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DESCRIPCIÓN

Compuesto heterocíclico

5 **Campo técnico**

La presente invención se refiere a un compuesto heterocíclico que es útil como principio activo de una composición farmacéutica, por ejemplo, una composición farmacéutica para la prevención y/o tratamiento de enfermedades relacionadas con fosfatidilinositol-3-cinasa δ (PI3K δ).

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Técnica anterior

La fosfatidilinositol-3-cinasa (PI3K) es una cinasa de señalización de lípidos, que está presente de forma universal en todas las especies, que varía de plantas o levaduras a mamíferos incluyendo seres humanos. La PI3K es una enzima para fosforilar el grupo hidroxilo en la posición 3 de fosfatidilinositol, fosfatidilinositol-4-fosfato, y fosfatidilinositol-4,5-difosfato, que son fosfolípidos de membrana celular, y a partir de cada uno de estos sustratos, se producen fosfatidilinositol-3-fosfato, fosfatidilinositol-3,4-difosfato, y fosfatidilinositol-3,4,5-trifosfato (PIP3). Estos fosfatidilinositales fosforilados así producidos actúan como un segundo mensajero intracelular. En particular, el PIP3 provoca la migración de diversas moléculas que tienen dominios de homología a pleckstrina (PH) hasta una posición próxima a la membrana celular para inducir la activación de las moléculas y, por tanto, se considera que es el fosfatidilinositol fosforilado más importante ("The Journal of Biological Chemistry", 1999, Vol. 274, pág. 8347-8350).

La PI3K se divide en tres clases, las clases I, II y III, de acuerdo con varias características, y desde el punto de vista de que la única enzima que produce PIP3 *in vivo* es PI3K de clase I, se considera que la PI3K de clase I es la clase más importante ("Biochimica et Biophysica Acta", 2008, Vol. 1784, pág. 159-185). La PI3K de clase I se subdivide en IA y IB. La PI3K de clase IA consiste en heterodímeros que incluyen una combinación de una subunidad catalítica de 110 kDa (p110 α , β o δ) y una subunidad reguladora de 50 a 85 kDa (p85 α , p85 β , p55 α , p55 γ o p50 α), y la PI3K de clase IB es un heterodímero de una subunidad catalítica de 110 kDa (p110 γ) y una subunidad reguladora de 101 kDa (p101) ("Nature Immunology", 2003, N.º 4, pág. 313-319). A continuación en el presente documento, los respectivos nombres de PI3K se denominan PI3K α , β , δ y γ , correspondientes a las subunidades catalíticas incluidas en la misma.

PI3K α y β están ampliamente presentes en un cuerpo biológico y se ha informado de que la insuficiencia de PI3K α y β en ratones es mortal en fetos en ambos casos ("The Journal of Biological Chemistry", 1999, Vol. 274, pág. 10963-10968; y "Mammalian Genome", 2002, Vol. 13, pág. 169-172). Como resultado de los estudios usando compuestos selectivos de subtipo, se ha informado de que PI3K α desempeña un papel importante en la señalización de insulina y un inhibidor de PI3K α provoca resistencia a la insulina ("Cell", 2006, Vol. 125, pág. 733-747). Además, se ha informado de que PI3K β está implicada en la agregación plaquetaria y un inhibidor de PI3K β tiene un efecto antitrombótico ("Nature Medicine", 2005, Vol. 11, pág. 507-514). Por otra parte, los ratones deficientes en PI3K δ o γ nacen todos normalmente, y no se han descubierto problemas en relación con el crecimiento, la esperanza de vida, la reproducción, o similares ("Science", 2000, Vol. 287, pág. 1040-1046; y "Molecular and Cellular Biology", 2002, Vol. 22, pág. 8580-8591). En particular, la expresión de PI3K δ está significativamente limitada a hemocitos y tejidos linfáticos, y se ha descubierto que los ratones deficientes en PI3K δ tienen un daño significativo en la activación de linfocitos. Es bien conocida una estrecha relación entre la activación de linfocitos y la inmunidad/inflamación, y los compuestos que inhiben selectivamente PI3K δ tienen potencial para ser inhibidores de inmunidad/inflamación, teniendo tanto una potente acción inhibitora sobre la activación de linfocitos como seguridad.

La interleucina-2 (IL-2) es un tipo de citocina que se produce principalmente a partir de linfocitos T activados. La IL-2 induce la proliferación y la activación de linfocitos por medio de un receptor de IL-2 que es un receptor para IL-2. La IL-2 es una molécula muy importante en la señalización de la activación de un sistema inmunitario, y sus inhibidores de producción (por ejemplo, Tacrolimus y Ciclosporina A) se han usado clínicamente como agentes inmunosupresores. Además, se han usado clínicamente anticuerpos monoclonales anti-receptor de IL-2, tales como Basiliximab y Daclizumab, como agentes inmunosupresores.

Los linfocitos B son uno de los principales subconjuntos de linfocitos, junto con los linfocitos T, y son células que son un agente principal de la inmunidad humoral. Se sabe que la inmunidad humoral desempeña un papel extremadamente importante en la prevención de infección por patógenos o similares, pero en enfermedades autoinmunitarias tales como artritis reumatoide y similares, se produce activación anormal de la inmunidad humoral, que está profundamente implicada en la patogénesis. De hecho, un anticuerpo anti-CD20, Rituximab, se ha usado clínicamente como fármaco para el tratamiento de la artritis reumatoide.

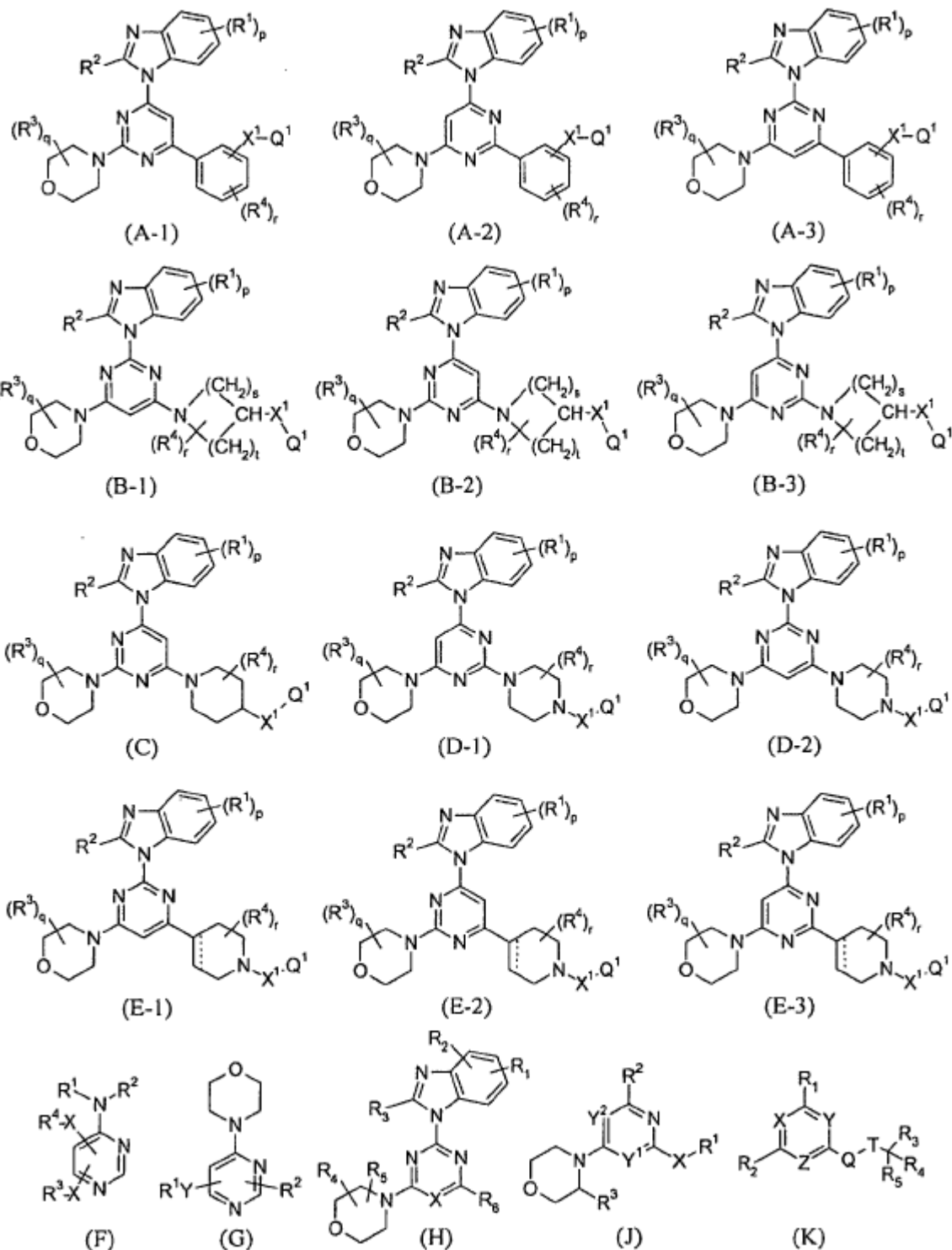
Como compuesto que tiene una acción inhibitora de PI3K, por ejemplo, se ha informado de los compuestos de fórmula (A-1) (documento de patente 1), fórmula (A-2) (documento de patente 2), fórmula (A-3) (documento de patente 3), fórmula (B-1) (documento de patente 4), fórmula (B-2) (documento de patente 5), fórmula (B-3) (documento de patente 6), fórmula (C) (documento de patente 7), fórmula (D-1) (documento de patente 8), fórmula (D-2) (documento de patente 9), fórmula (E-1) (documento de patente 10), fórmula (E-2) (documento de patente 11),

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fórmula (E-3) (documento de patente 12), fórmula (F) (documento de patente 13), fórmula (G) (documento de patente 14), fórmula (H) (documento de patente 15 y documento distinto de patente 1), fórmula (J) (documento de patente 16) y fórmula (K) (documento de patente 17) descritos a continuación. Sin embargo, el compuesto de fórmula (I) de la presente solicitud, como se describe posteriormente, es diferente en la estructura del grupo R¹ de la fórmula (I) de los compuestos de fórmulas (A-1) a (E-3), (H) y (K). Es diferente en estructura de los compuestos de fórmulas (F) y (G), en cuanto que tiene un grupo benzimidazolil-1-ilo. Como grupo R² de fórmula (J), se ha divulgado un grupo heteroarilo, pero no existe ninguna divulgación específica del grupo benzimidazolil-1-ilo, y no existe ninguna divulgación del compuesto de fórmula (I) de la presente invención en el documento de patente 16. Además, no existe ninguna descripción de una acción inhibitoria selectiva de PI3Kδ en ningún documento.

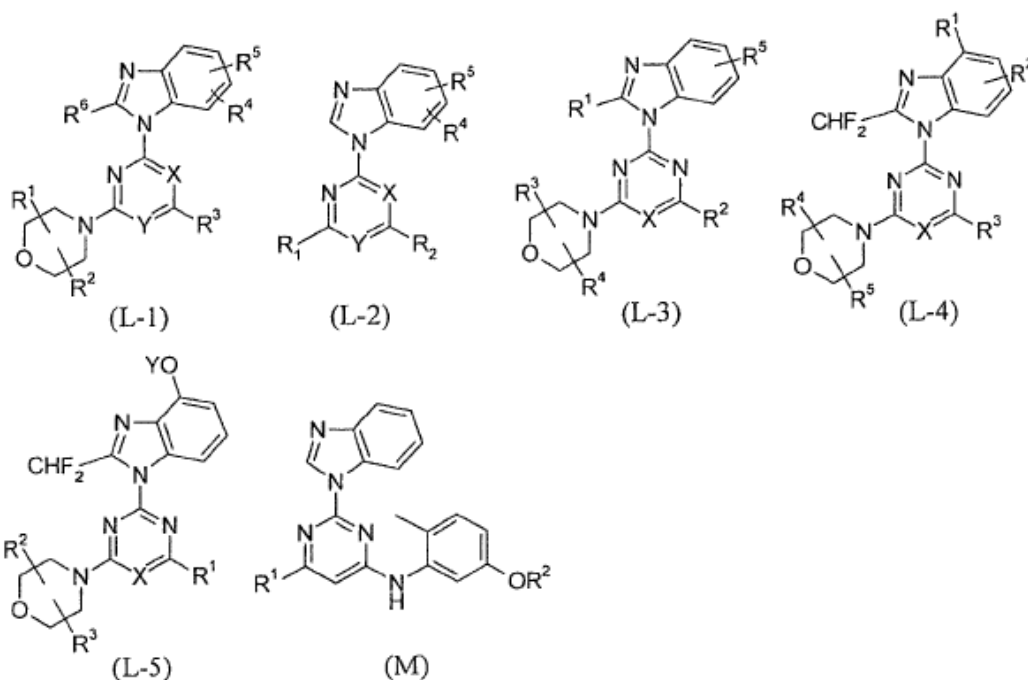
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(en las que R² en las fórmulas (A-1) a (E-3) representa un grupo difluorometilo o similares. R¹ y R² en la fórmula (F) se combinan entre sí para formar un grupo morfolino no sustituido o sustituido, junto con el N al que están unidos, X representa un enlace o similares, y R³ representa un grupo indolilo no sustituido o sustituido. R² en la fórmula (G) representa un grupo indol-4-ilo sustituido en la posición 5 o 6. R³ en la fórmula (H) representa un grupo difluorometilo o similares, y R⁶ representa un grupo morfolino que puede estar sustituido, o similares. En la fórmula (J), Y¹ e Y² representan N, CH, o similares, X representa NR⁴CR⁶R⁷ o similares, R¹ representa un grupo heterocíclico o similares, y R² representa un grupo heteroarilo o similares. En la fórmula (K), X, Y y Z representan N o CH, con la condición de que al menos dos de X, Y y Z representen N, R¹ representa heteroarilo o similares, R² representa un heterociclo o similares, Q representa un enlace, azetidinenil-4-amino, o similares, T representa -C(O)-, -C(=S)- o -S(O)₂-, y R⁵ representa halógeno o -O-S(O)₂-R⁷. Para las demás símbolos, se puede hacer referencia a la publicación).

Se ha informado de que los compuestos de fórmula (L-1) (documento de patente 18), fórmula (L-2) (documento de patente 19), fórmula (L-3) (documento de patente 20), fórmula (L-4) (documento de patente 21), y fórmula (L-5) (documento de patente 22), descritos a continuación, tienen una actividad antitumoral. Además, en el documento distinto de patente 2, se ha sugerido que un compuesto de amina secundaria de fórmula (M) tiene una acción inhibidora de Lck y una acción inhibidora de la producción de IL-2, y se aplica para enfermedades autoinmunitarias y reacción de rechazo en trasplante de órganos. Sin embargo, el compuesto de fórmula (I) de la presente invención tiene esencialmente un grupo difluorometilo, que es diferente en la estructura de los compuestos de fórmulas (L-1), (L-2) y (M). También es diferente en la estructura del grupo de R¹ de la fórmula (I) de los compuestos de fórmulas (L-3) y (L-5). Además, es diferente en la estructura del sustituyente en un anillo benzimidazol del compuesto de fórmulas (L-4). Además, no existe ninguna descripción de una acción inhibidora selectiva de PI3Kδ en la literatura.



(en la fórmula (L-1), tanto X como Y representan N, o uno de X e Y representa N y el otro representa CR⁷, y R⁶ representa H o alquilo C₁₋₆; en la fórmula (L-2), tanto X como Y representan N, o uno de X e Y representa N y el otro representa CR³, y R¹ representa un grupo morfolino o similares; en la fórmula (L-3), X representa N o CH, R¹ representa CH_nF_{3-n} (n es 1 o 2), y R² representa morfolino que puede estar sustituido, o similares; en la fórmula (L-4), X representa N o CH, y R¹ representa halógeno o un grupo hidroxilo; en la fórmula (L-5), X representa N o CH, R¹ representa un grupo morfolino que puede estar sustituido con 1 a 4 grupos alquilo C₁₋₆, e Y representa alquilo C₁₋₆; y en la fórmula (M), R¹ representa un grupo morfolino o similares. Para las demás símbolos, se puede hacer referencia a la publicación).

Además, se ha informado de un derivado de quinazolin-4-ona (documentos de patente 23 a 25) como inhibidor selectivo de PI3Kδ, y se indica su utilidad en inflamación, enfermedades inmunitarias o tumores hemáticos (leucemia y similares). Como otros inhibidores selectivos de PI3Kδ, se ha informado de un derivado de tiazolilurea (documento de patente 26) junto con su utilidad en inflamación, enfermedades inmunitarias, o similares.

Además, la invención que se refiere a un derivado de triazina o pirimidina que tiene una acción inhibidora selectiva de PI3Kδ, que es una invención en la técnica anterior por los autores de la presente invención, se ha divulgado

después de la fecha de prioridad de la presente solicitud (documento de patente 27). El compuesto de la presente invención es diferente en la estructura del grupo R¹ en la fórmula (I) del compuesto divulgado en la solicitud anterior.

