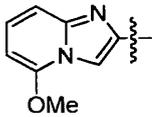
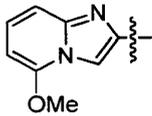
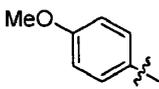
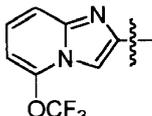
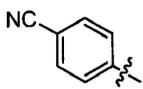
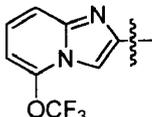
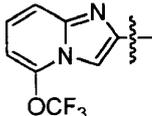
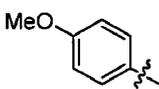
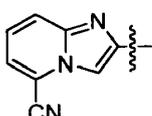
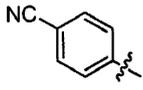
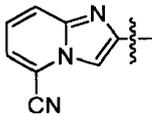
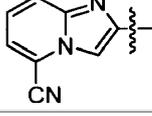
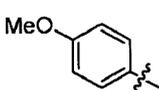
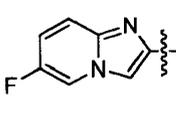
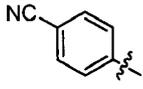
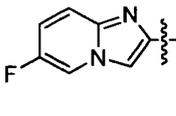
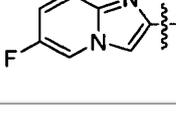
Núm. de Ejemplo	HET	X	Z	R ₂
234	A29			Me, Me
235	A29			Me, Me
236	A29			Me, Me
237	A29			Me, Me
238	A29			Me, Me
239	A29			Me, Me
240	A29			Me, Me
241	A29			Me, Me
242	A29			Me, Me
243	A29			Me, Me
244	A29			Me, Me

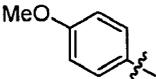
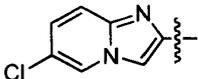
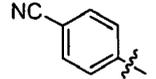
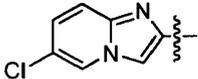
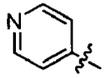
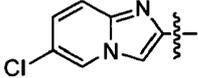
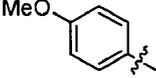
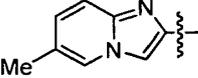
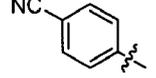
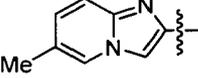
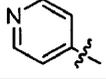
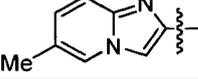
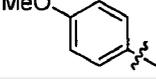
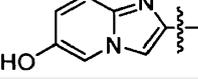
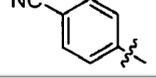
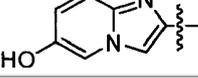
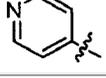
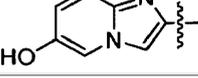
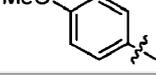
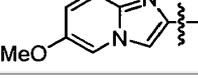
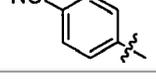
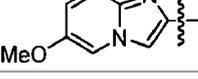
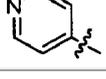
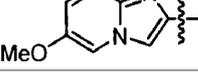
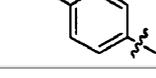
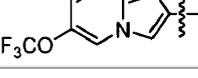
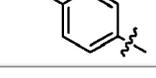
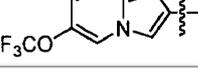
Núm. de Ejemplo	HET	X	Z	R ₂
245	A29			Me, Me
246	A29			Me, Me
247	A29			Me, Me
248	A29			Me, Me
249	A29			Me, Me
250	A29			Me, Me
251	A29			Me, Me
252	A29			Me, Me
253	A31			Me, Me
254	A31			Me, Me
255	A31			Me, Me

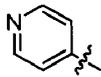
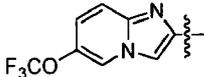
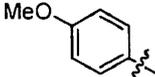
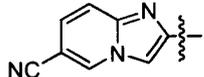
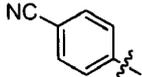
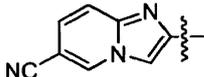
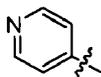
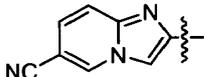
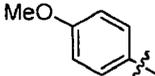
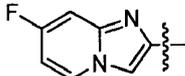
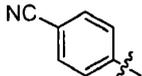
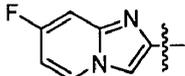
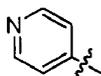
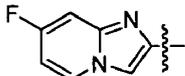
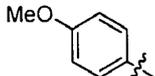
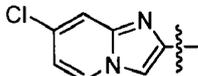
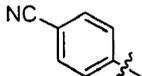
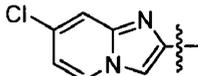
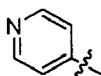
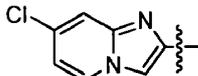
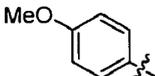
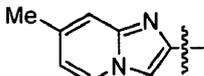
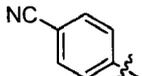
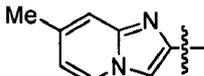
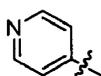
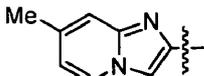
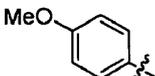
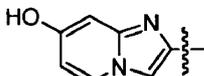
Núm. de Ejemplo	HET	X	Z	R ₂
256	A31			Me, Me
257	A31			Me, Me
258	A31			Me, Me
259	A31			Me, Me
260	A31			Me, Me
261	A31			Me, Me
262	A31			Me, Me
263	A31			Me, Me
264	A31			Me, Me
265	A31			Me, Me
266	A31			Me, Me
267	A31			Me, Me

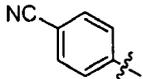
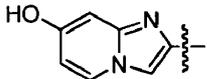
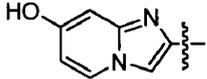
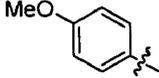
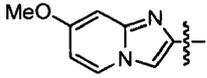
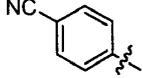
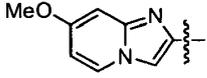
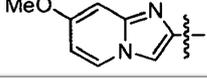
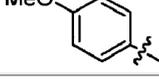
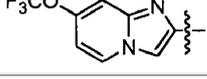
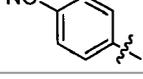
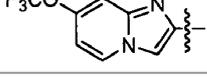
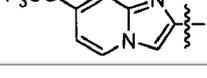
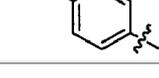
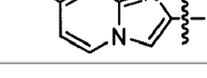
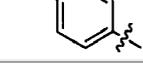
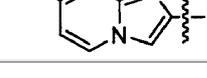
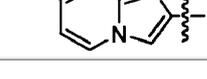
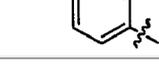
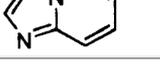
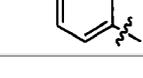
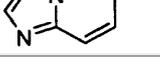
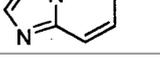
Núm. de Ejemplo	HET	X	Z	R ₂
268	A31			Me, Me
269	A31			Me, Me
270	A31			Me, Me
271	A31			Me, Me
272	A31			Me, Me
273	A31			Me, Me
274	A31			Me, Me
275	A31			Me, Me
276	A31			Me, Me
277	A31			Me, Me
278	A31			Me, Me