Técnica relacionada

5 Documentos de patente

[Documento de patente 1] Folleto de la publicación internacional WO 2008/032027

10 [Documento de patente 2] Folleto de la publicación internacional WO 2008/032077

[Documento de patente 3] Folleto de la publicación internacional WO 2008/032086

[Documento de patente 4] Folleto de la publicación internacional WO 2008/032028

15 [Documento de patente 5] Folleto de la publicación internacional WO 2008/032036

[Documento de patente 6] Folleto de la publicación internacional WO 2008/032041

20 [Documento de patente 7] Folleto de la publicación internacional WO 2008/032033

[Documento de patente 8] Folleto de la publicación internacional WO 2008/032060

[Documento de patente 9] Folleto de la publicación internacional WO 2008/032064

25 [Documento de patente 10] Folleto de la publicación internacional WO 2008/032072

[Documento de patente 11] Folleto de la publicación internacional WO 2008/032089

30 [Documento de patente 12] Folleto de la publicación internacional WO 2008/032091

[Documento de patente 13] Folleto de la publicación internacional WO 2007/042810

[Documento de patente 14] Folleto de la publicación internacional WO 2008/125839

35 [Documento de patente 15] Memoria descriptiva de la publicación de solicitud de patente europea n.º 1864665

[Documento de patente 16] Folleto de la publicación internacional WO 2009/007751

40 [Documento de patente 17] Folleto de la publicación internacional WO 2009/120094

[Documento de patente 18] Memoria descriptiva de la publicación de solicitud de patente europea n.º 1020462

[Documento de patente 19] Publicación internacional WO 00/43385

45 [Documento de patente 20] Folleto de la publicación de solicitud de patente europea n.º 1389617

[Documento de patente 21] Folleto de la publicación de solicitud de patente europea n.º 1557415

50 [Documento de patente 22] Folleto de la publicación de solicitud de patente europea n.º 1741714

[Documento de patente 23] Folleto de la publicación internacional WO 01/81346

[Documento de patente 24] Folleto de la publicación internacional WO 03/035075

55 [Documento de patente 25] Folleto de la publicación internacional WO 2005/113556

[Documento de patente 26] Folleto de la publicación internacional WO 2008/000421

60 [Documento de patente 27] Folleto de la publicación internacional WO 2010/092962

Documentos distintos de patente

[Documento distinto de patente 1] Journal of the National Cancer Institute, 2006, Vol. 98, pág. 545-556

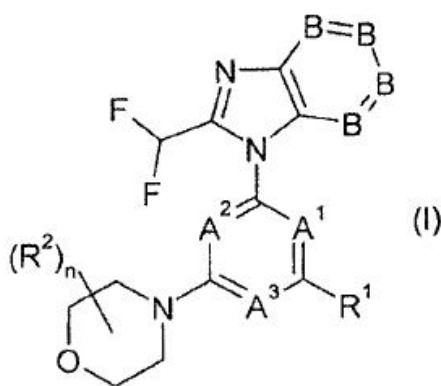
65 [Documento distinto de patente 2] Bioorganic & Medicinal Chemistry Letters, 2006, Vol. 16, pág. 5973-5977

Divulgación de la invención

5 La presente invención proporciona un compuesto de fórmula (I) o una sal del mismo, una composición farmacéutica que comprende el mismo, y el compuesto de fórmula (I) y su sal para su uso en un procedimiento para la prevención o el tratamiento de la reacción de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias o tumor hemático.

10 Los autores de la presente invención han estudiado extensamente una acción inhibitora selectiva de PI3Kδ y/o una acción inhibitora de la producción de IL-2 y/o una acción inhibitora de la proliferación de linfocitos B (incluyendo una acción inhibitora de la activación), y como resultado, han descubierto que un derivado novedoso de triazina o pirimidina tiene una excelente acción inhibitora selectiva de PI3Kδ y/o acción inhibitora de la producción de IL-2 y/o acción inhibitora de la proliferación de linfocitos B (incluyendo una acción inhibitora de la activación), y puede ser un agente para la prevención y/o tratamiento de las reacciones de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias y tumor hemático, completando así la presente invención.

15 Específicamente, la presente invención se refiere a un compuesto de fórmula (I) o una sal del mismo:



(en la que

20 A² y A³ son N y A¹ es CH o A¹ y A³ son N y A² es CH,

todos los B son CH y n es 0,

25 R¹ es -L¹-L²-Y, en el que -L¹-L²- es -NH- u -O-,

Y es un heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo D1, y el grupo D1 consiste en:

30 (1) -L^{5a}-(heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado, -NH-C(O)-O-[alquilo C₁₋₆ lineal o ramificado], -C(O)O-[alquilo C₁₋₆ lineal o ramificado], -C(O)-[alquilo C₁₋₆ lineal o ramificado], y oxo), en el que L^{5a} representa un enlace, -C(O)-[alquileno C₁₋₆ lineal o ramificado-], o -C(O)-, y

35 (2) -C(O)-(cicloalquilo que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado que puede estar sustituido con -OH, -OH y -O-[alquilo C₁₋₆ lineal o ramificado]).

40 A menos que se especifique lo contrario, en el caso en el que los símbolos de las fórmulas químicas en la presente memoria descriptiva se usen también en otras fórmulas químicas, los mismos símbolos indicarán los mismos significados.

Además, la presente invención se refiere a una composición farmacéutica que comprende el compuesto de fórmula (I) o una sal del mismo como principio activo. El compuesto de fórmula (I) o su sal es útil para la prevención y/o tratamiento de las reacciones de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias y tumor hemático. En un determinado modo de realización, la presente invención se refiere al compuesto de fórmula (I) o su sal para su uso en un procedimiento para la prevención y/o tratamiento de las reacciones de rechazo en trasplantes de riñón, hígado y corazón, en otro modo de realización para la prevención y/o tratamiento del rechazo crónico y rechazo agudo, y aún en otro modo de realización, para la prevención y/o tratamiento de rechazo relacionado con anticuerpos.

50 El procedimiento para la prevención o tratamiento de las reacciones de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias y tumores hemáticos incluye administrar a un sujeto una

cantidad eficaz del compuesto de fórmula (I) o una sal del mismo. Aquí, el "sujeto" es un ser humano o cualquier otro animal en necesidad de prevención o tratamiento del mismo, y en un determinado modo de realización, un ser humano en necesidad de prevención o tratamiento del mismo.

5 Efectos de la invención

El compuesto de fórmula (I) tiene una acción inhibitoria selectiva de PI3K δ y/o una acción inhibitoria de la producción de IL-2 y/o una acción inhibitoria de la proliferación de linfocitos B (incluyendo una acción inhibitoria de la activación) y, por lo tanto, se puede usar como agente para la prevención o tratamiento de las reacciones de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias y tumor hemático.

Modos de realización para llevar a cabo la invención

15 A continuación en el presente documento, se describirá en detalle la presente invención.

El "alquilo inferior" es alquilo lineal o ramificado que tiene de 1 a 6 átomos de carbono (que se denomina a continuación en el presente documento simplemente como C₁₋₆), y ejemplos del mismo incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, terc-butilo, n-pentilo, n-hexilo, y similares. En otro modo de realización, la alquilo inferior es alquilo C₁₋₄, aún en otro modo de realización, metilo, etilo, o terc-butilo, y en otro modo de realización más, metilo.

El "alquenilo inferior" es alquenilo C₂₋₆ lineal o ramificado, y ejemplos del mismo incluyen vinilo, propenilo, butenilo, pentenilo, 1-metilvinilo, 1-metil-2-propenilo, 1,3-butadienilo, 1,3-pentadienilo, y similares. En otro modo de realización, el alquenilo inferior es alquenilo C₂₋₄, y aún en otro modo de realización, propenilo.

El "alquilenilo inferior" es un grupo divalente formado por la retirada de cualquier átomo de hidrógeno del "alquilo inferior". En consecuencia, el "alquilenilo C₁₋₆" es alquilenilo lineal o ramificado que tiene de 1 a 6 átomos de carbono, y ejemplos del mismo incluyen metileno, etileno, trimetileno, tetrametileno, pentametileno, hexametileno, dimetilmetileno, etilmetileno, metiletileno, dimetiletileno, etiletileno, y similares. En otro modo de realización, el alquilenilo inferior es metileno, etileno, y aún en otro modo de realización, metileno.

El "alquenileno inferior" es alquenileno C₂₋₆ lineal o ramificado, y ejemplos del mismo incluyen vinileno, etilideno, propenileno, butenileno, pentenileno, hexenileno, 1,3-butadienileno, 1,3-pentadienileno, y similares. En otro modo de realización, el alquenileno inferior es alquenileno C₂₋₄, y aún en otro modo de realización, propenileno.

El "alquinileno inferior" es alquinileno C₂₋₆ lineal o ramificado, y ejemplos del mismo incluyen etinileno, propinileno, butinileno, pentinileno, hexinileno, 1,3-butadiinileno, 1,3-pentadiinileno, y similares. En otro modo de realización, el alquinileno inferior es alquinileno C₂₋₄, y aún en otro modo de realización, propinileno.

El "halógeno" es F, Cl, Br o I, en otro modo de realización, F, y aún en otro modo de realización, Cl.

El "cicloalquilo" es grupo de anillo hidrocarburo saturado C₃₋₁₀, que puede tener un puente y se pueden combinar con un grupo heterocíclico no aromático para formar un anillo espiro. Ejemplos específicos de los mismos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclohexenilo, ciclooctilo, biciclo[3.3.0]octano, hexahidro-1'H-espiro-1,3-dioxano-2,2'-pentaleno, 1,4-dioxaspiro[4.5]decano, biciclo[2.2.2]octilo, adamantilo, azaespiro[5.5]undecanilo, octahidrociclopenta[c]pirrol, indanilo, y similares. En otro modo de realización, el cicloalquilo es ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, octahidropentaleno, biciclo[2.2.2]octilo, o adamantilo, aún en otro modo de realización, cicloalquilo C₃₋₈, en otro modo de realización más, cicloalquilo C₃₋₆, en otro modo de realización más, ciclohexilo, en otro modo de realización más, octahidropentaleno, y en otro modo de realización más, adamantilo.

El "arilo" es un grupo de anillo hidrocarburo aromático monocíclico a tricíclico C₆₋₁₄, y ejemplos del mismo incluyen fenilo, naftilo, y similares. En otro modo de realización, el arilo es fenilo.

El "heterociclo aromático" es un heterociclo aromático que tiene de 5 a 6 miembros de anillo, que contiene al menos un heteroátomo seleccionado de O, N y S como átomo constituyente del anillo, y puede estar condensado con un anillo benceno o un heterociclo aromático. Ejemplos del mismo incluyen piridilo, pirrolilo, pirazinilo, pirimidinilo, piridazinilo, imidazolilo, triazolilo, triazinilo, tetrazolilo, tiazolilo, pirazolilo, isotiazolilo, oxazolilo, isooxazolilo, tiadiazolilo, oxadiazolilo, tienilo, furilo, indolilo, isoindolilo, benzoimidazolilo, indazolilo, quinolilo, isoquinolilo, quinazolinilo, quinoxalinilo, ftalazinilo, benzotiazolilo, benzoisotiazolilo, benzotiadiazolilo, benzoxazolilo, benzoisoxazolilo, benzofuranilo, benzotienilo, carbazolilo, dibenzo[b,d]furanilo, dibenzo[b,d]tienilo, tienopiridilo, tienopirimidinilo, tienopirazilo, 1,4-benzodioxin-2-ilo, [1,2,4]triazolo[4,3-a]piridilo, imidazo[1,2-a]piridilo, y similares. En otro modo de realización, el heterociclo aromático es imidazolilo, piridilo, pirazinilo, indolilo, indazolilo, benzoimidazolilo o benzotiazolilo.

El "heterociclo no aromático" es un heterociclo no aromático que tiene de 4 a 8 miembros de anillo, que contiene al menos un heteroátomo seleccionado de O, N y S como átomo constituyente del anillo, que puede tener enlaces insaturados en una parte del anillo y puede estar unido por un puente. El heterociclo no aromático puede estar condensado con un anillo benceno o un heterociclo aromático. Además, el átomo de azufre que es un átomo constituyente del anillo puede estar oxidado. Ejemplos del heterociclo no aromático incluyen azetidino, pirrolidino, piperidino, piperazino, azepano, diazepano, morfolino, tiomorfolino, quinuclidino, 1,1-dioxidestiomorfolino, tetrahidropiridinilo, oxetano, tetrahidrofuranilo, tetrahidropirano, tetrahidrotienilo, 4,5-dihidrotiazolilo, dioxolanilo, dioxanilo, tetrahidrotiopirano, tetrahidroisoquinolilo, oxazolidinilo, tropano, 3,9-diazaespiro[5.5]undecano, 2,8-diazaespiro[4.5]decano, octahidropirrol[1,2-a]pirazilo, 5,6,7,8-tetrahidro-1,7-naftalidilo, 3,4-dihidro-2H-1,4-benzoxazinilo, 1,3-benzodioxolilo, cromo, 1,4-benzotiazinilo, 4,5-dihidro-1,3-tiazolilo, y similares. En otro modo de realización, el heterociclo no aromático es azetidino, pirrolidino, piperidino, piperazino, morfolino, tetrahidrofuranilo, tetrahidropirano o azepano, aún en otro modo de realización, pirrolidino, piperidino, tetrahidropirano o azepano, en otro modo de realización más, piperidino, y en otro modo de realización más, pirrolidino.

En la presente memoria descriptiva, la expresión "que puede estar sustituido" significa ninguna sustitución o sustitución con 1 a 5 sustituyentes. En un determinado modo de realización, es ninguna sustitución o sustituciones con 1 a 3 sustituyentes, en otro modo de realización, ninguna sustitución o sustitución con 1 sustituyente, y aún en otro modo de realización, ninguna sustitución. Además, en el caso de tener una pluralidad de sustituyentes, los sustituyentes pueden ser iguales o diferentes entre sí.

El grupo D1 consiste en:

(1) -L^{5a}-(heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado, -NH-C(O)-O-[alquilo C₁₋₆ lineal o ramificado], -C(O)O-[alquilo C₁₋₆ lineal o ramificado], -C(O)-[alquilo C₁₋₆ lineal o ramificado], y oxo), en el que L^{5a} representa un enlace, -C(O)-[alquilo C₁₋₆ lineal o ramificado-], o -C(O)-, y

(2) -C(O)-(cicloalquilo que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado que puede estar sustituido con -OH, -OH y -O-[alquilo C₁₋₆ lineal o ramificado]).

Preferentemente, D1 es -L^{5a}-(heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado, -C(O)O-[alquilo C₁₋₆ lineal o ramificado], -C(O)-[alquilo C₁₋₆ lineal o ramificado] y oxo), en el que L^{5a} representa un enlace o -C(O)-.

A¹ y A³ son N y A² es CH, o A² y A³ son N y A¹ es CH. En un modo de realización preferente, A² y A³ son N y A¹ es CH.

Todos los B son CH.

R¹ es -L¹-L²-Y, en el que -L¹-L²- es -NH- u -O-. En un modo de realización preferente, R¹ es -L¹-L²-Y, en el que -L¹-L²- es -NH-.

Y es un heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo D1. En un modo de realización preferente, Y es piperidino, pirrolidino o azetidino, que pueden estar sustituidos todos ellos con uno o más sustituyentes seleccionados del grupo D1.

n es 0.

La presente invención también engloba aquellos compuestos en los que se combinan dos cualesquiera o más de los modos de realización preferentes como se describe anteriormente.

[(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il)](2R)-tetrahidrofuran-2-il]metanona,

[(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il)](tetrahidro-2H-piran-4-il)metanona,
4-[(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il]carbonil]piperidin-1-carboxilato de metilo,

[(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxi)pirrolidin-1-il)](tetrahidrofuran-3-il)metanona,

4-[(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxi)pirrolidin-1-il]carbonil]-1-metilpirrolidin-2-ona,

[(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il)(tetrahidrofuran-3-il)metanona,

4-{{(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il}carbonil)-1-metilpirrolidin-2-ona,

4-{{3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)azetidín-1-il}carbonil)-1-metilpirrolidin-2-ona

10 El compuesto de fórmula (I) puede existir en forma de tautómeros o isómeros geométricos dependiendo del tipo de sustituyentes. En la presente memoria descriptiva, el compuesto de fórmula (I) se describirá en una sola forma de isómero, aunque la presente invención incluye otros isómeros, formas aisladas de los isómeros, o una mezcla de los mismos.

15 Además, el compuesto de fórmula (I) puede tener átomos de carbono asimétricos o asimetría axial en algunos casos, y consecuentemente, puede existir en forma de isómeros ópticos basados en la misma. La presente invención incluye tanto una forma aislada de los isómeros ópticos del compuesto de fórmula (I) como una mezcla de los mismos.

20 Además, la presente invención también incluye un profármaco farmacéuticamente aceptable del compuesto representado por la fórmula (I). El profármaco farmacéuticamente aceptable es un compuesto que tiene un grupo que se puede convertir en un grupo amino, un grupo hidroxilo, un grupo carboxilo, o similares a través de solvólisis o en condiciones fisiológicas. Ejemplos del grupo que forma el profármaco incluyen los grupos descritos en Prog. Med., 5, 2157-2161 (1985) y "Pharmaceutical Research and Development" (Hirokawa Publishing Company, 1990),
25 Vol. 7, Molecular Design, 163-198.