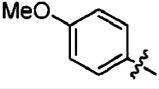
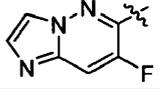
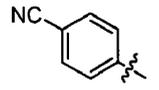
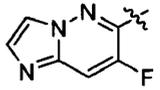
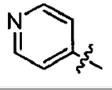
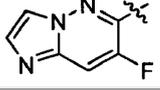
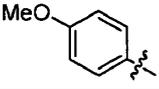
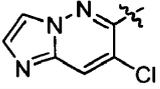
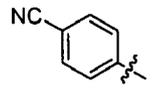
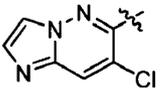
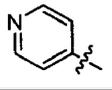
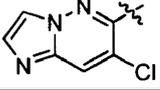
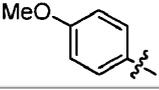
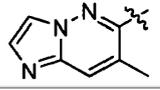
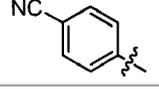
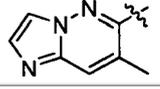
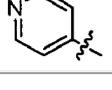
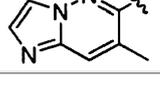
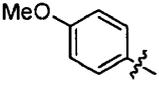
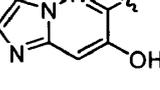
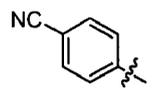
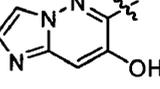
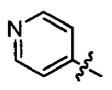
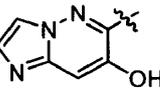
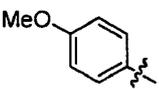
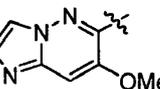
Núm. de Ejemplo	HET	X	Z	R ₂
279	A31			Me, Me
280	A31			Me, Me
281	A31			Me, Me
282	A31			Me, Me
283	A31			Me, Me
284	A31			Me, Me
285	A31			Me, Me
286	A31			Me, Me
287	A31			Me, Me
288	A31			Me, Me
289	A31			Me, Me

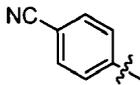
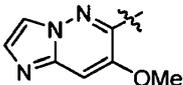
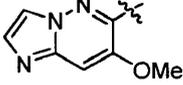
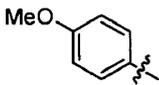
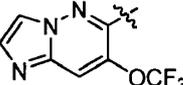
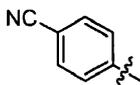
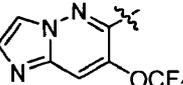
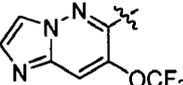
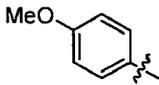
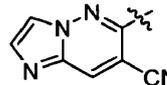
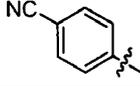
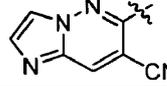
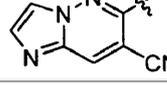
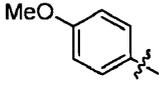
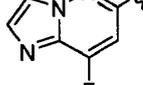
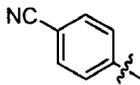
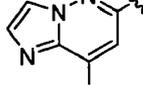
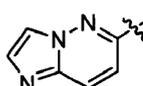
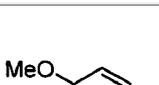
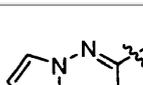
Núm. de Ejemplo	HET	X	Z	R ₂
290	A31			Me, Me
291	A31			Me, Me
292	A31			Me, Me
293	A31			Me, Me
294	A31			Me, Me
295	A31			Me, Me
296	A31			Me, Me
297	A31			Me, Me
298	A31			Me, Me
299	A31			Me, Me
300	A31			Me, Me

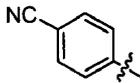
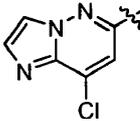
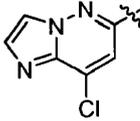
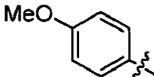
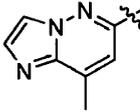
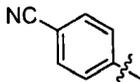
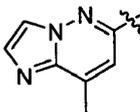
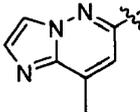
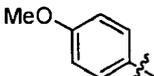
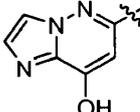
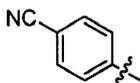
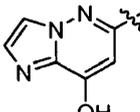
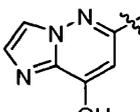
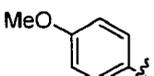
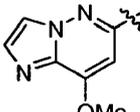
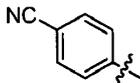
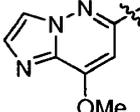
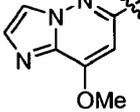
Núm. de Ejemplo	HET	X	Z	R ₂
301	A31			Me, Me
302	A31			Me, Me
303	A31			Me, Me
304	A31			Me, Me
305	A31			Me, Me
306	A31			Me, Me
307	A31			Me, Me
308	A31			Me, Me
309	A31			Me, Me
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311	A31			Me, Me
312	A31			Me, Me
313	A31			Me, Me
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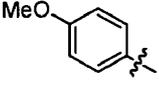
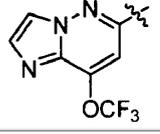
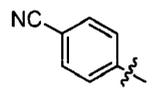
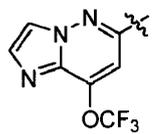
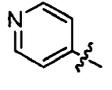
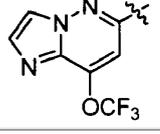
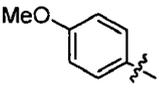
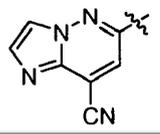
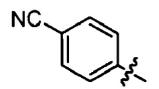
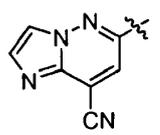
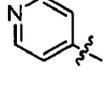
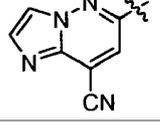
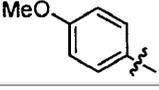
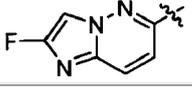
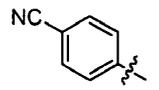
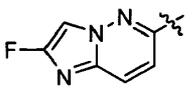
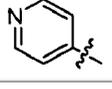
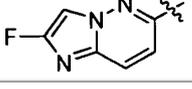
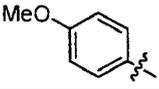
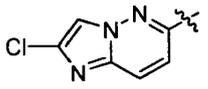
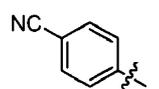
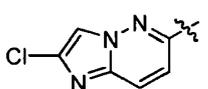
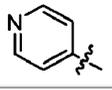
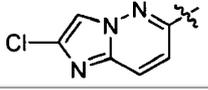
Núm. de Ejemplo	HET	X	Z	R ₂
315	A31			Me, Me
316	A31			Me, Me
317	A31			Me, Me
318	A31			Me, Me
319	A31			Me, Me
320	A31			Me, Me
321	A31			Me, Me
322	A31			Me, Me
323	A31			Me, Me
324	A31			Me, Me
325	A31			Me, Me
326	A31			Me, Me
327	A31			Me, Me
328	A31			Me, Me

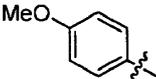
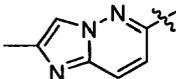
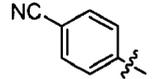
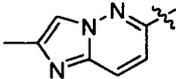
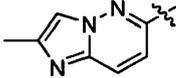
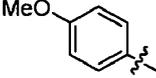
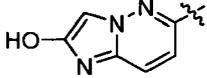
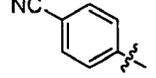
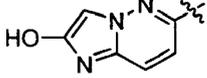
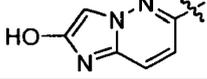
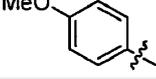
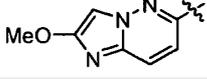
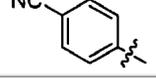
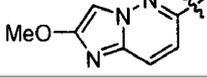
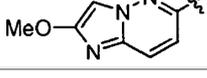
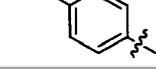
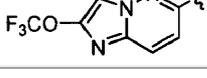
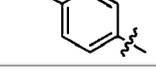
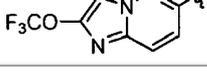
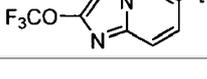
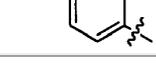
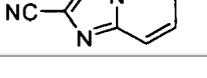
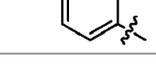
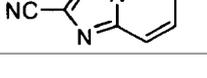
Núm. de Ejemplo	HET	X	Z	R ₂
329	A31			Me, Me
330	A31			Me, Me
331	A31			Me, Me
332	A31			Me, Me
333	A31			Me, Me
334	A31			Me, Me
335	A31			Me, Me
336	A31			Me, Me
337	A31			Me, Me
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339	A31			Me, Me
340	A31			Me, Me
341	A31			Me, Me
342	A31			Me, Me