Además, la sal del compuesto de fórmula (I) puede formar una sal de adición de ácido o una sal con una base dependiendo del tipo de sustituyentes, y dichas sales están incluidas en la presente invención siempre que sean sales farmacéuticamente aceptables. Ejemplos específicos de las mismas incluyen sales de adición de ácido con
30 ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido nítrico, y ácido fosfórico, y con ácidos orgánicos tales como ácido fórmico, ácido acético, ácido propiónico, ácido oxálico, ácido malónico, ácido succínico, ácido fumárico, ácido maleico, ácido láctico, ácido málico, ácido mandélico, ácido tartárico, ácido dibenzoltartárico, ácido ditoluoiltartárico, ácido cítrico, ácido metanosulfónico, ácido etanosulfónico, ácido bencenosulfónico, ácido p-toluenosulfónico, ácido aspártico, y ácido glutámico, y sales con bases inorgánicas
35 tales como sodio, potasio, magnesio, calcio y aluminio, o bases orgánicas tales como metilamina, etilamina, etanolamina, lisina y ornitina, sales con diversos aminoácidos tales como acetileucina, y derivados de aminoácidos, así como sales de amonio.

40 Además, la presente invención también incluye varios hidratos o solvatos, y sustancias cristalinas polimórficas del compuesto de fórmula (I) y sales farmacéuticamente aceptables de los mismos. Además, la presente invención también incluye compuestos marcados con varios isótopos radiactivos o no radiactivos.

45 El "inhibidor selectivo de PI3K δ " significa un inhibidor que muestra una actividad potente, en el que la actividad inhibidora de PI3K δ es 10 veces o más, en otro modo de realización, 30 veces o más, y aún en otro modo de realización, 100 veces o más, la actividad inhibidora de PI3K α en términos del valor de CI₅₀.

(Procedimientos de preparación)

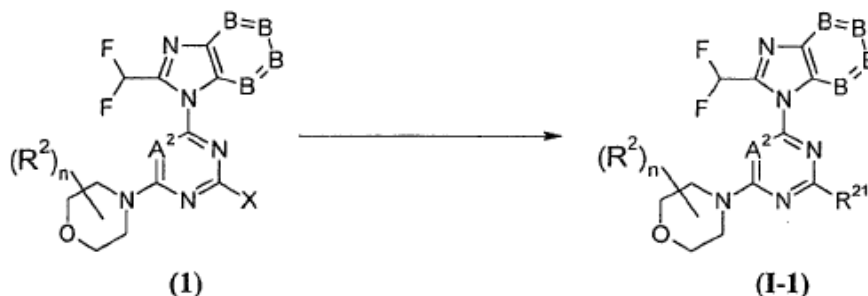
50 El compuesto de fórmula (I) y una sal farmacéuticamente aceptable del mismo se pueden preparar aplicando diversos procedimientos de síntesis conocidos en base a las características derivadas de su estructura básica o el tipo de sus sustituyentes. Durante la preparación, el reemplazo del grupo funcional relevante con un grupo protector adecuado (un grupo que se puede convertir fácilmente en el grupo funcional relevante) en la fase desde el material de partida hasta un intermedio puede ser eficaz dependiendo del tipo de grupo funcional en la tecnología de producción en algunos casos. Ejemplos de dicho grupo funcional incluyen un grupo amino, un grupo hidroxilo y un
55 grupo carboxilo, y dicho grupo protector para dicho grupo funcional puede incluir, por ejemplo, los grupos protectores descritos en Greene y Wuts, "Protective Groups in Organic Synthesis (3^a edición, 1999)", que se puede seleccionar y usar según sea apropiado, dependiendo de las condiciones de reacción. En dicho procedimiento, después de la introducción del grupo protector y una posterior reacción, el grupo protector se puede retirar, si fuera necesario, para obtener un compuesto deseado.

60 Además, se puede preparar el profármaco del compuesto de fórmula (I) introduciendo un grupo específico en la fase desde un material de partida hasta un intermedio, o llevando a cabo la reacción usando el compuesto de fórmula (I) obtenido, como en el caso del grupo protector mencionado anteriormente. La reacción se puede llevar a cabo usando procedimientos conocidos por los expertos en la técnica, tales como esterificación normal, amidación,
65 deshidratación, y similares.

A continuación en el presente documento, se describirán los procedimientos de preparación representativos para el compuesto de fórmula (I). Cada uno de los procedimientos de producción también se puede llevar a cabo con referencia a las referencias adjuntas a la presente descripción. Además, los procedimientos de preparación de la presente invención no se limitan a los ejemplos como se muestra a continuación.

5

(Procedimiento de producción 1)



10 (en el que X representa un grupo saliente, R²¹ representa -NH-alkileno inferior-C(O)-OH o -L¹-L²-Y, y L¹ representa -NR⁵-, -NR⁵-S(O)₂-, -NR⁵-C(O)-, -O-, -S- o -S(O)_m-. Lo mismo se debe aplicar a continuación en el presente documento).

15 El compuesto (I-1) de la presente invención se puede obtener por la reacción de sustitución ipso del compuesto (1) con, por ejemplo, -L¹-L²-Y.

Ejemplos del grupo saliente X incluyen grupos halógeno, metilsulfinilo, metilsulfonilo, y similares.

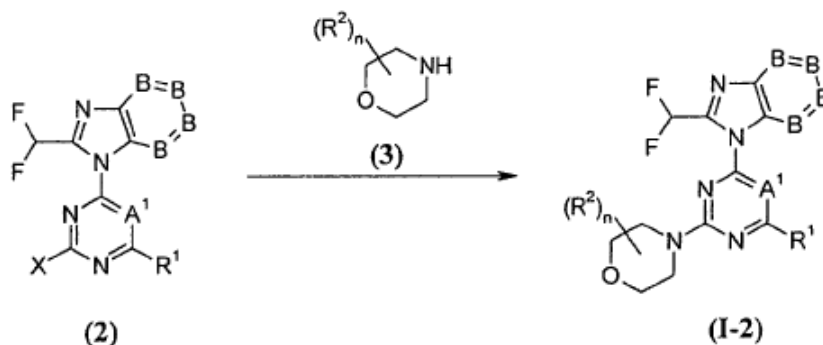
20 La presente reacción se lleva a cabo usando el compuesto (1) y, por ejemplo, un compuesto -L¹-L²-Y en cantidades equivalentes, o cualquiera de los mismos en una cantidad en exceso, y agitando una mezcla de los mismos en un disolvente que es inerte a la reacción, o en ausencia de un disolvente, en un intervalo desde enfriamiento hasta calentamiento y a reflujo, preferentemente de 0 °C a 100 °C, habitualmente durante de 0,1 horas a 5 días. Los ejemplos del disolvente usado en el presente documento no están particularmente limitados, pero incluyen hidrocarburos aromáticos tales como benceno, tolueno, xileno, y similares, éteres tales como éter dietílico, tetrahidrofurano, dioxano, dimetoxietano, y similares, hidrocarburos halogenados, tales como diclorometano, 1,2-dicloroetano, cloroformo, y similares, N,N-dimetilformamida, N,N-dimetilacetamida, dimetilsulfóxido, acetato de etilo, acetonitrilo, y una mezcla de los mismos. Es preferente en algunos casos, para el progreso suave de la reacción, usar bases orgánicas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, y similares, o bases inorgánicas tales como carbonato de potasio, carbonato de sodio, carbonato de cesio, hidróxido de potasio, y similares. Puede ser ventajoso en algunos casos, para el progreso suave de la reacción, llevar a cabo la reacción calentando la mezcla de reacción mediante irradiación de microondas.

[Documentos]

35 S. R. Sandler y W. Karo, "Organic Functional Group Preparations", 2^a edición, Vol. 1, Academic Press Inc., 1991

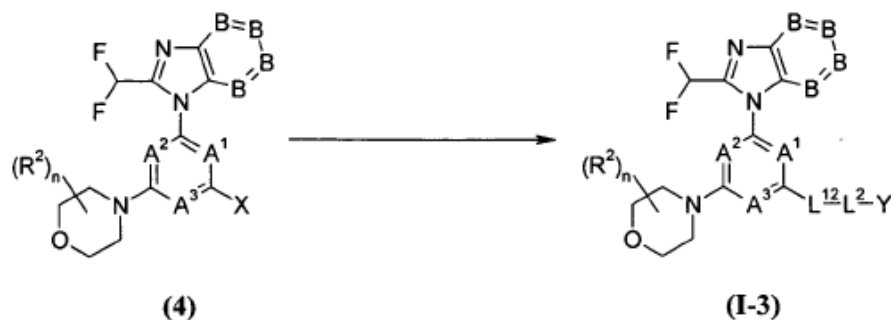
"Jikken Kagaku Koza (Courses in Experimental Chemistry) (5^a Edición) (Vol. 14)", editado por The Chemical Society de Japón, Maruzen, 2005

40 (Procedimiento de producción 2)



El compuesto de fórmula (I-2) se puede obtener por la reacción de un compuesto (2) y un compuesto (3). Las condiciones de reacción son las mismas que en el procedimiento de producción 1.

5 (Procedimiento de producción 3)



(en el que L¹² representa -alquíneno inferior.)

10 El compuesto (I-3) de la presente invención se pueden obtener por una reacción de acoplamiento de Sonogashira de un compuesto (4) y un derivado de alquino terminal.

Ejemplos del grupo saliente X incluyen halógeno, y similares.

15 La presente reacción se lleva a cabo usando el compuesto (4) y el derivado de alquino terminal en cantidades equivalentes, o cualquiera de los mismos en una cantidad en exceso, y agitando una mezcla de los mismos en un disolvente que es inerte a la reacción, en condiciones de temperatura que varían desde temperatura ambiente hasta calentamiento y a reflujo, habitualmente durante de 0,1 horas a 5 días, en presencia de una base y un catalizador de paladio. La presente reacción se lleva a cabo preferentemente en atmósfera de gas inerte. Los ejemplos del disolvente usado en el presente documento no están particularmente limitados, pero incluyen hidrocarburos aromáticos tales como benceno, tolueno, xileno, y similares, éteres tales como éter dietílico, tetrahidrofurano, dioxano, dimetoxietano, y similares, hidrocarburos halogenados tales como diclorometano, 1,2-dicloroetano, cloroformo, y similares, alcoholes tales como metanol, etanol, 2-propanol, butanol, y similares, N,N-dimetilformamida, dimetilsulfóxido, y un disolvente mezclado de los mismos. Como base, son preferentes bases inorgánicas tales como carbonato de potasio, carbonato de sodio, carbonato de cesio, hidróxido de potasio, y similares. Como catalizador de paladio, son preferentes tetraquis(trifenilfosfina)paladio, diclorobis(trifenilfosfina)paladio, cloruro de paladio-1,1'-bis(difenilfosfino)ferroceno, y similares. Además, puede ser ventajoso en algunos casos, para el progreso suave de la reacción, calentar la mezcla de reacción mediante irradiación de microondas.

30 [Documentos]

“Metal-Catalyzed Cross-Coupling Reactions”, editado por A. d. Meijere y F. Diederich, Vol. 1, VCH Publishers Inc., 1997

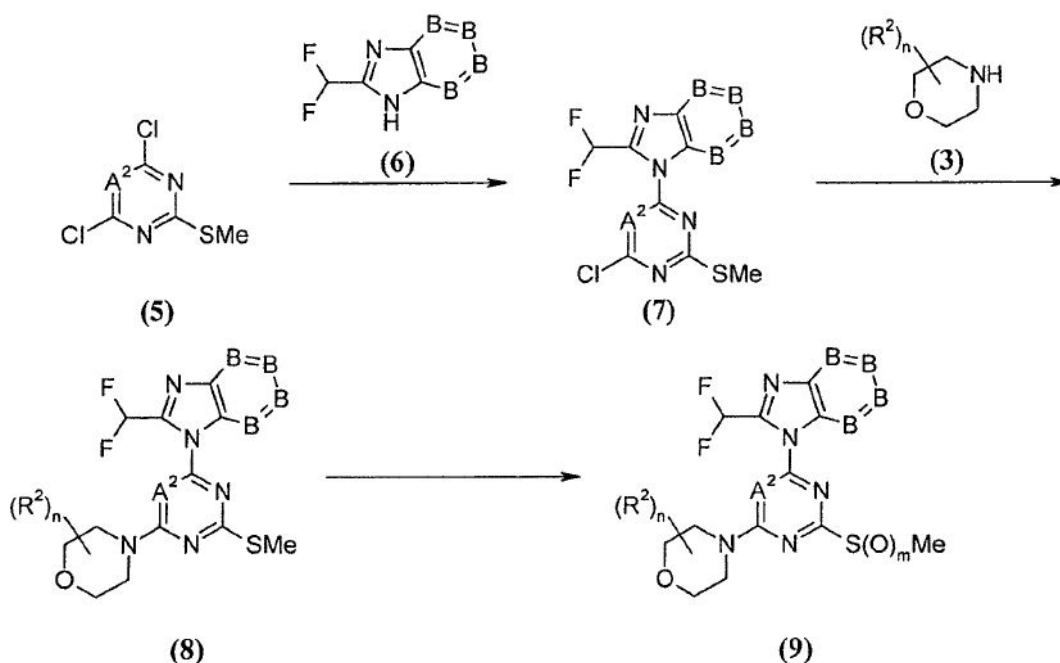
35 “Jikken Kagaku Koza (Courses in Experimental Chemistry) (5ª Edición)”, editado por The Chemical Society de Japón, Vol. 13 (2005) (Maruzen)

40 Varios sustituyentes en R¹ en el compuesto de fórmula (I) se pueden convertir fácilmente en otros grupos funcionales usando el compuesto de fórmula (I) como material de partida por medio de las reacciones descritas en los ejemplos como se describe posteriormente, las reacciones evidentes para un experto en la técnica, o procedimientos modificados de las mismas. Por ejemplo, las etapas que se pueden emplear normalmente por un experto en la técnica, tales como O-alkilación, N-alkilación, oxidación, reducción, alquilación reductora, formación de anillo, hidrólisis, amidación, acilación, desprotección, epoxilación, y similares, se pueden combinar y realizar arbitrariamente.

(Preparación del compuesto de partida)

50 En el procedimiento de preparación anterior, el compuesto de partida se puede preparar usando cualquiera de, por ejemplo, los siguientes procedimientos, los procedimientos descritos en los ejemplos de preparación como se describe posteriormente, procedimientos conocidos, o procedimientos modificados de los mismos.

(Síntesis 1 del material de partida)



El presente procedimiento de producción es un procedimiento para preparar un compuesto (9), en el que X es -S(O)_m-metilo en (1) que es el compuesto de partida en el procedimiento de producción 1.

5

Un compuesto (7) se puede obtener por la reacción de un compuesto (5) con un compuesto (6).

La condición de reacción es la misma que en el procedimiento de producción 1.

10

Un compuesto (8) se puede obtener por la reacción del compuesto (7) con el compuesto (3).

La condición de reacción es la misma que en el procedimiento de producción 1.

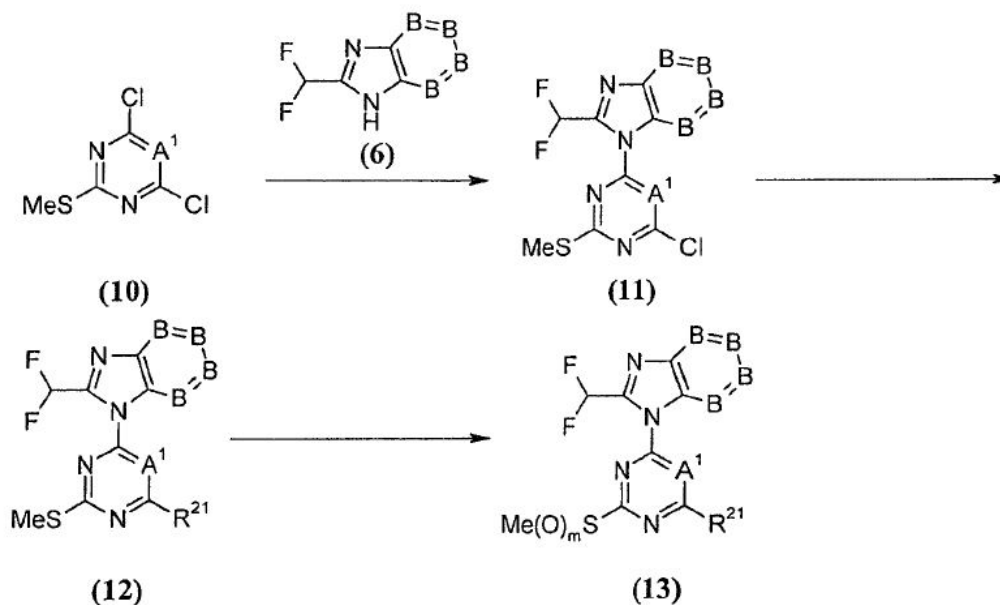
15

Un compuesto (9) se puede obtener por la reacción de oxidación del compuesto (8).

La presente reacción se puede llevar a cabo usando el compuesto (9) en una cantidad equivalente o una cantidad en exceso, en un intervalo desde de enfriamiento hasta calentamiento. Como disolvente, se pueden usar disolventes tales como hidrocarburos aromáticos e hidrocarburos halogenados por separado o en una mezcla de dos o más tipos de los mismos. Ejemplos del oxidante incluyen ácido m-cloroperbenzoico, ácido peracético, y una solución de peróxido de hidrógeno.