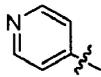
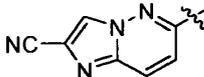
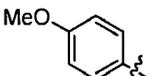
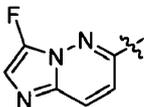
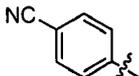
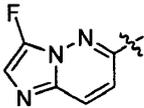
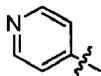
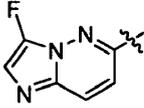
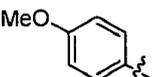
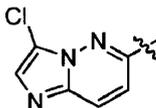
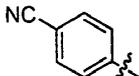
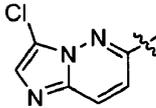
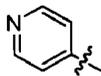
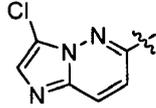
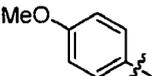
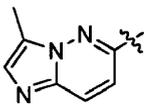
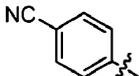
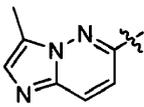
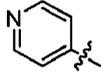
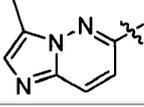
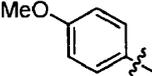
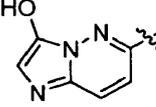
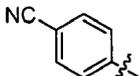
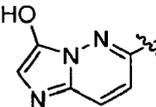
Núm. de Ejemplo	HET	X	Z	R ₂
343	A31			Me, Me
344	A31			Me, Me
345	A31			Me, Me
346	A31			Me, Me
347	A31			Me, Me
348	A31			Me, Me
349	A31			Me, Me
350	A31			Me, Me
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352	A31			Me, Me
353	A31			Me, Me
354	A31			Me, Me
355	A31			Me, Me

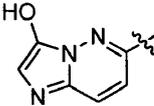
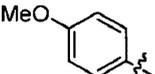
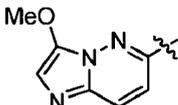
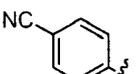
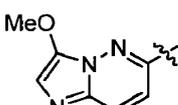
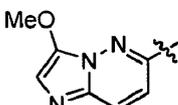
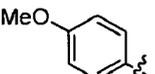
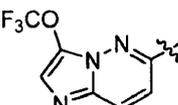
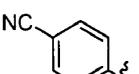
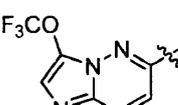
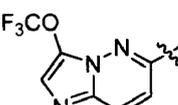
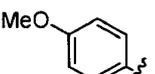
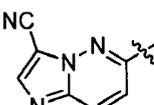
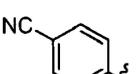
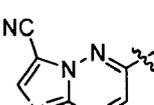
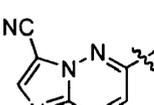
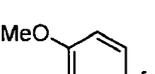
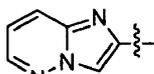
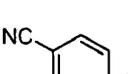
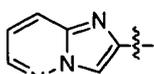
Núm. de Ejemplo	HET	X	Z	R ₂
356	A31			Me, Me
357	A31			Me, Me
358	A31			Me, Me
359	A31			Me, Me
360	A31			Me, Me
361	A31			Me, Me
362	A31			Me, Me
363	A31			Me, Me
364	A31			Me, Me
365	A31			Me, Me
366	A31			Me, Me
367	A31			Me, Me

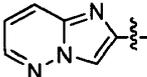
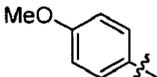
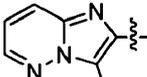
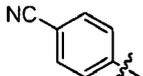
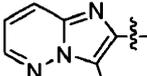
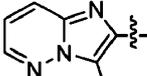
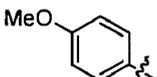
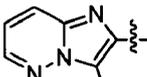
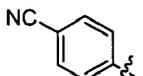
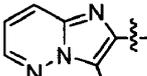
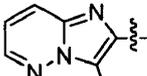
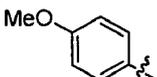
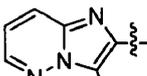
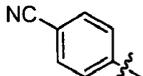
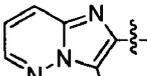
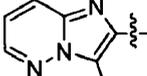
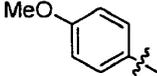
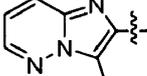
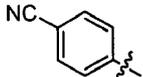
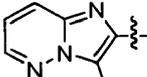
Núm. de Ejemplo	HET	X	Z	R ₂
368	A31			Me, Me
369	A31			Me, Me
370	A31			Me, Me
371	A31			Me, Me
372	A31			Me, Me
373	A31			Me, Me
374	A31			Me, Me
375	A31			Me, Me
376	A31			Me, Me
377	A31			Me, Me
378	A31			Me, Me

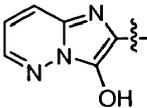
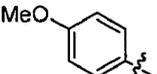
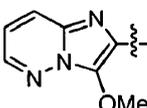
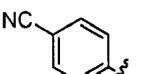
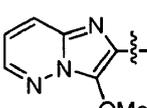
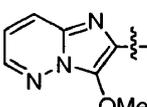
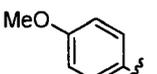
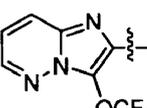
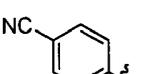
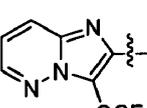
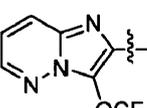
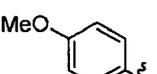
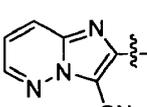
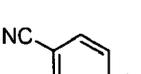
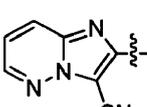
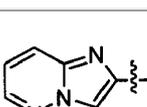
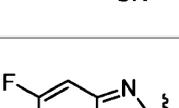
Núm. de Ejemplo	HET	X	Z	R ₂
379	A31			Me, Me
380	A31			Me, Me
381	A31			Me, Me
382	A31			Me, Me
383	A31			Me, Me
384	A31			Me, Me
385	A31			Me, Me
386	A31			Me, Me
387	A31			Me, Me
388	A31			Me, Me
389	A31			Me, Me
390	A31			Me, Me

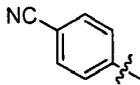
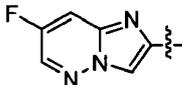
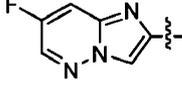
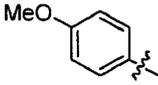
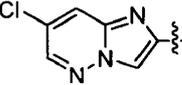
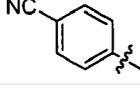
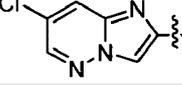
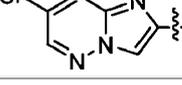
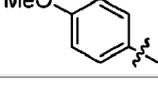
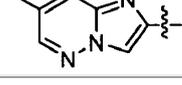
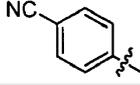
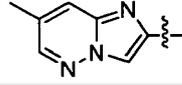
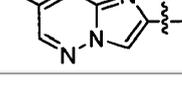
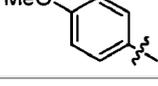
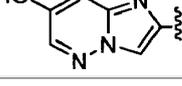
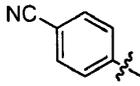
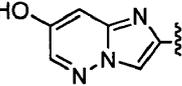
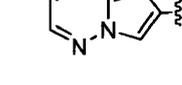
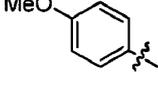
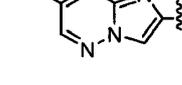
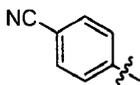
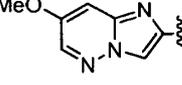
Núm. de Ejemplo	HET	X	Z	R ₂
391	A31			Me, Me
392	A31			Me, Me
393	A31			Me, Me
394	A31			Me, Me
395	A31			Me, Me
396	A31			Me, Me
397	A31			Me, Me
398	A31			Me, Me
399	A31			Me, Me
400	A31			Me, Me
401	A31			Me, Me
402	A31			Me, Me
403	A31			Me, Me
404	A31			Me, Me

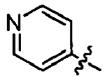
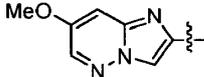
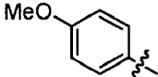
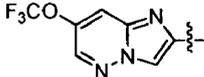
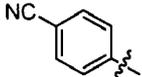
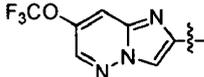
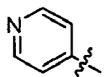
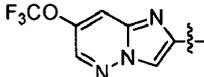
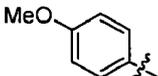
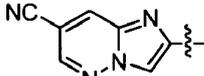
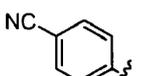
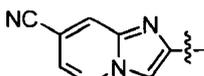
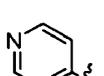
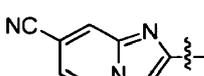
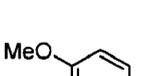
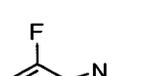
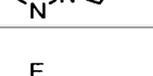
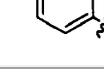
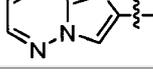
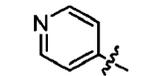
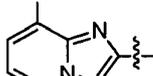
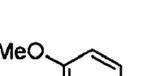
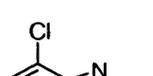
Núm. de Ejemplo	HET	X	Z	R ₂
405	A31			Me, Me
406	A31			Me, Me
407	A31			Me, Me
408	A31			Me, Me
409	A31			Me, Me
410	A31			Me, Me
411	A31			Me, Me
412	A31			Me, Me
413	A31			Me, Me
414	A31			Me, Me
415	A31			Me, Me
416	A31			Me, Me

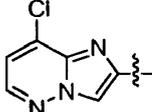
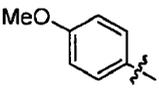
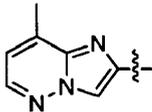
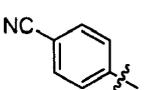
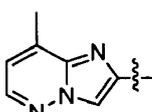
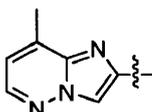
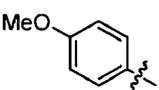
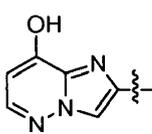
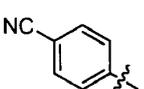
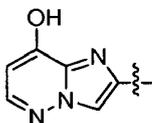
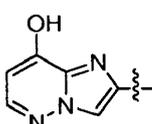
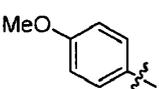
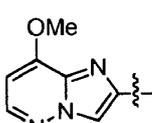
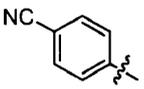
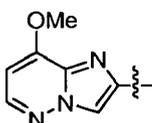
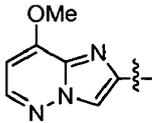
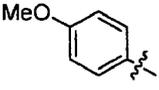
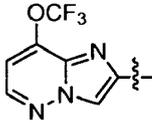
Núm. de Ejemplo	HET	X	Z	R ₂
417	A31			Me, Me
418	A31			Me, Me
419	A31			Me, Me
420	A31			Me, Me
421	A31			Me, Me
422	A31			Me, Me
423	A31			Me, Me
424	A31			Me, Me
425	A31			Me, Me
426	A31			Me, Me
427	A31			Me, Me
428	A31			Me, Me

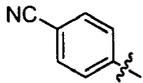
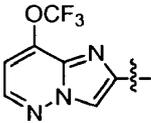
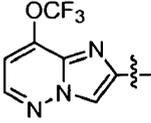
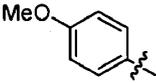
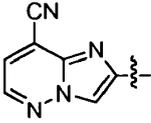
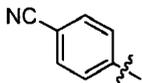
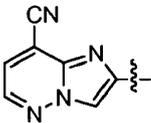
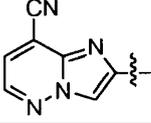
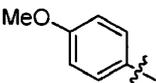
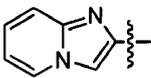
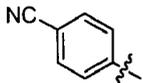
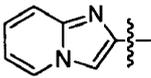
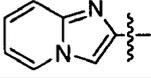
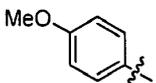
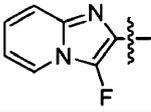
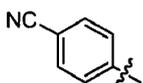
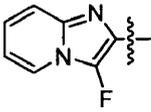
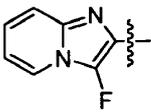
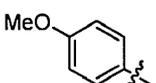
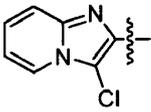
Núm. de Ejemplo	HET	X	Z	R ₂
429	A31			Me, Me
430	A31			Me, Me
431	A31			Me, Me
432	A31			Me, Me
433	A31			Me, Me
434	A31			Me, Me
435	A31			Me, Me
436	A31			Me, Me
437	A31			Me, Me
438	A31			Me, Me
439	A31			Me, Me
440	A31			Me, Me

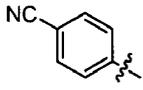
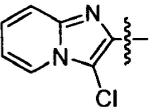
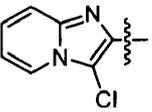
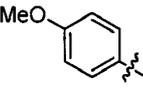
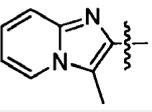
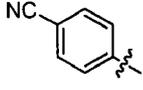
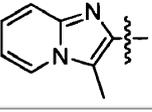
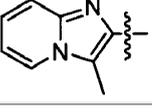
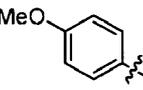
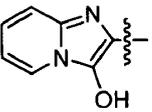
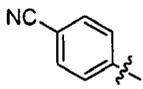
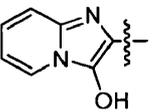
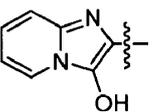
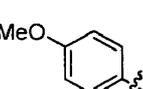
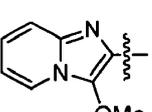
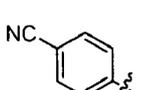
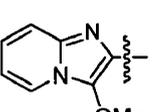
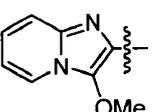
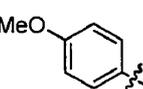
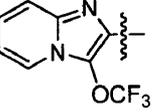
Núm. de Ejemplo	HET	X	Z	R ₂
441	A31			Me, Me
442	A31			Me, Me
443	A31			Me, Me
444	A31			Me, Me
445	A31			Me, Me
446	A31			Me, Me
447	A31			Me, Me
448	A31			Me, Me
449	A31			Me, Me
450	A31			Me, Me
451	A31			Me, Me