20

(Síntesis 2 del material de partida)



El presente procedimiento de producción es un procedimiento para preparar un compuesto (13), en el que X es -S(O)_m-metilo y R¹ es R²¹, en (2) que es el compuesto de partida en el procedimiento de producción 2.

- 5 Un compuesto (11) se puede obtener por la reacción del compuesto (10) con el compuesto (6).
- Las condiciones de reacción son las mismas que en el procedimiento de producción 1.
- 10 Un compuesto (12) se puede obtener por la reacción de sustitución ipso del compuesto (11) con, por ejemplo, -L¹-L²-Y.
- Las condiciones de reacción son las mismas que en el procedimiento de producción 1.
- 15 Un compuesto (13) se puede obtener por la reacción de oxidación del compuesto (12).
- Las condiciones de reacción son las mismas que en la reacción de oxidación descrita en síntesis 1 del material de partida.
- 20 Otros compuestos de partida (1), (2), y (4) se pueden preparar por, por ejemplo, los procedimientos descritos en los siguientes documentos: WO2002/088112, EP1389617, WO2008/032033, WO2008/032036, WO2008/032041 o WO2008/032060.
- 25 Los compuestos de fórmula (I) se pueden aislar y purificar como sus compuestos libres, sales farmacéuticamente aceptables, hidratos, solvatos o sustancias cristalinas polimórficas de los mismos. Las sales farmacéuticamente aceptables del compuesto de la fórmula (I) se pueden preparar llevando a cabo el tratamiento de una reacción de formación de sal convencional.
- 30 El aislamiento y la purificación se llevan a cabo empleando operaciones químicas normales tales como extracción, cristalización fraccionada, varios tipos de cromatografía fraccionada, y similares.
- 35 Se pueden preparar varios isómeros seleccionando un compuesto de partida apropiado o se pueden separar usando la diferencia en las propiedades fisicoquímicas entre los isómeros. Por ejemplo, los isómeros ópticos se pueden obtener por medio de un procedimiento general para el diseño de resolución óptica de racematos (por ejemplo, cristalización fraccionada para la inducción de sales diastereómeras con bases o ácidos ópticamente activos, cromatografía usando una columna quiral o similares, y otros) y, además, los isómeros también se pueden preparar a partir de un compuesto de partida ópticamente activo.
- 40 La actividad farmacológica del compuesto de fórmula (I) se confirmó mediante las pruebas mostradas a continuación.

1. Actividad inhibidora de la enzima PI3K δ

Para el experimento, se usaron un kit de ensayo HTRF de PI3-cinasa (Millipore Corporation, n.º de catálogo 33-016) y una enzima PI3K δ humana (Millipore Corporation, n.º de catálogo 14-604). El procedimiento de medición fue de acuerdo con las instrucciones adjuntas. La visión general del mismo es como sigue.

5 Se mezclaron PI3K δ (10 ng/pocillo), fosfatidilinositol-4,5-bisfosfato (10 μ M), ATP (30 μ M), y el compuesto de prueba en una placa de 384 pocillos (total 20 μ l), y se incubaron a temperatura ambiente durante 30 minutos. Se añadieron EDTA y fosfatidilinositol-3,4,5-trifosfato biotinilado a los mismos para detener la reacción. A continuación, se añadieron un anticuerpo anti-GST marcado con europio, un dominio PH de GRP1 unido a GST, y estreptavidina-APC a los mismos, seguido de incubación durante la noche. Se midió una proporción HTRF usando un lector de
10 placa HTRF. Se calculó el valor de CI₅₀ del compuesto, tomando la tasa de inhibición sin adición de la enzima como un 100 % y la tasa de inhibición sin adición de compuesto de prueba y con adición de una enzima como un 0 %, por medio de un procedimiento logístico.

2. Actividad inhibidora de la enzima PI3K α

15 Se mezclaron PI3K α humana (12 ng/pocillo, Millipore Corporation, n.º de catálogo 14-602), fosfatidilinositol (0,2 μ g/pocillo), y el compuesto de prueba en una placa de 384 pocillos en un tampón de reacción (Hepes 50 mM, NaCl 10 mM, MgCl₂ 10 mM, EGTA 2 mM, DTT 2 mM, pH 7,3) (total 10 μ l), y se incubaron a 37 °C durante 3 horas. Después de la reacción, se añadieron 10 μ l de un reactivo Kinase-Glo Plus (Promega, n.º de catálogo V3772) a los
20 mismos, y se midió una luminiscencia con un luminómetro. Se calculó el valor de CI₅₀ del compuesto, tomando la tasa de inhibición sin adición de la enzima como un 100 % y la tasa de inhibición sin adición de compuesto de prueba como un 0 %, mediante un procedimiento logístico.

25 Se muestran los resultados de los valores de CI₅₀ (nM) de varios compuestos representativos en la tabla 1. En la tabla, Ej representa el n.º de compuesto de ejemplo como se describe posteriormente de los compuestos de prueba.

[Tabla 1]

Ej	PI3K δ	PI3K α
1#	29	2800
4#	60	>3000
10#	5,8	>3000
13#	36	980
16#	69	>10000
18#	50	7700
20#	19	1800
25#	69	6200
28#	35	>3000
29#	45	>3000
30#	12	>3000
33#	11	>3000
34#	14	>3000
35#	18	4200
36#	17	6700
37#	20	1900
38#	23	2200
39#	27	3900
40#	20	>10000
43-1#	8	13000
43-2#	8,6	8000
44#	14	5000
45#	56	6800
67#	47	990
69#	22	10000

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Ej	PI3K δ	PI3K α
75#	25	5400
77#	18	5400
78#	8,5	2900
85#	21	5500
87#	4,9	>10000
99#	16	>10000
100#	5,7	>3000
120#	27	6400
121#	13	4900
123#	4,5	>3000
132#	12	>10000
133#	5,2	5900
134#	4,7	6600
135#	3,0	8000
136#	4,0	>10000
137#	5,2	>10000
158#	11	6700
193#	4,9	8200
194#	5,8	3300
195#	4,1	>10000
196#	4,8	>10000
215#	13	>10000
216#	13	>10000
224#	3,3	7300
248#	34	720
371#	35	5000
389#	11	>10000
423#	24	>10000
441#	48	1400
A4#	31	730
A290	7,4	3800
A293	19	3200
A298	28	3500
A299	26	4900
A300	26	6500
A449	20	1400
A451	35	2200
A463	27	3100
A464	10	2200
A466	15	2000
A475	25	1400
A561	14	2900
A564	19	3000
A567	11	1600

los compuestos marcados no están englobados en las reivindicaciones

3. Prueba de inhibición de la producción de IL-2 *in vivo* en rata

5 Para el experimento, se usaron ratas LEW/CrCrj macho (Charles River Laboratories, Japón, Inc.) (6 semanas de edad, peso corporal de 130 a 180 g). El compuesto de prueba se suspendió en una solución de metilcelulosa al 0,5 % y se administró por vía oral a 5 ml/kg. Se indujo la producción de IL-2 mediante inyección en la vena de la cola de concanavalina A (Funakoshi Corporation, n.º de catálogo L-1000) a una dosis de 15 mg/kg.

10 La prueba se llevó a cabo de acuerdo con el protocolo mostrado a continuación. A las 2 horas o 16 horas antes de la administración de concanavalina A, se administró por vía oral el compuesto de prueba a las ratas. A las 3 horas después de la administración de concanavalina A, se extrajo sangre. Se cuantificó la concentración de IL-2 en sangre usando un kit ELISA (R&D Systems, Inc., n.º de catálogo DY502E). Se calculó una tasa de inhibición a partir de la cantidad de IL-2 producida en un grupo al que se administró el compuesto de prueba con respecto a la cantidad de IL-2 producida en un grupo de control al que se administró un vehículo.

15 Como resultado, se confirmó que cuando se administraban los compuestos de prueba (10 mg/kg), por ejemplo, 2 horas antes de la administración de concanavalina A, los varios compuestos representativos de los ejemplos 10, 29, 33, 34, 37, 43-1 y A4 mostraban actividades inhibitoras de un 77 %, 51 %, 75 %, 72 %, 81 %, 73 % y 58 %, respectivamente, y tenían excelentes actividades inhibitoras de la producción de IL-2.

20 4. Prueba de inhibición de la proliferación de linfocitos B en rata

25 Se mezclaron células de bazo ($1,0 \times 10^5$ células/pocillo) preparadas a partir de ratas LEW/CrCrj macho (Charles River Laboratories, Japón, Inc.), fragmento F(ab')₂ de ratón anti-IgM de rata (3 µg/pocillo, SouthernBiotech Associates, Inc., n.º de catálogo 3082-14) y el compuesto de prueba disuelto en DMSO (concentración final de DMSO del 0,1 %) en una placa de 96 pocillos usando un medio de cultivo RPMI-1640 que contenía FCS al 10 % (total 200 µl). Se cultivaron en una incubadora de CO₂ durante 48 horas y se añadió [³H]timidina (925 GBq/mmol, Moravek Biochemicals, Inc., n.º de catálogo MT6038) a los mismos a 0,037 MBq/pocillo a las 4 horas antes de la finalización del cultivo. Se recogieron las células en un filtro de vidrio GF/C usando un recolector celular, y se midió una radiactividad en el filtro usando un contador de centelleo líquido. Se calculó el valor de CI₅₀ del compuesto, tomando la dpm (desintegración por minuto) sin adición de IgM como una tasa de inhibición de un 100 % y la dpm sin adición del compuesto de prueba como una tasa de inhibición de un 0 %, por un procedimiento logístico.

35 Se muestran los resultados de varios compuestos representativos en la tabla 2.

[Tabla 2]

Ej	CI ₅₀ (nM)
10#	2,9
36#	6,8
37#	1,52
38#	2,9
40#	9,0
43-1#	2,1
43-2#	3,1
85#	2,6
87#	3,5
99#	2,5
121#	2,0
132#	1,5
134#	3,4
135#	2,5
136#	1,7
137#	4,6
158#	10
193#	4,1
195#	3,0

Ej	CI ₅₀ (nM)
196#	3,6
215#	6,7
216#	5,7
224#	1,5
248#	1,4
389#	4,4
423#	3,1
441#	1,8
A290	2,2
A293	2,6
A298	1,2
A299	2,5
A300	2,6
A449	0,4
A451	1,2
A463	1,4
A466	1,8
A475	1,1
A561	3,9
A564	2,2
A567	1,8

los compuestos marcados no están englobados en las reivindicaciones

- 5 Como se muestra en las pruebas anteriores, se confirmó que varios compuestos representativos tienen excelente acción inhibitoria selectiva de PI3K δ , y/o acción inhibitoria de la producción de IL-2, y/o acción inhibitoria de la proliferación de linfocitos B (incluyendo una acción inhibitoria de la activación). En consecuencia, el compuesto de fórmula (I) se puede usar como un agente para la prevención o tratamiento de las reacciones de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias y/o tumor hemático.
- 10 Además, puesto que el compuesto de fórmula (I) es un inhibidor de PI3K δ que tiene una acción inhibitoria de PI3K δ significativamente potente que una acción inhibitoria de PI3K α , puede ser un excelente agente inmunosupresor que no provoca resistencia a la insulina basada en la acción inhibitoria de PI3K α .
- 15 Los varios tipos de órganos incluyen el riñón, el hígado y el corazón. La reacción de rechazo en un trasplante de órganos implica rechazo crónico y rechazo agudo, y su mecanismo está en gran medida clasificado en rechazo relacionado con anticuerpos y rechazo relacionado con linfocitos T. El compuesto de fórmula (I) o una sal del mismo es útil particularmente como un agente para la prevención y/o tratamiento de rechazo relacionado con anticuerpos.
- 20 Una composición farmacéutica que contiene uno o dos o más tipos del compuesto de fórmula (I) o una sal del mismo como principio activo se puede preparar usando excipientes que se usan normalmente en la técnica, es decir, excipientes para preparaciones farmacéuticas, vehículos para preparaciones farmacéuticas, y similares de acuerdo con los procedimientos usados normalmente.
- 25 La administración se puede lograr mediante administración oral a través de comprimidos, pastillas, cápsulas, gránulos, polvos, soluciones, o similares, o administración parenteral, tal como el uso de inyecciones tales como inyecciones intraarticulares, intravenosas e intramusculares, supositorios, colirios, pomadas oftálmicas, preparaciones líquidas transdérmicas, pomadas, parches transdérmicos, preparaciones líquidas transmucosa, parches transmucosa, inhaladores, y similares.
- 30 La composición sólida para su uso en la administración oral se usa en forma de comprimidos, polvos, gránulos, o similares. En dicha composición sólida, se mezcla uno o más principios activos con al menos un excipiente inactivo tal como lactosa, manitol, glucosa, hidroxipropilcelulosa, celulosa microcristalina, almidón, polivinilpirrolidona y/o aluminometasilicato de magnesio. En un procedimiento normal, la composición puede contener aditivos inactivos, tales como un lubricante tal como estearato de magnesio, un agente disgregante tal como carboximetilalmidón de

sodio, un estabilizante, o un agente auxiliar de solubilización. Si es necesario, los comprimidos o pastillas se pueden recubrir con azúcar o una película de una sustancia de recubrimiento gástrico-soluble o entérico.

5 La composición líquida para administración oral contiene emulsiones, soluciones, suspensiones, jarabes, elixires, o similares farmacéuticamente aceptables, y también contiene diluyentes inertes usados en general, por ejemplo, agua purificada y etanol. Además del diluyente inerte, la composición líquida también puede contener agentes auxiliares tales como un agente auxiliar de solubilización, un agente humectante, y un agente de suspensión, edulcorantes, saborizantes, agentes aromáticos o antisépticos.

10 Las inyecciones para administración parenteral incluyen soluciones acuosas o no acuosas, suspensiones y emulsiones estériles. El disolvente acuoso incluye, por ejemplo, agua destilada para inyección y solución salina fisiológica. Ejemplos del disolvente no acuoso incluyen propilenglicol, polietilenglicol, aceites vegetales tales como aceite de oliva, alcoholes tales como etanol, Polisorbato 80 (Farmacopea japonesa) y similares. Dicha composición puede contener además un agente de tonicidad, un antiséptico, un agente humectante, un agente emulsionante, un agente dispersante, un estabilizante o un agente auxiliar de solubilización. Estos se esterilizan, por ejemplo, mediante filtración a través de un filtro de retención de bacterias, combinación de un bactericida o irradiación. Además, estos también se pueden usar preparando una composición sólida estéril, y disolviéndola o suspendiéndola en agua estéril o un disolvente estéril para inyección antes de su uso.

20 El agente para uso externo incluye pomadas, escayolas, cremas, gelatinas, cataplasmas, pulverizaciones, lociones, colirios y pomadas oftálmicas. Los agentes contienen bases de pomada, bases de loción, preparaciones líquidas acuosas o no acuosas, suspensiones y emulsiones usadas en general. Ejemplos de bases de pomada o bases de loción incluyen polietilenglicol, propilenglicol, vaselina blanca, cera de abeja decolorada, aceite de ricino polioxietilenglicol, monoestearato de glicerilo, alcohol estearílico, alcohol cetílico, laurmacrogol y sesquioleato de sorbitán.

30 Como agentes transmucosa tales como un inhalador y un agente transnasal, se usan aquellos en forma de un estado sólido, líquido o semi-sólido, y se pueden preparar de acuerdo con un procedimiento conocido de forma convencional. Por ejemplo, pueden añadirse apropiadamente a los mismos un excipiente conocido, y también un agente de ajuste del pH, un antiséptico, un tensioactivo, un lubricante, un estabilizante, un agente espesante, o similares. Para su administración, se puede usar un dispositivo apropiado para inhalación o soplado. Por ejemplo, se puede administrar un compuesto solo o como un polvo de mezcla formulada, o como una solución o suspensión en combinación con un vehículo farmacéuticamente aceptable, usando un dispositivo conocido o pulverizador, tal como un dispositivo de inhalación de administración medida. Un inhalador de polvo seco o similares puede ser para un uso de administración individual o múltiple, y se puede usar un polvo seco o una cápsula que contiene polvo. De forma alternativa, este puede estar en una forma tal como una pulverización en aerosol presurizado que usa un propulsor apropiado, por ejemplo, un gas adecuado tal como clorofluoroalcano, hidrofuroalcano y dióxido de carbono.

40 Típicamente, en administración oral, la dosis diaria es apropiadamente desde aproximadamente 0,001 a 100 mg/kg, preferentemente desde 0,1 a 30 mg/kg, y más preferentemente desde 0,1 a 10 mg/kg de peso corporal, administrada en una porción o en de 2 a 4 porciones separadas. En el caso de administración intravenosa, la dosis diaria se administra adecuadamente desde aproximadamente 0,0001 a 10 mg/kg de peso corporal, una vez al día o dos o más veces al día. Además, un agente transmucosa se administra a una dosis de desde aproximadamente 0,001 a 100 mg/kg de peso corporal, una vez al día o dos o más veces al día. La dosis se decide apropiadamente en respuesta al caso individual teniendo en consideración los síntomas, la edad y el sexo, y similares.