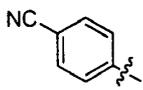
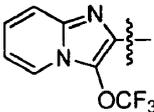
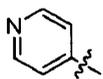
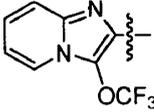
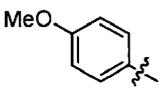
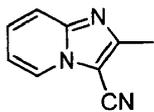
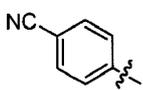
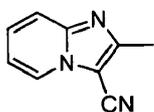
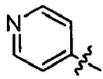
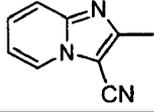
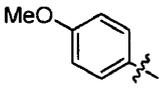
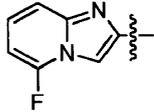
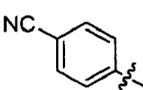
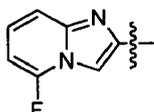
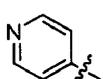
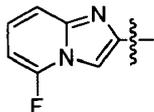
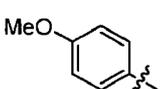
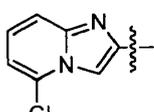
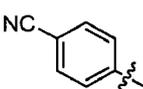
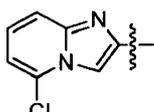
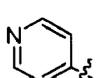
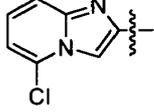
Núm. de Ejemplo	HET	X	Z	R ₂
452	A31			Me, Me
453	A31			Me, Me
454	A31			Me, Me
455	A31			Me, Me
456	A31			Me, Me
457	A31			Me, Me
458	A31			Me, Me
459	A31			Me, Me
460	A31			Me, Me
461	A31			Me, Me
462	A31			Me, Me
463	A31			Me, Me
464	A31			Me, Me

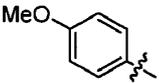
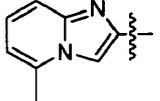
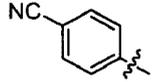
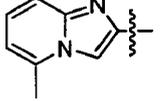
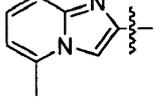
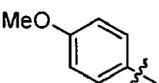
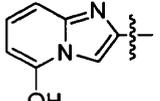
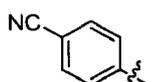
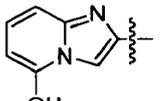
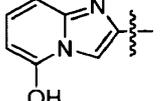
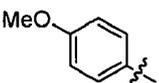
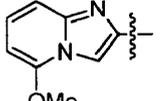
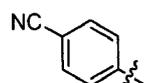
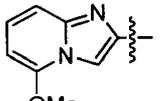
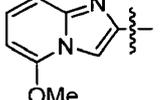
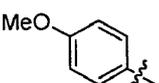
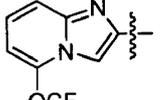
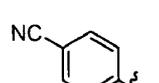
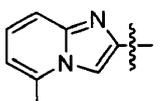
Núm. de Ejemplo	HET	X	Z	R ₂
465	A31			Me, Me
466	A31			Me, Me
467	A31			Me, Me
468	A31			Me, Me
469	A31			Me, Me
470	A31			Me, Me
471	A31			Me, Me
472	A31			Me, Me
473	A31			Me, Me
474	A31			Me, Me
475	A31			Me, Me
476	A31			Me, Me

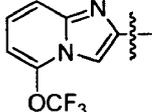
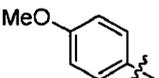
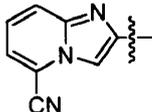
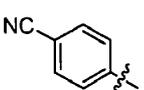
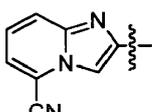
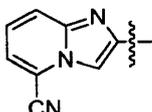
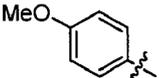
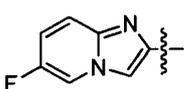
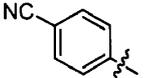
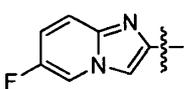
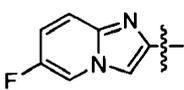
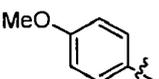
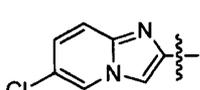
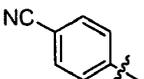
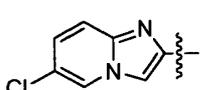
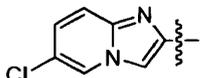
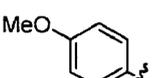
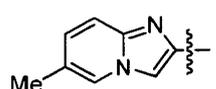
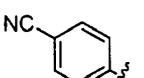
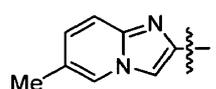
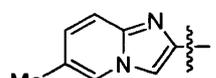
Núm. de Ejemplo	HET	X	Z	R ₂
477	A31			Me, Me
478	A31			Me, Me
479	A31			Me, Me
480	A31			Me, Me
481	A31			Me, Me
482	A31			Me, Me
483	A31			Me, Me
484	A31			Me, Me
485	A31			Me, Me
486	A31			Me, Me
487	A31			Me, Me

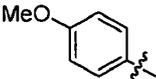
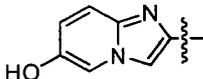
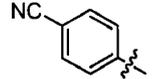
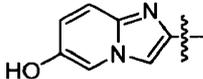
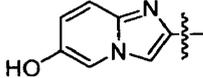
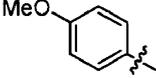
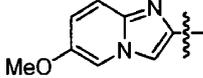
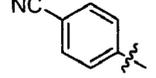
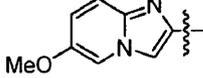
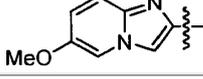
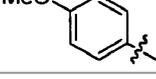
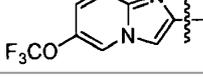
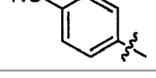
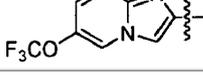
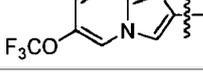
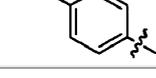
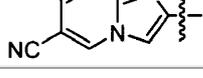
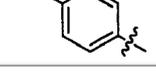
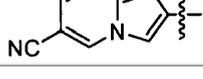
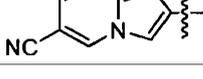
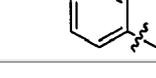
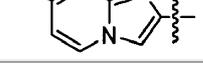
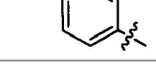
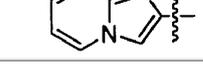
Núm. de Ejemplo	HET	X	Z	R ₂
488	A31			Me, Me
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490	A31			Me, Me
491	A31			Me, Me
492	A31			Me, Me
493	A29			--ciclopropilo--
494	A29			--ciclopropilo--
495	A29			--ciclopropilo--
496	A29			--ciclopropilo--
497	A29			--ciclopropilo--
498	A29			--ciclopropilo--
499	A29			--ciclopropilo--

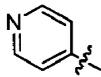
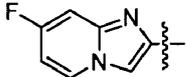
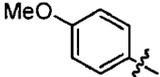
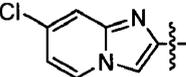
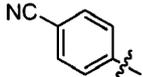
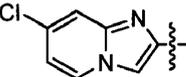
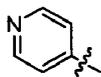
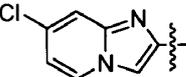
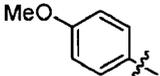
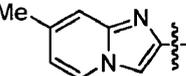
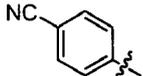
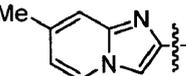
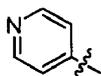
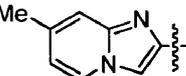
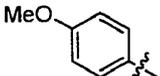
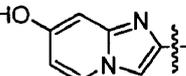
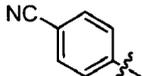
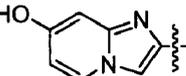
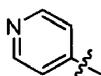
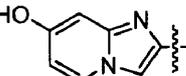
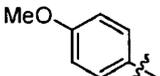
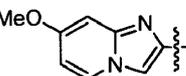
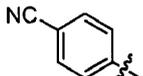
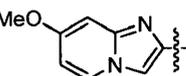
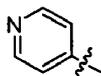
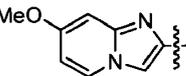
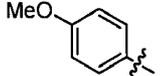
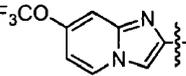
Núm. de Ejemplo	HET	X	Z	R ₂
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501	A29			--ciclopropilo-
502	A29			-ciclopropilo-
503	A29			-ciclopropilo-
504	A29			--ciclopropilo--
505	A29			-ciclopropilo-
506	A29			-ciclopropilo--
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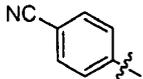
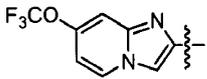
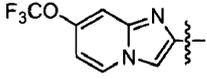
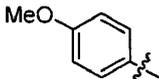
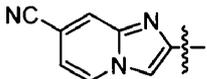
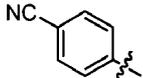
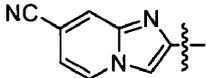
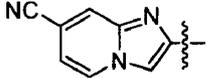
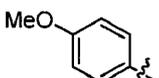
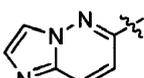
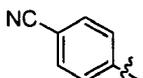
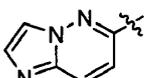
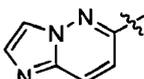
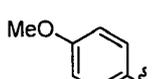
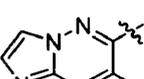
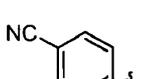
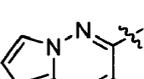
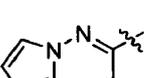
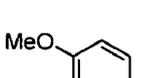
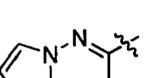
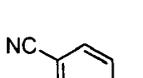
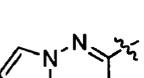
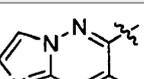
Núm. de Ejemplo	HET	X	Z	R ₂
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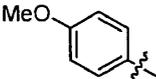
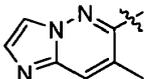
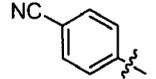
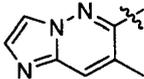
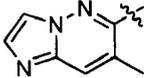
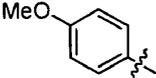
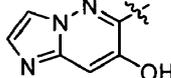
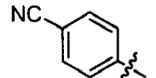
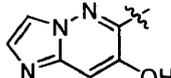
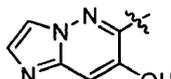
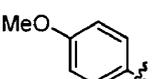
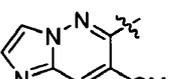
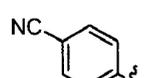
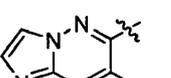
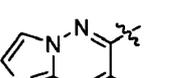
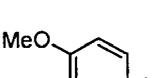
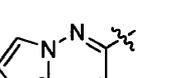
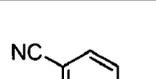
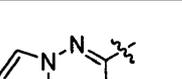
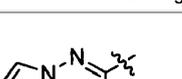
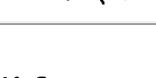
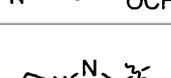
Núm. de Ejemplo	HET	X	Z	R ₂
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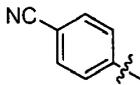
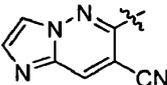
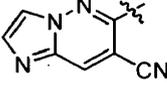
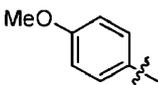
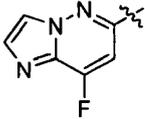
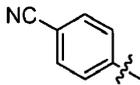
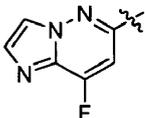
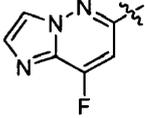
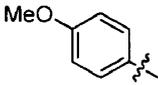
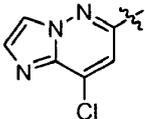
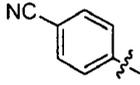
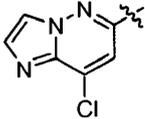
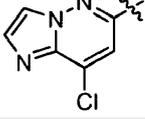
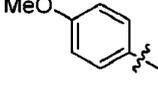
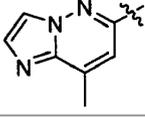
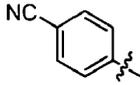
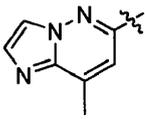
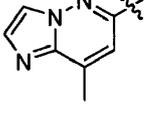
Núm. de Ejemplo	HET	X	Z	R ₂
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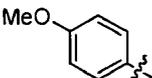
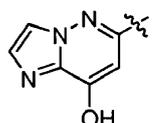
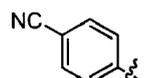
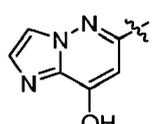
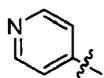
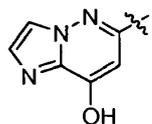
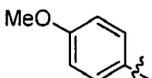
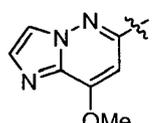
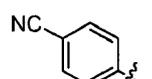
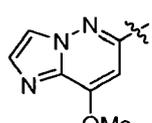
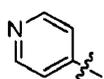
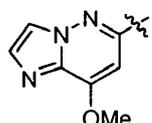
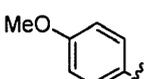
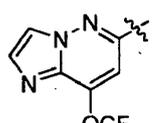
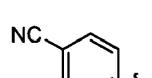
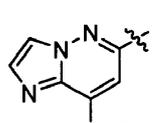
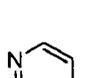
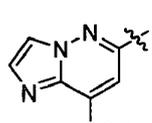
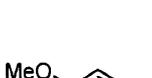
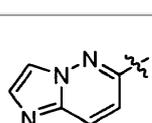
Núm. de Ejemplo	HET	X	Z	R ₂
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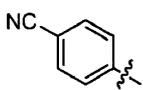
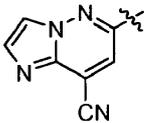
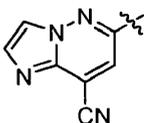
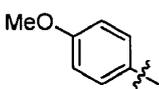
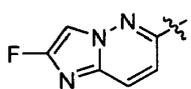
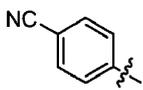
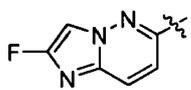
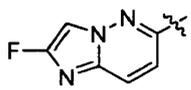
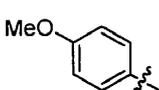
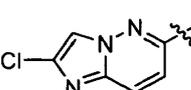
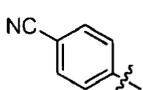
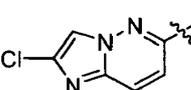
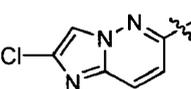
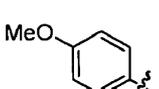
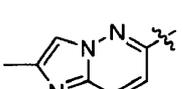
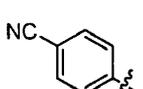
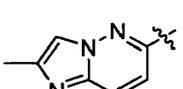
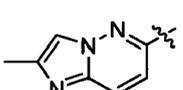
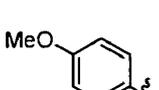
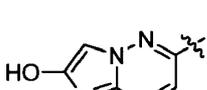
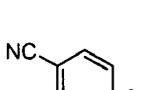
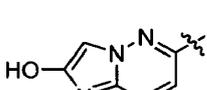
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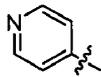
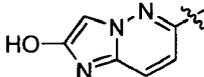
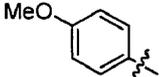
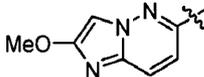
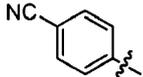
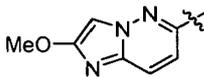
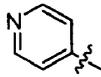
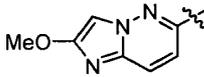
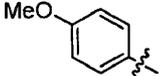
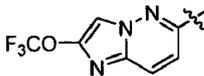
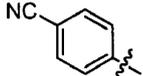
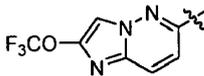
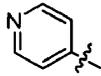
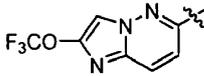
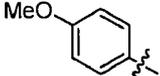
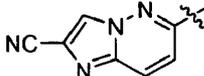
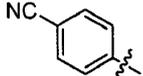
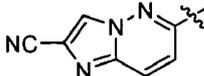
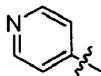
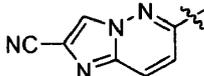