50 Aunque varían dependiendo de las vías de administración, formas de dosificación, sitios de administración, o los tipos de excipientes y aditivos, la composición farmacéutica de la presente invención contiene de un 0,01 a un 100 % en peso, y en un determinado modo de realización, de un 0,01 a un 50 % en peso de uno o más tipos del compuesto de fórmula o una sal del mismo, que es un principio activo.

55 El compuesto de fórmula (I) se puede usar en combinación con varios agentes para el tratamiento o prevención de las enfermedades, en las que el compuesto de fórmula (I) se considera eficaz. En dicho uso en combinación, los fármacos se pueden administrar simultáneamente o por separado sucesivamente o a intervalos deseados de tiempo. Las formulaciones para administración simultánea pueden en forma mezclada o pueden tener formas separadas.

(Ejemplos)

60 A continuación en el presente documento, se describirán con más detalle los procedimientos de preparación para el compuesto de fórmula (I) y los compuestos de partida del mismo con referencia a los ejemplos, pero la presente invención no está limitada a los compuestos descritos en los ejemplos a continuación. Además, los procedimientos de producción para los compuestos de partida se describirán, cada uno, en los ejemplos de preparación. Además, los procedimientos de preparación para el compuesto de fórmula (I) no se limitan a los procedimientos de preparación de los ejemplos específicos mostrados a continuación, sino que el compuesto de fórmula (I) se puede

preparar por una combinación de los procedimientos de preparación o un procedimiento que sea evidente para un experto en la técnica.

5 Además, se pueden usar las siguientes abreviaturas en algunos casos de los ejemplos de preparación, ejemplos y tablas a continuación.

10 EjP: N.º de ejemplo de preparación, Ej: N.º de ejemplo, Sin: N.º de ejemplo preparado por el mismo procedimiento, SinP: N.º de ejemplo de preparación preparado por el mismo procedimiento, Estr: Fórmula estructural, DAT: Datos fisicoquímicos, ESI+: valores m/z en espectroscopía de masas (ionización ESI, que representa $(M+H)^+$ a menos que se especifique de otro modo), ESI-: valores m/z (ionización ESI, que representa $(M-H)^+$ a menos que se especifique de otro modo), RMN1: δ (ppm) en RMN de 1H en DMSO- d_6 , RMN2: δ (ppm) en RMN de 1H en $CDCl_3$, s: singlete (espectro), d: doblete (espectro), t: triplete (espectro), q: cuádruplete (espectro), a: línea ancha (espectro) (por ejemplo: s.a.), TR: tiempo de retención (min) en HPLC, [M] en los ejemplos de preparación y los ejemplos: [mol/l], SFC preparativa: cromatografía preparativa de fluido supercrítico, DEA: dietilamina.

15 Además, por ejemplo, una descripción de "26+44" en Sin de las tablas de ejemplos indica que la preparación se realiza por el mismo procedimiento que en el ejemplo 26, y posteriormente se prepara el producto por el mismo procedimiento que en el ejemplo 44 como material de partida. Además, en las tablas de ejemplos de preparación hay, por ejemplo, una descripción de Sin. 87 en la columna SinP del ejemplo de preparación 148, lo que indica que el ejemplo de preparación 148 se prepara por el mismo procedimiento que en el ejemplo 87. En las tablas de ejemplo hay, por ejemplo, una descripción de SinP. 8 en la columna Sin del ejemplo 295, lo que indica que el ejemplo 295 se prepara por el mismo procedimiento que en el ejemplo de preparación 8. HCl en la fórmula estructural indica clorhidrato y el número antes de HCl indica una proporción molar. Por ejemplo, 2HCl significa diclorhidrato. Además, Me en la fórmula estructural indica un grupo metilo, Et indica un grupo etilo, Ph indica un grupo fenilo, iBu indica un grupo isobutilo, tBu indica un grupo terc-butilo y Boc indica un grupo terc-butoxicarbonilo. El compuesto que tiene "*" en la estructura indica que el compuesto es una sustancia ópticamente activa.

Ejemplo de preparación 1

30 A una solución de 4,6-dicloro-2-(metilsulfanil)pirimidina (5 g) en N,N-dimetilformamida (50 ml) se le añadió carbonato de potasio (5,3 g) y 2-(difluorometil)-1H-benzimidazol (3,9 g), y se agitó la mezcla a temperatura ambiente durante 5 horas. A la mezcla de reacción se le añadió agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo) para obtener 1-[6-cloro-2-(metilsulfanil)pirimidin-4-il]-2-(difluorometil)-1H-benzimidazol (5,49 g) como un polvo blanco.

Ejemplo de preparación 2

40 A una solución de 1-[6-cloro-2-(metilsulfanil)pirimidin-4-il]-2-(difluorometil)-1H-benzimidazol (2,2 g) en N,N-dimetilformamida (11 ml) se le añadió carbonato de potasio (1,4 g) y morfina (0,88 ml), y se agitó la mezcla a temperatura ambiente durante 1 hora. A la solución de reacción se le añadió agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo) para obtener 2-(difluorometil)-1-[2-(metilsulfanil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (2,1 g) como un polvo blanco.

Ejemplo de preparación 3

50 A una solución de 2-(difluorometil)-1-[2-(metilsulfanil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (3 g) en diclorometano (60 ml) se le añadió ácido m-cloroperbenzoico, (75 % húmedo) (1,9 g) bajo enfriamiento con hielo, y se agitó la mezcla a 0 °C durante 15 minutos. A la mezcla de reacción se le añadió una solución acuosa saturada de bicarbonato de sodio, seguido de extracción con diclorometano. Se lavó la capa orgánica con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de sílice (cloroformo:metanol) para obtener 2-(difluorometil)-1-[2-(metilsulfanil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (2,8 g) como una sustancia amorfa de color amarillo pálido.

Ejemplo de preparación 4

60 A una solución de 2-(difluorometil)-1-[2-(metilsulfanil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (2,1 g) en diclorometano (21 ml) se le añadió ácido m-cloroperbenzoico, (75 % húmedo) (2,7 g) bajo enfriamiento con hielo, y se agitó la mezcla a 0 °C durante 15 minutos. A la mezcla de reacción se le añadió una solución acuosa saturada de bicarbonato de sodio, seguido de extracción con diclorometano. Se lavó la capa orgánica con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de sílice (cloroformo:metanol) para obtener 2-(difluorometil)-

1-[2-(metilsulfonyl)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (2,27 g) como una sustancia amorfa de color amarillo pálido.

Ejemplo de preparación 5

5 A una mezcla de 1-[6-cloro-2-(metilsulfanil)pirimidin-4-il]-2-(difluorometil)-1H-benzimidazol (1 g) y N,N-dimetilacetamida (10 ml) se le añadieron 4-(hidroximetil)piperidin-1-carbamato de terc-butilo (1 g) y carbonato de cesio (3 g), y se agitó la mezcla a 120 °C durante 3 horas. Se vertió la mezcla de reacción en agua, seguido de extracción con hexano-acetato de etilo (1:1). Se lavó la capa orgánica con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo) para obtener 4-[[6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(metilsulfanil)pirimidin-4-il]oxi]metil]piperidin-1-carbamato de terc-butilo (680 mg) como una sustancia amorfa blanca.

15 Ejemplo de preparación 6

Se disolvió N-(2-[[6-cloro-2-(metilsulfanil)pirimidin-4-il]amino]-5-metilfenil)acetamida (270 mg) en un disolvente mezclado de etanol (2,8 ml) y 1,4-dioxano (2,8 ml), y se añadió al mismo ácido clorhídrico 6 M (9,6 ml), seguido de calentamiento y reflujo durante 3 horas. Después de enfriar al aire hasta temperatura ambiente, se ajustó el pH a de 6 a 7 usando bicarbonato de sodio acuoso saturado, seguido de extracción con acetato de etilo. Se secó la capa orgánica sobre sulfato de magnesio anhidro y se evaporó el disolvente a presión reducida para obtener N¹-[6-cloro-2-(metilsulfanil)pirimidin-4-il]-4-metilbenceno-1,2-diamina (230 mg).

Ejemplo de preparación 7

25 Se agitó una mezcla de 2-(metilsulfanil)-6-(morfolin-4-il)pirimidin-4-amina (500 mg), 2-bromo-1-metil-3-nitrobenceno (1 g), tris(dibencilidenacetona)dipaladio (0) (202 mg), (9,9-dimetil-9H-xanten-4,5-diil)bis(difenilfosfina) (192 mg), y carbonato de cesio (1,0 g) en tolueno en un reactor de microondas a 140 °C durante 1 hora. Se filtró la mezcla de reacción a través de celite y se concentró a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo) para obtener N-(2-metil-6-nitrofenil)-2-(metilsulfanil)-6-(morfolin-4-il)pirimidin-4-amina (756 mg) como un polvo amarillo.

Ejemplo de preparación 8

35 Se disolvió N-(2-metil-6-nitrofenil)-2-(metilsulfanil)-6-(morfolin-4-il)pirimidin-4-amina (750 mg) en etanol (22,5 ml), y se añadió al mismo cloruro de hierro (III) hexahidrato (56 mg) y carbón activado (75 mg), seguido de agitación a 80 °C. Se añadió gota a gota hidrazina monohidrato al mismo, seguido de calentamiento y reflujo durante la noche. Se enfrió la mezcla de reacción hasta temperatura ambiente y se filtró a través de celite. Se concentró el líquido madre y se purificó el residuo usando una cromatografía en columna en gel de sílice (hexano:acetato de etilo) para obtener 3-metil-N²-[2-(metilsulfanil)-6-(morfolin-4-il)pirimidin-4-il]benceno-1,2-diamina (544 mg) como un polvo amarillo pálido.

Ejemplo de preparación 9

45 A [[(2S)-1-[[trans-4-([6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]amino]-4-(metilsulfanil)-1-oxobutan-2-il]carbamato de terc-butilo (760 mg) se le añadió yoduro de metilo (3,5 ml), seguido de agitación a temperatura ambiente durante la noche. Se evaporó el yoduro de metilo a presión reducida para obtener un compuesto deseado yoduro de [[(3S)-3-[[terc-butoxicarbonil]amino]-4-[[trans-4-([6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]amino]-4-oxobutil](dimetil)sulfonio (919 mg).

50 Ejemplo de preparación 10

Se disolvieron 4,6-dicloro-2-(metilsulfanil)pirimidina (50 mg) y (2-amino-4-metilfenil)carbamato de terc-butilo (57 mg) en dimetilacetamida (250 µl), y se añadió al mismo N,N-diisopropiletilamina (69 µl), seguido de agitación a 100 °C durante 7 horas. Después de la finalización de la reacción, se enfrió la mezcla hasta temperatura ambiente, y se añadió agua a la misma, seguido de extracción con acetato de etilo. Se lavaron los extractos con salmuera saturada, se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (acetato de etilo:hexano) para obtener un compuesto deseado 2-[[6-cloro-2-(metilsulfanil)pirimidin-4-il]amino]-4-metilfenil)carbamato de terc-butilo (50 mg) como un polvo blanco.

60 Ejemplo de preparación 11

Se disolvió 2-[[6-cloro-2-(metilsulfanil)pirimidin-4-il]amino]-4-metilfenil)carbamato de terc-butilo (8,5 g) en 1,4-dioxano (85 ml), y se añadió al mismo una solución 4 M (56 ml) de cloruro de hidrógeno en 1,4-dioxano, seguido de agitación a temperatura ambiente durante 8 horas. Después de la finalización de la reacción, se añadieron a la misma una solución acuosa saturada de bicarbonato de sodio y una solución acuosa 4 M de hidróxido de sodio. La

mezcla se desactivó, se preparó libre, y se extrajo con acetato de etilo. Se secó la capa orgánica sobre sulfato de magnesio anhidro y se evaporó el disolvente a presión reducida para obtener [6-cloro-2-(metilsulfanil)pirimidin-4-il]-4-metilbenceno-1,2-diamina (6 g) como un polvo amarillo.

5 Ejemplo de preparación 12

Se disolvieron N²[6-cloro-2-(metilsulfanil)pirimidin-4-il]-4-metilbenceno-1,2-diamina (6 g) y anhídrido difluoroacético (7,4 g) en acetonitrilo (60 ml), seguido de agitación a temperatura ambiente durante 1 hora. Después de confirmarse que el material de partida había desaparecido, se añadió al mismo una solución 4 M (53 ml) de cloruro de hidrógeno en 1,4-dioxano, seguido de agitación a 100 °C durante 10 horas. Después de la finalización de la reacción, se enfrió la mezcla hasta temperatura ambiente, y se añadió agua a la misma, seguido de extracción con acetato de etilo. La capa orgánica se lavó con salmuera saturada. Se secó la capa orgánica obtenida sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (acetato de etilo:hexano) para obtener 1-[6-cloro-2-(metilsulfanil)pirimidin-4-il]-2-(difluorometil)-6-metil-1H-benzimidazol (2,9 g) como un polvo blanco.

Ejemplo de preparación 13

Se disolvieron (3a'R,5's,6a'S)-5,5-dimetilhexahidro-1'H-espiro [1,3-dioxano-2,2'-pentalen]-5'-ol (1,0 g) y 1H-isoindol-1,3(2H)-diona (780 mg) y trifenilfosfina (1,39 g) en tetrahydrofurano (17 ml), y se añadió gota a gota una solución 2,2 M (2,41 ml) de azodicarbonato de etilo en tetrahydrofurano a los mismos a 0 °C, seguido de agitación a 0 °C durante 1 hora y a temperatura ambiente durante 4 horas. A la solución de reacción se le añadió gel de sílice, seguido de concentración y purificación usando cromatografía en columna en gel de sílice (hexano:acetato de etilo) para obtener 2-[(3a'R,5'r,6a'S)-5,5-dimetilhexahidro-1'H-espiro[1,3-dioxano-2,2'-pentalen]-5' -il]-1H-isoindol-1,3(2H)-diona (1,1 g) como un polvo blanco.

Ejemplo de preparación 14

A una mezcla de carboxilato de etil-4-(4-cianofenil)-1-piperazina (10 g), borohidruro de sodio (3,4 g), y tetrahydrofurano (50 ml) se le añadió una mezcla de yodo (9,8 g) y tetrahydrofurano (50 ml) en un flujo de gas nitrógeno mientras se enfriaba con hielo, seguido de agitación a la misma temperatura durante 1 hora, y después calentamiento adicional y reflujo durante 3 horas. La solución de reacción se enfrió en hielo y se le añadió a la misma una solución 6 M de ácido clorhídrico para ajustar el pH hasta 1. La solución de reacción se agitó a 70 °C durante 30 minutos. Después de dejar que se enfriara, se añadió a la misma hidróxido de sodio para ajustar el pH hasta 10, seguido de extracción con acetato de etilo. Se lavaron los extractos con salmuera saturada, se secó la capa orgánica sobre sulfato de sodio anhidro, y se evaporó el disolvente a presión reducida. El residuo se preparó en polvo usando tetrahydrofurano, acetato de etilo y éter diisopropílico, para obtener carboxilato de etil-4-[4-(aminometil)fenil]-1-piperazina (5,2 g).

40 Ejemplo de preparación 15

Se disolvió 2-(difluorometil)-1-[2-(metilsulfanil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (2,1 g) en cloruro de metileno (21 ml), y se añadió a los mismos ácido m-cloroperbenzoico, (75 % húmedo) (2,7 g) bajo enfriamiento con hielo, seguido de agitación a 0 °C durante 15 minutos. Se añadió al mismo bicarbonato de sodio acuoso saturado, seguido de extracción con cloruro de metileno. Se lavaron los extractos con agua y salmuera saturada, se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo usando cromatografía en columna en gel de sílice (cloroformo:metanol) para obtener 2-(difluorometil)-1-[2-(metilsulfonil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (2,27 g) como una sustancia amorfa de color amarillo pálido.

50 Ejemplo de preparación 16

A una mezcla de 2-[(3a'R,5'r,6a'S)-5,5-dimetilhexahidro-1'H-espiro[1,3-dioxano-2,2'-pentalen]-5'-il]-1H-isoindol-1,3(2H)-diona (1,1 g), tetrahydrofurano (22 ml) y etanol (22 ml) se le añadió hidrazina monohidrato (0,75 ml), seguido de calentamiento y a reflujo durante 2 horas. La materia insoluble se retiró por filtración a través de celite y se concentró a presión reducida. Al residuo, se le añadió cloroformo, seguido de secado sobre sulfato de sodio, y después se evaporó el disolvente a presión reducida para obtener (3a'R,5,6a'S)-5,5-dimetilhexahidro-espiro[1,3-dioxano-pentalen]-5'-amina (0,74 g) como un polvo blanco.

60 Ejemplo de preparación 17

Se disolvió 9-oxo-3-azaespiro[5.5]undecano-3-carboxilato de bencilo (230 mg) en metanol (4,5 ml) y cloruro de metileno (1,5 ml), y se añadieron a los mismos acetato de amonio (1,47 g), seguido de agitación a temperatura ambiente durante 10 minutos. Posteriormente, se añadieron a los mismos triacetoxiborohidruro de sodio (323 mg), seguido de agitación a temperatura ambiente durante la noche. A la solución de reacción se le añadió bicarbonato de sodio acuoso saturado, seguido de extracción con cloroformo. Se lavó la capa orgánica con salmuera saturada y

se secó sobre sulfato de sodio anhidro. Se evaporó el disolvente a presión reducida para obtener 9-amino-3-azaespiro[5.5]undecano-3-carboxilato de bencilo (255 mg).