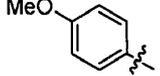
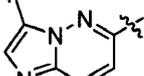
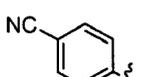
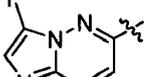
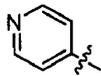
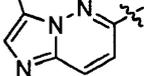
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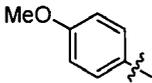
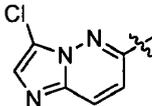
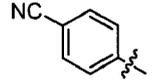
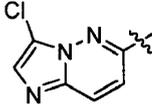
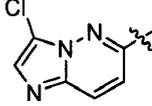
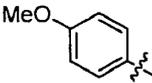
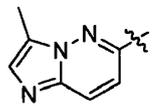
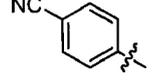
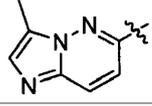
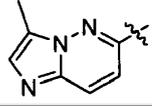
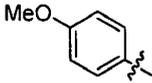
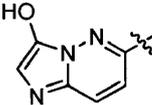
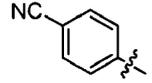
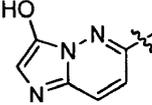
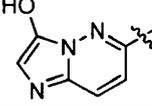
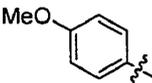
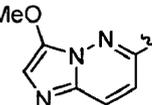
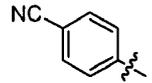
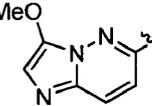
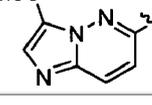
Núm. de Ejemplo	HET	X	Z	R ₂
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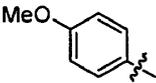
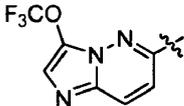
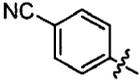
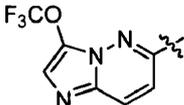
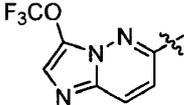
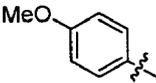
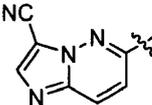
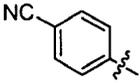
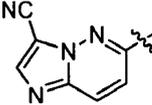
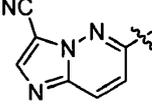
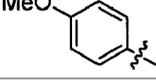
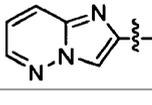
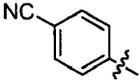
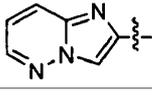
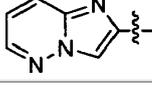
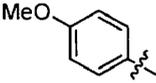
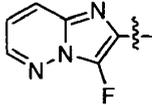
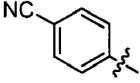
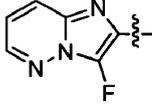
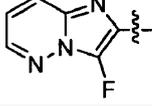
Núm. de Ejemplo	HET	X	Z	R ₂
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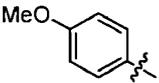
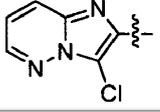
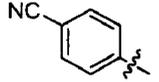
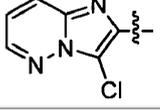
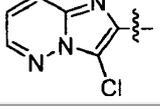
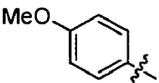
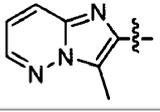
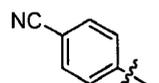
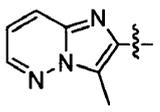
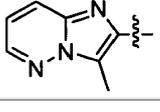
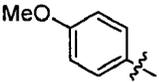
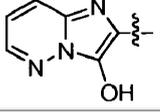
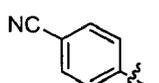
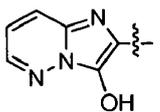
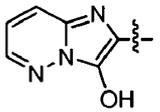
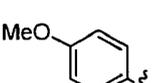
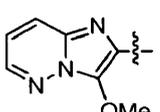
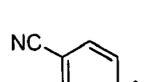
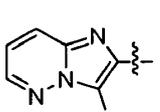
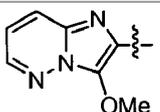
Núm. de Ejemplo	HET	X	Z	R ₂
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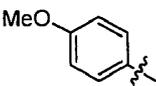
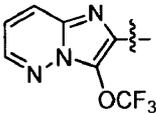
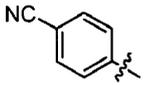
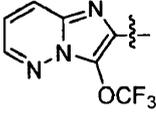
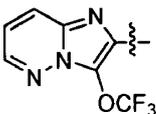
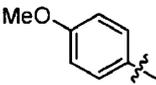
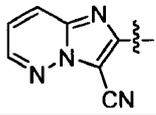
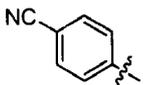
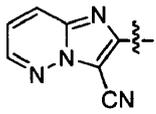
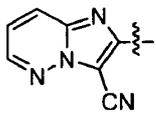
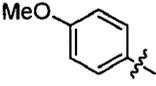
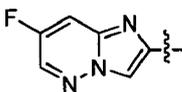
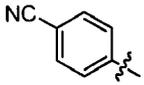
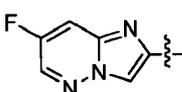
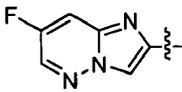
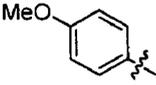
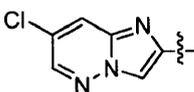
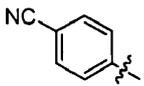
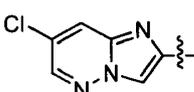
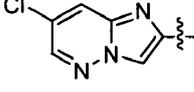
Núm. de Ejemplo	HET	X	Z	R ₂
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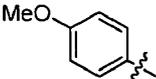
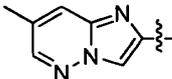
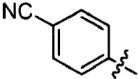
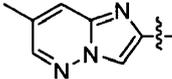
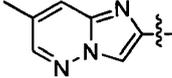
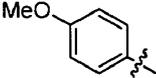
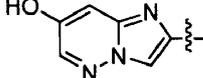
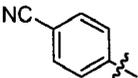
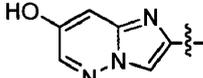
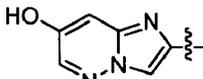
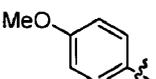
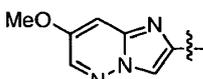
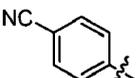
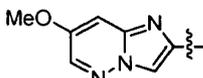
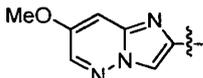
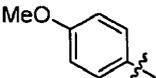
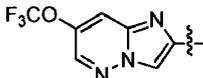
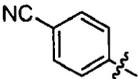
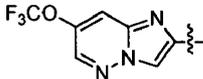
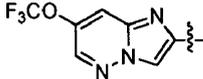
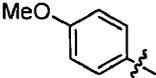
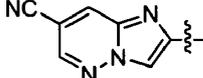
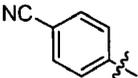
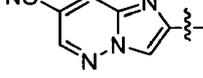
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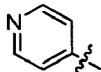
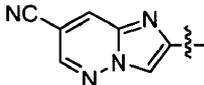
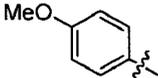
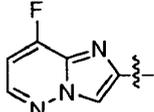
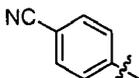
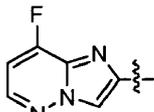
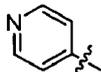
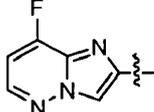
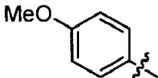
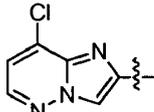
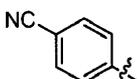
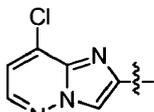
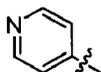
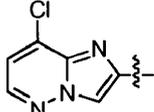
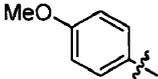
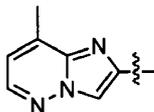
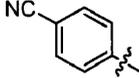
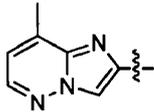
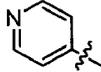
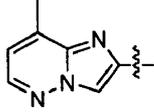
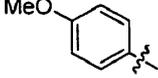
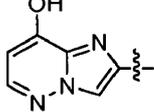
Núm. de Ejemplo	HET	X	Z	R ₂
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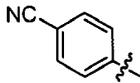
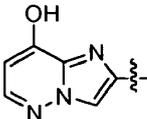
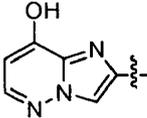
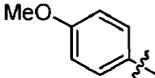
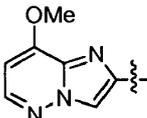
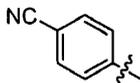
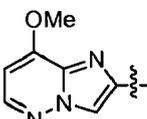
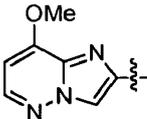
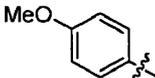
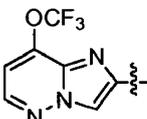
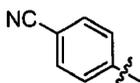
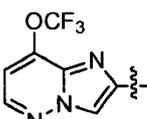
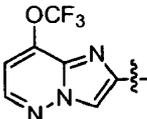
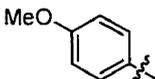
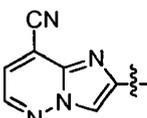
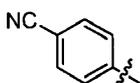
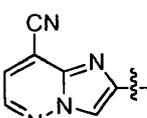
Núm. de Ejemplo	HET	X	Z	R ₂
661	A29			--ciclopropilo--
662	A29			--ciclopropilo--
663	A29			-ciclopropilo-
664	A29			-ciclopropilo-
665	A29			--ciclopropilo--
666	A29			--ciclopropilo--
667	A29			-ciclopropilo-
668	A29			--ciclopropilo--
669	A29			-ciclopropilo-
670	A29			--ciclopropilo--
671	A29			--ciclopropilo--
672	A29			-ciclopropilo-

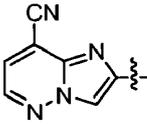
Núm. de Ejemplo	HET	X	Z	R ₂
673	A29			-ciclopropilo-
674	A29			-ciclopropilo--
675	A29			-ciclopropilo--
676	A29			--ciclopropilo--
677	A29			--ciclopropilo--
678	A29			-ciclopropilo-
679	A29			--ciclopropilo--
680	A29			-ciclopropilo-
681	A29			--ciclopropilo--
682	A29			--ciclopropilo--
683	A29			-ciclopropilo-
684	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
685	A29			--ciclopropilo--
686	A29			--ciclopropilo--
687	A29			--ciclopropilo--
688	A29			--ciclopropilo--
689	A29			--ciclopropilo--
690	A29			--ciclopropilo--
691	A29			--ciclopropilo--
692	A29			--ciclopropilo--
693	A29			--ciclopropilo--
694	A29			--ciclopropilo--
695	A29			--ciclopropilo--
696	A29			--ciclopropilo--

Núm. de Ejemplo	HET	X	Z	R ₂
697	A29			--ciclopropilo--
698	A29			-ciclopropilo-
699	A29			--ciclopropilo--
700	A29			--ciclopropilo--
701	A29			--ciclopropilo--
702	A29			--ciclopropilo--
703	A29			--ciclopropilo--
704	A29			--ciclopropilo--
705	A29			--ciclopropilo--
706	A29			--ciclopropilo--
707	A29			--ciclopropilo--
708	A29			--ciclopropilo--
709	A29			--ciclopropilo--
710	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
711	A29			--ciclopropilo-
712	A29			-ciclopropilo-
713	A29			-ciclopropilo-
714	A29			-ciclopropilo-
715	A29			--ciclopropilo--
716	A29			--ciclopropilo--
717	A29			--ciclopropilo--
718	A29			--ciclopropilo--
719	A29			--ciclopropilo--
720	A29			--ciclopropilo--
721	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
722	A29			-ciclopropilo-
723	A29			--ciclopropilo--
724	A29			--ciclopropilo--
725	A29			--ciclopropilo--
726	A29			--ciclopropilo--
727	A29			--ciclopropilo--
728	A29			-ciclopropilo-
729	A29			--ciclopropilo--
730	A29			--ciclopropilo--
731	A29			-ciclopropilo-

Núm. de Ejemplo	HET	X	Z	R ₂
732	A29			--ciclopropilo--

en donde si un ejemplo específico contiene múltiples casos de R₂, estos se separarán por medio de comas en la Tabla (p. ej. Me, Me o Et, Me) y en donde si la columna de R₂ contiene un valor "--grupo--" p. ej. "--ciclopropilo--", en ese caso ambos valores de R₂ se toman juntos para constituir un anillo espiro.

- 5
19. Un compuesto de acuerdo con la reivindicación 1, que es 4-(4-(imidazo[1,2-b]piridazin-2-ilmetoxi)fenil)-2,2-dimetil-5-(piridin-4-il)furan-3(2H)-ona o una de sus sales farmacéuticamente aceptables.
- 10
20. Una composición farmacéutica que comprende: (i) el compuesto de una cualquiera de las reivindicaciones 1-19 o una de sus sales farmacéuticamente aceptables; y (ii) un portador o excipiente farmacéuticamente aceptable.
- 15
21. Una composición farmacéutica de acuerdo con la reivindicación 20 para su uso en el tratamiento de: un trastorno del SNC; trastornos alimentarios; obesidad; ludopatía compulsiva; trastornos sexuales; narcolepsia; trastornos del sueño; diabetes; síndrome metabólico; esquizofrenia; afecciones esquizo-afectivas; enfermedad de Huntington; trastornos bipolares; afecciones distónicas; o discinesia tardía en un ser humano que lo necesite; o para su uso en el tratamiento de la cesación del hábito de fumar en un ser humano que lo necesite.
- 20
22. Una composición farmacéutica para su uso de acuerdo con la reivindicación 21, en donde la composición es para su uso en el tratamiento de la esquizofrenia o las afecciones esquizo-afectivas.
- 25
23. Una composición farmacéutica para su uso de acuerdo con la reivindicación 21, en donde la composición es para su uso en el tratamiento de la enfermedad de Huntington.
24. Una composición farmacéutica para su uso de acuerdo con la reivindicación 21, en donde la composición es para su uso en el tratamiento de la obesidad o el síndrome metabólico.
- 30
25. Una composición farmacéutica para su uso de acuerdo con la reivindicación 21, en donde la composición es para su uso en el tratamiento de los trastornos bipolares.