Ejemplo de preparación 80

5 Se suspendieron trans-4-(dibencilamino)ciclohexanol (200 mg), 2-(3-bromopropoxi)tetrahidro-2H-pirano (604 mg), hidróxido de potasio en polvo (179 mg), y bromuro de tetrabutilamonio (44 mg) en xileno (2 ml), seguido de agitación a temperatura ambiente durante 2 horas. A la mezcla de reacción se le añadieron acetato de etilo y agua, y se extrajo la capa orgánica y se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El disolvente se evaporó a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=100:0-80:20) para obtener trans-N,N-dibencil-4-[3-(tetrahidro-2H-piran-2-iloxi)propoxi]ciclohexanamina (174 mg).

Ejemplo de preparación 81

15 Se disolvió trans-N,N-dibencil-4-[3-(tetrahidro-2H-piran-2-iloxi)propoxi]ciclohexanamina (170 ml) en metanol (1 ml), y se añadió al mismo una solución 4 M (972 µl) de cloruro de hidrógeno en 1,4-dioxano, seguido de agitación a temperatura ambiente durante 2 horas. Se neutralizó la solución de reacción con una solución acuosa saturada de bicarbonato de sodio y se extrajo con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y después se secó sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida para obtener 3-[[trans-4-(dibencilamino)ciclohexil]oxi]propan-1-ol (110 mg).

Ejemplo de preparación 82

25 A 3-[[trans-4-(dibencilamino)ciclohexil]oxi]propan-1-ol (110 mg) se le añadieron cloruro de tosilo (60 mg) y piridina (51 µl) bajo enfriamiento con hielo, seguido de agitación a temperatura ambiente durante 1 hora. A la mezcla de reacción se le añadieron N,N-dimetilformamida (1,1 ml), carbonato de potasio (43 mg) y pirrolidina (26 µl), seguido de agitación a temperatura ambiente durante la noche. A la mezcla de reacción se le añadieron acetato de etilo y agua, y se extrajo la capa orgánica, se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio anhidro. Después, se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=90:10-70:30) para obtener trans-N,N-dibencil-4-[3-(pirrolidin-1-il)propoxi]ciclohexanamina (70 mg).

Ejemplo de preparación 83

35 Se disolvió trans-N,N-dibencil-4-[3-(pirrolidin-1-il)propoxi]ciclohexanamina (115 mg) en etanol (2,3 ml), y se añadió a la misma hidróxido de paladio al 20 %/carbono húmedo al 50 %, seguido de reducción catalítica a temperatura ambiente durante 4 horas a 3 atm en una atmósfera de hidrógeno. Se retiró el catalizador por filtración después de sustitución de nitrógeno, y después se concentró a presión reducida para obtener trans-4-[3-(pirrolidin-1-il)propoxi]ciclohexanamina (48 mg).

Ejemplo de preparación 84

45 Se disolvió fosfonoacetato de trietilo (107 mg) en tetrahidrofurano (1 ml), y se añadió al mismo hidruro de sodio al 60 % (19 mg), seguido de agitación a temperatura ambiente durante 30 minutos. Se añadió gota a gota una solución de (trans-4-formilciclohexil)carbamato de terc-butilo (90 mg) en tetrahidrofurano (1 ml) al mismo, seguido de agitación a temperatura ambiente durante 2 horas. Se añadió al mismo acetato de etilo y agua, seguido de extracción con acetato de etilo. Se lavaron los extractos con salmuera saturada y después se secaron sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=95:5-50:50) para obtener (2E)-3-{trans-4-[(terc-butoxicarbonil)amino]ciclohexil}acrilato de etilo (100 mg).

Ejemplo de preparación 85

55 Se suspendió hidruro de sodio al 60 % (394 mg) en 1,2-dimetoxietano (20 ml), y se añadieron al mismo 4-hidroxibencilcarbamato de terc-butilo (1 g) y 15-corona-5-éter (1,09 g), seguido de agitación a temperatura ambiente durante 30 minutos. Se añadió al mismo 4,6-dicloro-2-(metilsulfonil)pirimidina, seguido de agitación a 80 °C durante la noche. Se enfrió la solución de reacción hasta temperatura ambiente y después se añadió a la misma una solución acuosa de cloruro de amonio (50 ml), seguido de extracción con acetato de etilo. Se lavaron los extractos con agua y salmuera saturada, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se retiró por filtración el desecante y se evaporó el disolvente a presión reducida. Se purificó el residuo usando cromatografía en columna en gel de sílice (hexano:acetato de etilo=95:5-85:15) para obtener {4-[(4,6-dicloropirimidin-2-il)oxi]bencil}carbamato de terc-butilo (762 mg).

65 Ejemplo de preparación 86

Se agitó una mezcla de 4,6-dicloro-2-(metilsulfanil)pirimidina (700 mg), 2-(difluorometil)-4-etoxi-1H-benzimidazol (761 mg), carbonato de potasio (744 mg) y N,N-dimetilformamida (7 ml) a temperatura ambiente durante la noche. A la mezcla se le añadió agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de sodio anhidro. Se retiró por filtración el desecante y después se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (cloroformo:metanol=100:0-80:20) para obtener 1-[6-cloro-2-(metilsulfanil)pirimidin-4-il]-2-(difluorometil)-4-etoxi-1H-benzimidazol (464 mg) (ejemplo de preparación 86-1) y 1,1'-[2-(metilsulfanil)pirimidina-4,6-diil]bis[2-(difluorometil)-4-etoxi-1H-benzimidazol] en acetato de etilo y se calentó. Después de dejar que se enfriara, se recogió la materia insoluble por filtración para obtener 1,1'-[2-(metilsulfanil)pirimidina-4,6-diil]bis[2-(difluorometil)-4-etoxi-1H-benzimidazol] (275 mg) (ejemplo de preparación 86-2).

Ejemplo de preparación 87

A una mezcla de trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxi)ciclohexanamina (700 mg) y N,N-dimetilformamida (7,0 ml) se le añadieron N-(terc-butoxicarbonil)-N-metil-L-metionina (622 mg), 1H-benzotriazol-1-ol (319 mg), y clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (452 mg), seguido de agitación a temperatura ambiente durante la noche. Después de la finalización de la reacción, se añadió agua a la misma, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y después se secó sobre sulfato de magnesio anhidro. Se retiró por filtración el desecante y después se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en gel de sílice (hexano:acetato de etilo=90:10-40:60) para obtener [(2S)-1-[[trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxi)ciclohexil]amino]-4-(metilsulfanil)-1-oxobutan-2-il]metilcarbamato de terc-butilo (859 mg).

Ejemplo de preparación 88

A una mezcla de [(2S)-1-({trans-4-[(terc-butoxicarbonil)amino]ciclohexil}amino)-4-(metilsulfanil)-1-oxobutan-2-il]carbamato de metilo (1,5 g), cloruro de metileno (15 ml) y metanol (15 ml) se le añadió yoduro de metilo (11,6 ml), seguido de agitación a temperatura ambiente durante la noche. Se evaporó el disolvente a presión reducida, y a una mezcla del residuo y dimetilformamida (7,5 ml) se le añadió carbonato de cesio (3,6 g), seguido de agitación durante la noche. A la solución de reacción se le añadió agua, seguido de extracción con acetato de etilo. La capa orgánica se lavó con salmuera saturada. Se secó la capa orgánica sobre sulfato de sodio anhidro, se retiró por filtración el desecante, y después se evaporó el disolvente a presión reducida. Al residuo, se le añadió etanol, y se recogió el sólido resultante por filtración y se secó a presión reducida para obtener [(3S)-1-({trans-4-[(terc-butoxicarbonil)amino]ciclohexil}-2-oxopirrolidin-3-il]carbamato de metilo (0,88 g).

Ejemplo de preparación 89

A una solución de 1,1-[2-(metilsulfanil)pirimidin-4,6-diil]bis[2-(difluorometil)-1H-benzimidazol] (2 g) en N,N-dimetilacetamida (10 ml) se le añadieron (3S)-3-(hidroximetil)pirrolidin-1-carboxilato de terc-butilo (965 mg) y carbonato de cesio (2,1 g), seguido de agitación a 60°C durante 5 horas. Después de la finalización de la reacción, a la solución de reacción se le añadió agua helada y se recogió por filtración el sólido precipitado. Después del secado, se disolvió lo resultante en diclorometano y se purificó por cromatografía en columna en gel de sílice (hexano:acetato de etilo=90:10-65:35) para obtener (3S)-3-[[{6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(metilsulfanil)pirimidin-4-il}oxi]metil]pirrolidin-1-carboxilato de terc-butilo (2,01 g).

Ejemplo de preparación 90

Se agitó una mezcla de 1-[6-cloro-2-(metilsulfanil)pirimidin-4-il]-2-(difluorometil)-1H-benzimidazol (350 mg), clorhidrato de [(3R)-1-(trans-4-aminociclohexil)-2-oxopirrolidin-3-il]carbamato de metilo (344 mg), carbonato de potasio (178 mg), N-etil-N-isopropilpropan-2-amina (1,1 ml), y N,N-dimetilacetamida (1,75 ml) a 60 °C durante la noche. A la solución de reacción se le añadieron agua y acetato de etilo. Se recogió por filtración la materia insoluble, seguido de extracción con acetato de etilo. Se evaporó el disolvente a presión reducida, y después se combinaron el residuo y la materia insoluble. Se añadió a los mismos acetato de etilo, y la mezcla se suspendió, se agitó y después se recogió por filtración. Se lavó lo resultante con agua y se secó para obtener {(3R)-1-[trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(metilsulfanil)pirimidin-4-il}amino)ciclohexil]-2-oxopirrolidin-3-il}carbamato de metilo (446 mg).

Ejemplo 1 (no englobado en las reivindicaciones)

Se agitó una mezcla de 2-difluorometil-1-[2-(metilsulfonil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (770 mg), (3S)-3-aminopirrolidin-1-carboxilato de terc-butilo (525 mg), carbonato de potasio (390 mg) y N,N-dimetilacetamida (19 ml) en un reactor de microondas a 100 °C durante 1 hora. Se enfrió la mezcla de reacción hasta temperatura ambiente y después se vertió en agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=80:20-

50:50) para obtener (3S)-3-({4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-ilpirimidin-2-il}amino)pirrolidin-1-carboxilato de terc-butilo (310 mg) como una sustancia amorfa de color amarillo pálido.

Ejemplo 22 (no englobado en las reivindicaciones)

5 Se agitó una mezcla de 2-(difluorometil)-1-[2-(metilsulfonil)-6-morfolin-4-ilpirimidin-4-il]-1H-benzimidazol (100 mg), 1-bencil-3-(metilamino)pirrolidina (93 mg), carbonato de potasio (50 mg), y N,N-dimetilacetamida (2,5 ml) en un reactor de microondas a 100 °C durante 1 hora. Se enfrió la mezcla de reacción hasta temperatura ambiente y después se vertió en agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se
10 se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=80:20-50:50). Se combinaron las fracciones deseadas y se concentraron a presión reducida. Se disolvió el residuo en 1,4-dioxano, y se añadió a al mismo una solución 4 M (61 µl) de cloruro de hidrógeno en 1,4-dioxano. Además, se añadió a los mismos éter
15 diisopropílico (10 ml). El polvo resultante se recogió por filtración, se lavó con éter diisopropílico, y se secó a presión reducida para obtener clorhidrato de N-(1-bencilpirrolidin-3-il)-4-[2-(difluorometil)-1H-benzimidazol-1-il]-N-metil-6-morfolin-4-ilpirimidin-2-amina (28 mg) como un polvo amarillo pálido.

Ejemplo 26 (no englobado en las reivindicaciones)

20 A una mezcla de diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-[(3S)-pirrolidin-3-il]pirimidin-2-amina (58 mg) y N,N-dimetilformamida (1,2 ml) se le añadieron fenilacetaldehído (21 mg), triacetoxiborohidruro de sodio (75 mg), y ácido acético (0,29 ml), y se agitó la mezcla a temperatura ambiente durante la noche. A la mezcla de reacción se le añadió una solución acuosa saturada de bicarbonato de sodio, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato
25 de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=80:20-50:50, y después cloroformo:metanol=100:0-80:20) para obtener 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-[(3S)-1-(2-feniletil)pirrolidin-3-il]pirimidin-2-amina (30 mg) como un polvo blanco.

30 Ejemplo 43 (no englobado en las reivindicaciones)

A una solución de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-(piperidin-4-ilmetil)pirimidin-2-amina (400 mg) en 1,2-dicloroetano (8 ml) se le añadió 4-fluorociclohexanona (210 mg), y se agitó la mezcla a temperatura ambiente durante 10 minutos. Posteriormente se añadió a la misma triacetoxiborohidruro de sodio (382 mg), seguido
35 de agitación a temperatura ambiente durante la noche. A la mezcla de reacción se le añadió una solución acuosa saturada de bicarbonato de sodio, seguido de extracción con cloroformo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de sodio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=70:30-40:60) para obtener los dos tipos de compuestos a continuación, cada uno como un polvo blanco.

40 4-[2-(Difluorometil)-1H-benzimidazol-1-il]-N-[[1-(trans-4-fluorociclohexil)piperidin-4-il]metil]-6-(morfolin-4-il)pirimidin-2-amina (109 mg)

El valor R_f en TLC en gel de amino sílice (hexano:acetato de etilo=50:50) del presente compuesto fue de 0,35.

45 4-[2-(Difluorometil)-1H-benzimidazol-1-il]-N-[[1-(cis-4-fluorociclohexil)piperidin-4-il]metil]-6-(morfolin-4-il)pirimidin-2-amina (87 mg)

El valor R_f en TLC en gel de amino sílice(hexano:acetato de etilo=50:50) del presente compuesto fue de 0,28.

50 La 4-[2-(difluorometil)-1H-benzimidazol-1-il]-N-[[1-(trans-4-fluorociclohexil)piperidin-4-il]metil]-6-(morfolin-4-il)pirimidin-2-amina (80 mg) obtenida anteriormente se disolvió en un disolvente mezclado de cloroformo (1,5 ml) y metanol (0,3 ml), y se añadió a la misma una solución 4 M (0,37 ml) de cloruro de hidrógeno en 1,4-dioxano. La mezcla se agitó a temperatura ambiente durante 10 minutos. Se concentró la mezcla de reacción para obtener
55 diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-N-[[1-(trans-4-fluorociclohexil)piperidin-4-il]metil]-6-(morfolin-4-il)pirimidin-2-amina (Ejemplo 43-1, 87 mg) como un polvo blanco.

De modo similar, se obtuvo diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-N-[[1-(cis-4-fluorociclohexil)piperidin-4-il]metil]-6-(morfolin-4-il)pirimidin-2-amina (Ejemplo 43-2, 70 mg) como un polvo blanco a partir de la 4-[2-(difluorometil)-1H-benzimidazol-1-il]-N-[[1-(cis-4-fluorociclohexil)piperidin-4-il]metil]-6-(morfolin-4-il)pirimidin-2-amina (62 mg) obtenida anteriormente.

Ejemplo 44 (no englobado en las reivindicaciones)

65 A una mezcla de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-N-[(1-fenilpiperidin-4-il)metil]pirimidin-2-amina (38 mg), cloroformo (0,75 ml), y metanol (0,35 ml) se le añadió una solución 4 M (0,2 ml) de cloruro de

hidrógeno en 1,4-dioxano, y se agitó la mezcla a temperatura ambiente durante 10 minutos. Se concentró la mezcla de reacción a presión reducida para obtener diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-N-[(1-fenilpiperidin-4-il)metil]pirimidin-2-amina (43 mg) como un polvo blanco.

5 Ejemplo 45 (no englobado en las reivindicaciones)

10 A una mezcla de diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-[(3S)-pirrolidin-3-il]pirimidin-2-amina (75 mg) y N,N-dimetilformamida (1,5 ml) se le añadió bromuro de 2-(dimetilamino)etilo (26 mg) y carbonato de potasio (85 mg), y se agitó la mezcla a temperatura ambiente durante la noche. A la mezcla de
15 reacción se le añadió agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=50:50-0:100, y posteriormente cloroformo:metanol=100:0-80:20). Se combinaron las fracciones deseadas y se concentraron a presión reducida. Se disolvió el residuo en 1,4-dioxano (0,5 ml) y se añadió al mismo una solución 4 M (80 µl) de
20 cloruro de hidrógeno en 1,4-dioxano. Se añadió adicionalmente al mismo éter diisopropílico (10 ml). El polvo resultante se recogió por filtración, se lavó con éter diisopropílico, y se secó a presión reducida para obtener diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-N-[(3S)-1-[2-(dimetilamino)etil]pirrolidin-3-il]-6-morfolin-4-ilpirimidin-2-amina (10 mg) como un polvo blanco.

20 Ejemplo 52 (no englobado en las reivindicaciones)

25 A una mezcla de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-(piperidin-4-ilmetil)pirimidin-2-amina (100 mg) y etanol (2 ml) se le añadieron 2-(fluorometil)oxirano (19 µl) y N,N-diisopropiletilamina (79 µl), y se agitó la mezcla en un reactor de microondas a 120 °C durante 1 hora. A la mezcla de reacción se le añadió agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de
30 magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de amino sílice (acetato de etilo:hexano) para obtener 1-{4-[(4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)metil]piperidin-1-il}-fluoropropan-2-ol (81 mg) como un polvo blanco.

30 Ejemplo 53

35 A una mezcla de (3S)-3-({4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-ilpirimidin-2-il]amino)pirrolidin-1-carboxilato de terc-butilo (300 mg) y 1,4-dioxano (3 ml) se le añadió una solución 4 M (1,5 ml) de cloruro de hidrógeno en 1,4-dioxano, y se agitó la mezcla a temperatura ambiente durante 2 horas. A la mezcla de reacción se le añadió éter diisopropílico (10 ml). El polvo resultante se recogió por filtración, se lavó con éter diisopropílico, y se secó a presión reducida para obtener diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-[(3S)-pirrolidin-3-il]pirimidin-2-amina (354 mg) como un polvo amarillo pálido.

40 Ejemplo 54

45 A una mezcla de 4-({4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-ilpirimidin-2-il]amino)piperidin-1-carboxilato de terc-butilo (42 mg) y metanol (0,84 ml) se le añadió una solución 4 M de cloruro de hidrógeno en 1,4-dioxano, y se agitó la mezcla a temperatura ambiente durante 4 horas. Se neutralizó la mezcla de reacción mediante la adición de solución acuosa saturada de bicarbonato de sodio, y se extrajo con cloroformo. Se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=50:50) para obtener 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-piperidin-4-ilpirimidin-2-amina (27 mg) como un polvo amarillo pálido.

50 Ejemplo 66 (no englobado en las reivindicaciones)

55 A una mezcla de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-piperidin-4-ilpirimidin-2-amina (18 mg) y N,N-dimetilformamida (0,36 ml) se le añadieron N,N-dimetilglicina (4,8 mg), 1-hidroxibenzotriazol (6,2 mg), y clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (8,8 mg), y se agitó la mezcla a temperatura ambiente durante 6 horas. A la mezcla de reacción se le añadió agua, seguido de extracción con cloroformo. La capa orgánica se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de amino sílice (acetato de etilo, y posteriormente cloroformo:metanol=96:4). Se combinaron las fracciones deseadas y se concentraron a presión reducida. Se solidificó el residuo se solidificaron mediante la adición de una pequeña cantidad de éter diisopropílico para obtener
60 4-[2-(difluorometil)-1H-benzimidazol-1-il]-N-{1-[(dimetilamino)acetil]piperidin-4-il}-6-morfolin-4-ilpirimidin-2-amina (9 mg) como un polvo blanco.

Ejemplo 71 (no englobado en las reivindicaciones)

65 A una mezcla de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-(piperidin-4-ilmetil)-1,3,5-triazin-2-amina (50 mg) y piridina (2 ml) se le añadió anhídrido acético (14 µl), y se agitó la mezcla a temperatura ambiente durante la noche. A la mezcla de reacción se le añadió tolueno, seguido de concentración a presión reducida. Se disolvió el

residuo en diclorometano, y se añadió al mismo gel de sílice, seguido de concentración a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo, y posteriormente cloroformo:metanol) para obtener N-[(1-acetilpiperidin-4-il)metil]-4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-1,3,5-triazina-2-amina (44 mg) como un polvo blanco.

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Ejemplo 74 (no englobado en las reivindicaciones)

A una mezcla de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il-N-(piperidin-4-ilmetil)pirimidin-2-amina (50 mg) y 1,2-dimetoxietano (1 ml) se le añadieron bromobenceno (24 µl), tris(dibencilidenacetona)dipaladio (0) (6,5 mg), dicitclohexil(2',4',6'-triiisopropilbifenil-2-il)fosfina (11 mg) y fosfato de potasio (96 mg), y se agitó la mezcla en un reactor de microondas a 130 °C durante 1 hora. Se filtró la mezcla de reacción a través de celite, y al filtrado se le añadió gel de sílice, seguido de concentración a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo) para obtener 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-N-[(1-fenilpiperidin-4-il)metil]pirimidin-2-amina (39 mg) como un polvo blanco.

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Ejemplo 80 (no englobado en las reivindicaciones)

Se agitó una mezcla de 4-[(6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(metilsulfinil)pirimidin-4-il)oxi]metil]piperidin-1-carbamato (240 mg), morfolina (0,3 ml) y N,N-dimetilacetamida (2 ml) a temperatura ambiente durante 1 hora. A la mezcla de reacción se le añadió agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con agua y salmuera saturada, y después se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y después se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=70:30-50:50) para obtener 4-[(6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il)oxi]metil]piperidin-1-carbamato de terc-butilo (246 mg) como un polvo blanco.

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Ejemplo 82 (no englobado en las reivindicaciones)

Se disolvió 1-[4-cloro-6-(morfolin-4-il)pirimidin-2-il]-2-(difluorometil)-1H-benzimidazol (100 mg) en dimetilformamida (1 ml), y se añadieron al mismo 3-metoxiprop-1-ina (45 µl), tetraquistrifenilfosfina-paladio (0) (16 mg), yoduro de cobre (I) (1,3 mg) y carbonato de potasio (227 mg), seguido de agitación en un reactor de microondas a 80 °C durante 1 hora. Se añadieron a los mismos una solución acuosa de cloruro de amonio y cloroformo, y se extrajo la capa orgánica, se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio anhidro. Después, se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=60:40). Se añadió al mismo un disolvente mezclado de éter diisopropílico y hexano, y se recogió por filtración el sólido resultante y se lavó adicionalmente con hexano para obtener 2-(difluorometil)-1-[4-(3-metoxiprop-1-in-1-il)-6-(morfolin-4-il)pirimidin-2-il]-1H-benzimidazol (10 mg) como un polvo amarillo.

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Ejemplo 83 (no englobado en las reivindicaciones)

Se disolvió trans-4-[(4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)metil]ciclohexanocarboxilato de metilo (150 mg) en un disolvente mezclado de metanol (750 µl) y tetrahidrofurano (750 µl), y se añadió al mismo una solución acuosa 1 M de hidróxido de sodio (899 ml), seguido de agitación a temperatura ambiente durante 2 horas. Después de la finalización de la reacción, se añadió a la misma ácido clorhídrico bajo enfriamiento con hielo hasta que la solución de reacción se volvió débilmente ácida, seguido de agitación a 0 °C durante 1 hora. Se recogió el sólido resultante por filtración y se lavó con hexano para obtener ácido trans-4-[(4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)metil]ciclohexanocarboxílico (74 mg) como un polvo blanco.

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Ejemplo 84 (no englobado en las reivindicaciones)

Se disolvió yoduro de [(3S)-3-[(terc-butoxicarbonil)amino]-4-[(trans-4-[(6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il)oxi]ciclohexil]amino)-4-oxobutil](dimetil)sulfonio (919 mg) en tetrahidrofurano (1,4 ml), y se enfrió hasta 0 °C bajo un flujo de aire de nitrógeno, y se añadió gota a gota una solución 1,6 M (0,7 ml) de hexametildisilazanolitio en tetrahidrofurano al mismo, seguido de agitación a 0 °C durante 2 horas. Adicionalmente se añadió gota a gota una solución 1,6 M (0,7 ml) de hexametildisilazanolitio en tetrahidrofurano al mismo, seguido de agitación a 0 °C durante 1 hora. Se añadió al mismo una solución acuosa saturada de cloruro de amonio, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Se evaporó el disolvente a presión reducida y se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=70:30-0:100) para obtener [(3S)-1-[trans-4-[(6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)piridin-4-il)oxi]ciclohexil]-2-oxopirrolidin-3-il]carbamato de terc-butilo (154 mg).

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Ejemplo 85 (no englobado en las reivindicaciones)

Se disolvió N-[(4-aminobiciclo[2.2.2]oct-1-il)metil]-4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-amina (150 mg) en etanol (3 ml), y se añadieron a la misma N,N-diisopropiletilamina (81 µl) y 2,2-dimetiloxirano (36 µl), seguido de agitación a 120 °C durante 1 hora y a 140 °C durante 1 hora usando un reactor de microondas. Se

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concentró la solución de reacción y se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=20:80, y posteriormente cloroformo:metanol=98:2) para obtener 1-((4-((4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il) amino)metil]biciclo[2.2.2]oct-1-il)amino)-2-metilpropan-2-ol (148 mg) como una sustancia amorfa blanco.

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Ejemplo 86 (no englobado en las reivindicaciones)

Se disolvió 1-((trans-4-((4-[2-(difluorometil)-6-metil-1H-benzimidazol-1-il]-6-((3S)-3-metilmorfolin-4-il)pirimidin-2-il)amino)metil]ciclohexil) amino)-2-metilpropan-2-ol (100 mg) en tetrahidrofurano (2 ml), y se añadieron al mismo di-1H-imidazol-1-ilmetanona (131 mg) y trietilamina (50 µl), seguido de agitación durante 3 horas al mismo tiempo de calentamiento y reflujo. Después de la finalización de la reacción, se añadió agua a la misma, seguido de extracción con acetato de etilo. Se lavaron los extractos con salmuera saturada y se secaron sobre sulfato de magnesio anhidro, y después se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=60:40) para obtener 3-((trans-4-((4-[2-(difluorometil)-6-metil-1H-benzimidazol-1-il]-6-((3S)-3-metilmorfolin-4-il)pirimidin-2-il)amino)metil]ciclohexil)-5,5-dimetil-1,3-oxazolidin-2-ona (100 mg) como un polvo blanco.

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Ejemplo 87 (no englobado en las reivindicaciones)

A (3S)-3-amino-1-[trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]pirrolidin-2-ona (75 mg), trietilamina (22 µl), y diclorometano (750 µl) se les añadió metilclorocarbonato (12 µl), seguido de agitación a temperatura ambiente durante 1 hora. Después de la finalización de la reacción, se añadió a los mismos una solución acuosa saturada de bicarbonato de sodio, seguido de extracción con cloroformo. Se lavó la capa orgánica con salmuera saturada y después se secó sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (cloroformo:metanol) para obtener ((3S)-1-[trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]-2-oxopirrolidin-3-il]carbamato de metilo (55 mg) como un polvo blanco.

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Ejemplo 88 (no englobado en las reivindicaciones)

A (3S)-3-amino-1-[trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]pirrolidin-2-ona (75 mg), N-etil-N-isopropilpropan-2-amina (73 µl) y 1,2-dicloroetano (750 µl) se le añadió cloruro de metanosulfonilo (17 µl), seguido de agitación a temperatura ambiente durante 1 hora. Después de la finalización de la reacción, se añadió a los mismos una solución acuosa saturada de bicarbonato de sodio, seguido de extracción con cloroformo. Se lavó la capa orgánica con salmuera saturada y después se secó sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (cloroformo:metanol) para obtener N-((3S)-1-[trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]-2-oxopirrolidin-3-il]metanosulfonamida (82 mg) como un polvo amarillo pálido.

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Ejemplo 89 (no englobado en las reivindicaciones)

Se suspendió 2-bromo-N-[trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]acetamida (100 mg) en dimetilformamida (2 ml), y se añadieron al mismo carbonato de potasio (30 mg) y ciclobutilamina (60 µl), seguido de agitación a temperatura ambiente durante la noche. A la solución de reacción se le añadió agua, seguido de extracción con acetato de etilo. Se lavaron los extractos con agua y salmuera saturada, se secó la capa orgánica sobre sulfato de sodio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en gel de amino sílice (hexano:acetato de etilo=40:60-10:90) para obtener N a 2 a -ciclobutil-N-[trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexil]glicinamida (79 mg).

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Ejemplo 90 (no englobado en las reivindicaciones)

Se disolvió trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)ciclohexanamina (200 mg) en etanol (4 ml), y se añadió a la misma acetaldehído (28 µl), seguido de agitación a temperatura ambiente durante 5 horas. Se añadió al mismo borohidruro de sodio (34 mg), seguido de agitación adicional a temperatura ambiente durante 1 hora. Se añadieron al mismo agua y acetato de etilo, se lavó la capa orgánica con salmuera saturada y después se secó sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=50:50-0:100, y posteriormente cloroformo:metanol=100:0-98:2) para obtener trans-4-((6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)-N-etilciclohexanamina (84 mg).

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Ejemplo 91 (no englobado en las reivindicaciones)

Se disolvió N-[2-(ciclopentilsulfanil)etil]-4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-1,3,5-triazin-2-amina (60 mg) en cloruro de metileno (1,2 ml), y se añadió a la misma ácido m-cloroperbenzoico, (75 % húmedo) (32 mg) a

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0 °C, seguido de agitación durante 10 minutos. Se añadió a la misma agua, seguido de extracción con cloroformo. Se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=20:80, y posteriormente metanol:cloroformo=98:2-90:10) para obtener N-[2-(ciclopentilsulfonil)etil]-4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-1,3,5-triazin-2-amina (53 mg) como un polvo blanco.

Ejemplo 92 (no englobado en las reivindicaciones)

Se disolvió 2-(difluorometil)-1-[6-(1,4-dioxaspiro[4.5]deca-8-ilmetoxi)-2-(metilsulfonil)pirimidin-4-il]-1H-benzimidazol (1,3 g) en diclorometano (20 ml), y se añadió al mismo ácido m-cloroperbenzoico, (75 % húmedo) (712 mg) a 0 °C, seguido de agitación durante 30 minutos. A la solución de reacción se le añadió bicarbonato de sodio acuoso saturado, seguido de extracción con cloroformo. Se lavaron los extractos con agua y salmuera saturada, se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se disolvió el residuo en dimetilformamida (10 ml), y se añadió al mismo morfolina (1,22 ml), seguido de agitación a temperatura ambiente durante 2 horas. Se vertió la solución de reacción en agua, seguido de extracción con acetato de etilo. Se lavaron los extractos con agua y salmuera saturada, se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=95:5-80:20) para obtener 2-(difluorometil)-1-[6-(1,4-dioxaspiro[4.5]deca-8-ilmetoxi)-2-(morfolin-4-il)pirimidin-4-il]-1H-benzimidazol (1,21 g) como un polvo blanco.

Ejemplo 93 (no englobado en las reivindicaciones)

Se disolvió 2-(difluorometil)-1-[6-(1,4-dioxaspiro[4.5]deca-8-ilmetoxi)-2-(morfolin-4-il)pirimidin-4-il]-1H-benzimidazol (1,2 g) en un disolvente mezclado de tetrahidrofurano (12 ml) y agua (12 ml), y se añadió al mismo ácido 4-metilbencenosulfónico monohidrato (2,27 g), seguido de agitación a temperatura ambiente durante 3 horas. A la solución de reacción se le añadió bicarbonato de sodio acuoso saturado, seguido de extracción con acetato de etilo. Se lavaron los extractos con agua y salmuera saturada, se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=80:20-40:60) para obtener 4-[[6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi]metil]ciclohexanona (941 mg) como un polvo blanco.

Ejemplo 94 (no englobado en las reivindicaciones)

Se disolvió N-[2-(ciclopentilsulfonil)etil]-4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-1,3,5-triazin-2-amina (60 mg) en cloruro de metileno (1,2 ml), y se añadió a la misma ácido m-cloroperbenzoico, (75 % húmedo) (73 mg) a 0 °C, seguido de agitación durante 10 minutos. Se añadió a la misma agua, seguido de extracción con cloroformo. Se secó la capa orgánica sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=50:50-0:100) para obtener N-[2-(ciclopentilsulfonil)etil]-4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-1,3,5-triazin-2-amina (58 mg) como un polvo blanco.

Ejemplo 237 (no englobado en las reivindicaciones)

A una solución de [3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)azetidín-1-il](cis-4-hidroxíciclohexil)metanona (60 mg) en cloruro de metileno (1,2 ml) se le añadió un reactivo de Dess-Martin (53 mg) bajo enfriamiento con hielo, seguido de agitación a temperatura ambiente durante la noche. A la mezcla de reacción se le añadió acetato de etilo y una solución acuosa saturada de bicarbonato de sodio, se extrajo la capa orgánica, se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio anhidro, y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (cloroformo:metanol=100:0-90:10) para obtener 4-[[3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il]oxi)azetidín-1-il]carbonil]ciclohexanona (20 mg).

Ejemplo 238 (no englobado en las reivindicaciones)

Se disolvió 4-(morfolin-4-ilmetil)bencenosulfonamida (35 mg) en N,N-dimetilacetamida (1,25 ml), y se añadió a la misma hidruro de sodio al 60 % (24 mg), seguido de agitación a temperatura ambiente durante 30 minutos. A la mezcla de reacción se le añadió 1-[6-cloro-2-(morfolin-4-il)pirimidin-4-il]-2-(difluorometil)-1H-benzimidazol (50 mg), seguido de agitación a 120 °C durante 1 hora. Se enfrió la mezcla hasta temperatura ambiente, y después se añadió a la misma una solución acuosa saturada de cloruro de sodio, acetato de etilo, y tetrahidrofurano, seguida de neutralización con una solución acuosa al 10 % de hidrogenosulfato de potasio, y después se extrajo la capa orgánica. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio, y se secó sobre sulfato de magnesio anhidro. Se retiró por filtración el desecante y después se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=20:80-0:100 y posteriormente cloroformo:metanol=100:0-80:20) para obtener N-{6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}-4-(morfolin-4-ilmetil)bencenosulfonamida (13 mg).

Ejemplo 239 (no englobado en las reivindicaciones)

Se disolvió ácido trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)ciclohexanocarboxílico (232 mg) en tetrahidrofurano (2,3 ml), y se añadieron al mismo clorofornio de isobutilo (70 µl) y 4-metilmorfolina (60 µl) a 0 °C, seguido de agitación a 0 °C durante 30 minutos y a temperatura ambiente durante 2 horas. Posteriormente, se añadió al mismo amoniaco acuoso al 28 % (300 µl) a 0 °C, seguido de agitación durante 2 horas. Se evaporó el disolvente a presión reducida y se purificó por cromatografía en gel de sílice (hexano:acetato de etilo=40:60-0:100 y cloroformo:metanol=100:0-95:5) para obtener trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)ciclohexanocarboxamida (230 mg).

Ejemplo 240 (no englobado en las reivindicaciones)

A una solución de N-{4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il}ciclohexano-1,3-diamina (70 mg) en dimetilacetamida (1,4 ml) se le añadieron trietilamina (56 µl) y éter bis(2-bromometílico) (31 µl), seguido de agitación a 120 °C durante 2 horas usando un reactor de microondas. A la solución de reacción se le añadió agua, seguido de extracción con acetato de etilo. Los extractos se lavaron con agua y salmuera saturada. Se secó la capa orgánica sobre sulfato de magnesio anhidro, se retiró por filtración el desecante, y después se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=60:40-20:80) para obtener 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-N-[3-(morfolin-4-il)ciclohexil]pirimidin-2-amina (42 mg).

Ejemplo 241 (no englobado en las reivindicaciones)

A una mezcla de diclorhidrato de 4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-morfolin-4-il)-N-[(3S)-pirrolidin-3-il]pirimidin-2-amina (100 mg) y cloruro de metileno (1 ml) se le añadieron trietilamina (0,1 ml) y cloruro de benzoilo (28,5 µl) bajo un flujo de aire de nitrógeno al mismo tiempo de enfriamiento con hielo, seguido de agitación a la misma temperatura durante 4 horas. A la mezcla de reacción se le añadió agua (30 ml), seguido de extracción con acetato de etilo (100 ml). Se lavó la capa orgánica con salmuera saturada (50 ml) y se secó sobre sulfato de sodio anhidro. Se retiró por filtración el desecante y se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (cloroformo:metanol=100:0-90:10). Esto se solidificó con acetato de etilo y éter diisopropílico, después se recogió por filtración, y se secó para obtener [(3S)-3-({4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il}amino)pirrolidin-1-il](fenil)metanona (66 mg) como un polvo blanco.

Ejemplo 242 (no englobado en las reivindicaciones)

A una solución de trans-N-{4-[2-(difluorometil)-6-metil-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il}ciclohexano-1,4-diamina (150 mg) en etanol (3 ml) se le añadió 1H-1,2,3-benzotriazol-1-ilmetanol (59 mg), seguido de agitación a temperatura ambiente durante 5 horas. A esta mezcla se le añadió borohidruro de sodio (25 mg), seguido de agitación adicional a temperatura ambiente durante 1 hora. A la mezcla de reacción se le añadió agua, seguido de extracción con acetato de etilo. La capa orgánica se lavó con una solución acuosa saturada de cloruro de sodio y se secó sobre sulfato de magnesio anhidro. Se retiró por filtración el desecante y después se evaporó el disolvente a presión reducida. Se separó el residuo y se purificó por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=50:50-0:100 y cloroformo:metanol=100:0-98:2) para obtener trans-N'-{4-[2-(difluorometil)-6-metil-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il}-N,N-dimetilciclohexano-1,4-diamina (50 mg) (ejemplo 242-1) y trans-N-{4-[2-(difluorometil)-6-metil-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il}-N'-metilciclohexano-1,4-diamina (100 mg) (ejemplo 242-2).

Ejemplo 243 (no englobado en las reivindicaciones)

A una solución de trans-N-{4-[2-(difluorometil)-6-metil-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il}ciclohexano-1,4-diamina (50 mg) en cloruro de metileno (1 ml) se le añadieron trietilamina (46 µl) y cloruro de 4-clorobutilo (16 µl), seguido de agitación durante 1 hora en un baño de agua. Se concentró la solución de reacción a presión reducida y al residuo se le añadieron tetrahidrofurano (5 ml) e hidruro de sodio al 60 % (13 mg), seguido de agitación a 0 °C durante 30 minutos y a temperatura ambiente durante 1 hora. A la solución de reacción se le añadió agua, seguido de extracción con acetato de etilo, y se lavaron los extractos con agua y salmuera saturada, y se secaron sobre sulfato de magnesio anhidro. Se retiró por filtración el desecante y después se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=50:50-0:100 y cloroformo:metanol=100:0-90:10) para obtener 1-[trans-4-({4-[2-(difluorometil)-6-metil-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il}amino)ciclohexil]pirrolidin-2-ona (40 mg).

Ejemplo 244 (no englobado en las reivindicaciones)

A una mezcla N-{4-[2-(difluorometil)-1H-benzimidazo-1-il]-6-(morfolin-4-il)pirimidin-2-il}-L-alaninato de terc-butilo (80 mg) y cloruro de metileno (3 ml) se le añadió una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (0,84 ml), seguido de agitación durante 4 horas. Después de la finalización de la reacción, se evaporó el disolvente a presión

reducida y después de secó para obtener clorhidrato de N-{4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]-L-alanina (83 mg).

Ejemplo 245 (no englobado en las reivindicaciones)

5 A una solución de 2-(benciloxi)etil{(3S)-1-[trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il} oxo)ciclohexil]-2-oxopirrolidin-3-il}carbamato (84 mg) en metanol (1 ml) se le añadió paladio al 10 %-carbono (50 % húmedo) (84 mg), seguido de agitación a temperatura ambiente durante la noche a 3 atm en una atmósfera de hidrógeno. Se retiró el catalizador y se concentró el filtrado a presión reducida. Se purificó el residuo por
10 cromatografía en gel de sílice (cloroformo:metanol=100:0-92:8) para obtener 2-hidroxiethyl{(3S)-1-[trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxo)ciclohexil]-2-oxopirrolidin-3-il}carbamato (30 mg).

Ejemplo 246 (no englobado en las reivindicaciones)

15 A una mezcla de 2-{4-[(4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)metil]piperidin-1-il}ciclopentanocarboxilato de metilo (50 mg) y tetrahidrofurano (1 ml) se le añadió una solución 1,06 M de metillitio en éter dietílico a 0 °C, seguido de agitación a la misma temperatura durante 4 horas. A la mezcla de reacción se le añadió una solución acuosa saturada de cloruro de amonio, seguido de extracción con acetato de etilo. Se lavó la
20 capa orgánica con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y después se concentró a presión reducida. Se purificó el residuo por cromatografía en columna en gel de amino sílice (hexano:acetato de etilo=1:2-0:100) para obtener 2-(2-{4-[(4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)metil]piperidin-1-il}ciclopentil)propan-2-ol (11,1 mg).

Ejemplo 247 (no englobado en las reivindicaciones)

25 Se suspendió trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxo)ciclohexanol (100 mg) en N,N-dimetilformamida (4 ml), y se añadió al mismo 1,1'-carbonildiimidazol (73 mg), seguido de agitación a 60 °C durante 2 horas. Además, se añadió al mismo 1,1'-carbonildiimidazol (182 mg), seguido de agitación a 60 °C durante 2 horas. A esta mezcla se le añadió carbonato de guanidina (405 mg) a temperatura ambiente, seguido de
30 agitación a temperatura ambiente durante la noche. Se añadió a la misma agua, seguido de extracción con acetato de etilo, se lavó la capa orgánica con agua y salmuera saturada, y se secó sobre sulfato de sodio anhidro, y después se evaporó el disolvente a presión reducida. Se purificó el residuo por cromatografía en columna en gel de sílice (MeOH al 10 %/cloroformo: cloroformo=10:90-90:10) para obtener trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxo)ciclohexilcarbamidilcarbamato (103 mg).

Ejemplo 248 (no englobado en las reivindicaciones)

40 Se agitó una mezcla de clorhidrato de 2-(difluorometil)-1-[2-(metilsulfonyl)-6-(morfolin-4-il)pirimidin-4-il]-1H-benzimidazol (200 mg) y [(3S)-1-(trans-4-aminociclohexil)-2-oxopirrolidin-3-il]carbamato de metilo (214 mg), carbonato de potasio (135 mg), N-etil-N-diisopropilpropan-2-amina (0,38 ml) y N,N-dimetilacetamida (3 ml) se agitó a 100 °C durante 6 horas. Después de dejar que se enfriara, a la solución de reacción se le añadió agua, seguido de extracción con acetato de etilo. Se lavó la capa orgánica con salmuera saturada y se secó sobre sulfato de sodio anhidro. Se retiró por filtración el desecante y se evaporó el disolvente a presión reducida. Se purificó el residuo por
45 cromatografía en columna en gel de sílice (cloroformo/metanol=100:0-80:20) para obtener {(3S)-1-[trans-4-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)ciclohexil]-2-oxopirrolidin-3-il}carbamato de metilo (102 mg) como un polvo blanco.

Ejemplo 249

50 Se disolvió N-(azetidín-3-il)-6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-amina (100 mg) en N,N-dimetilformamida (1 ml), y se añadieron a la misma ácido 4-metoxiciclohexanocarboxílico (43 mg), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) (142 mg), y N, N-diisopropiletilamina (213 µl), seguido de agitación a temperatura ambiente durante 3 horas. A la mezcla de reacción se le añadió agua (100 ml), seguido de extracción con acetato de etilo (100 ml). Se lavaron los extractos con agua y
55 salmuera saturada, y después se secó sobre sulfato de magnesio anhidro. Se retiró por filtración el desecante y después se evaporó el disolvente a presión reducida. Se separó/purificó el residuo por cromatografía en columna en gel de sílice (de hexano:acetato de etilo=50:50-0:100 a cloroformo:metanol=100:0-80:20) para obtener [3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il} amino)azetidín-1-il][cis-4-metoxiciclohexil]metanona (26 mg) (ejemplo 249-1) y [3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il} amino)azetidín-1-il] (trans-4-metoxiciclohexil)metanona (7,1 mg) (ejemplo 249-2).

Ejemplo 422 (no englobado en las reivindicaciones)

65 A una mezcla de 2-{4-[(4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)metil]piperidin-1-il}ciclopentano-carboxilato de metilo (50 mg) y tetrahidrofurano (1 ml) se le añadieron a solución 1,01 M de diisobutilaluminio (240 µl) en tolueno a 0 °C, seguido de agitación a la misma temperatura durante 6 horas. A la

mezcla de reacción se le añadió metanol y sulfato de sodio decahidrato, seguido de agitación a temperatura ambiente durante 1 hora. Se retiró la materia insoluble por filtración y después se concentró a presión reducida, y se purificó el residuo por cromatografía en columna en gel de sílice (hexano:acetato de etilo=50:50-0:100) para obtener (2-{4-[(4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)pirimidin-2-il]amino)metil]piperidin-1-il}ciclopentil)metanol (33 mg) deseado.

Ejemplo 432

Se resolvió ópticamente N-{6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}-1-(tetrahydro-2H-piran-4-il)azepan-4-amina racémica (300 mg) usando cromatografía de fluido supercrítico para obtener la sustancia ópticamente activa, N-{6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}-1-(tetrahydro-2H-piran-4-il)azepan-4-aminas (135 mg (TR 6,76 min) y 137 mg (TR 8,03 min)) como sustancias amorfas blancas, respectivamente. Fraccionamiento por SFC: AD-H/4,6x250 mm /CO₂ 75%, MeOH (0,1% DEA) 25%/flujo 3 ml/min/Conc. 2 mg/ml/tr=6,76 min, 8,03 min

Ejemplo A1 (no englobado en las reivindicaciones)

A una solución de 1-metilpiperidin-4-amina (4,6 mg) en N,N-dimetilformamida (200 µl) se le añadió una solución de N,N-diisopropiletilamina (8,7 µl) en N,N-dimetilformamida (50 µl) y una solución de 1-[4-cloro-6-(morfolin-4-il)-1,3,5-triazin-il]-2-(difluorometil)-1H-benzimidazol (9,2 mg) en N,N-dimetilformamida (300 µl), seguido de agitación a 80 °C durante la noche. A la mezcla de reacción se le añadió una solución acuosa saturada de bicarbonato de sodio y cloroformo a temperatura ambiente, seguido de separación de fases líquido-líquido, y se concentró la capa orgánica a presión reducida. Se purificó el residuo por HPLC preparativa para obtener 4-[2-(difluorometil)-1H-benzimidazolil]-N-(1-metilpiperidin-4-il)-6-(morfolin-4-il)-1,3,5-triazin-2-amina (11,1 mg).

Ejemplo B1 (no englobado en las reivindicaciones)

A una solución de 1-(4-hidroxifenil)etanol (5,4 mg) en N,N-dimetilformamida (200 µl) se le añadieron carbonato de potasio (6,9 mg) y una solución de 1-[4-cloro-6-(morfolin-4-il)-1,3,5-triazin-il]-2-(difluorometil)-1H-benzimidazol (9,2 mg) en N,N-dimetilformamida (300 µl), seguido de agitación a 80 °C durante la noche. A la solución de reacción se le añadió agua y cloroformo a temperatura ambiente, seguido de separación de fases líquido-líquido, y se evaporó la capa orgánica a presión reducida. Se purificó el residuo por HPLC preparativa para obtener 1-[4-((4-[2-(difluorometil)-1H-benzimidazol-1-il]-6-(morfolin-4-il)-1,3,5-triazin-2-il]oxi)fenil)etanol (1,4 mg).

Las condiciones para la HPLC llevada a cabo para determinar el TR en los ejemplos A1 y B1 se muestran a continuación.

Columnas: Wakosil-II 5 C18AR (Wako Pure Chemical Industries, Ltd.) (diámetro de partícula: 5 µl, diámetro interno: 2,0 mm, longitud: 30 mm)

Fase móvil: Solución A solución acuosa 5 mM de ácido trifluoroacético, Solución B metanol

Caudal: 1,2 ml/min; longitud de onda de detección: 254 nm; temperatura de columna: 35,0°C; cantidad de inyección: 5 µl

[Tabla 3]

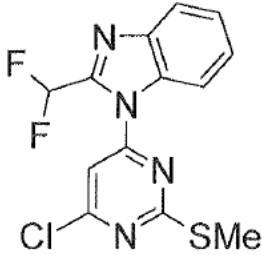
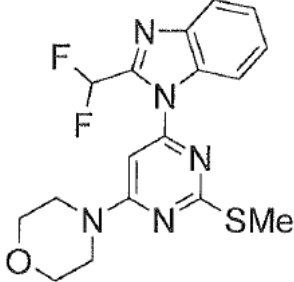
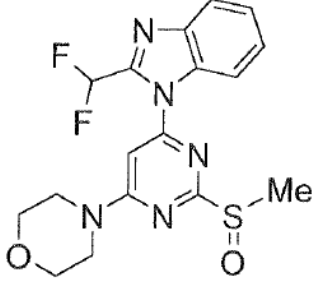
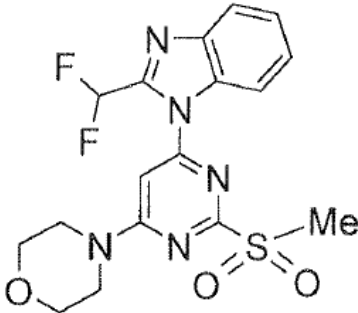
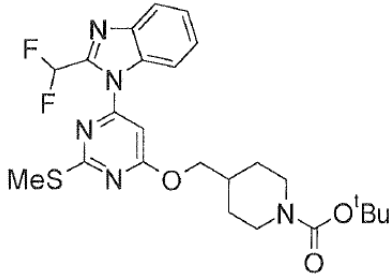
Tiempo (min)	sol A (%)	sol B (%)	Elución
0-4	95 → 0	5 → 100	Gradiente
4-4,5	0	100	Isocrática

Los compuestos de los ejemplos de preparación y los ejemplos mostrados en las tablas a continuación se prepararon de la misma manera que en los ejemplos de preparación y ejemplos como se describe anteriormente.

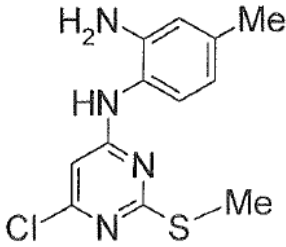
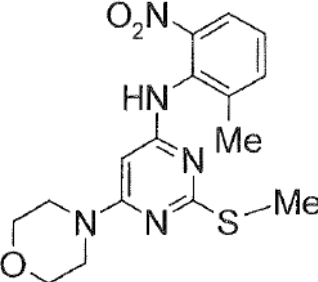
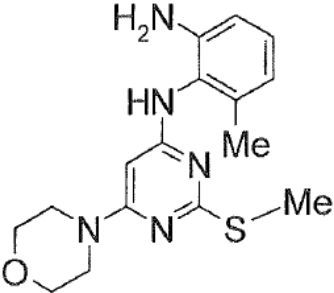
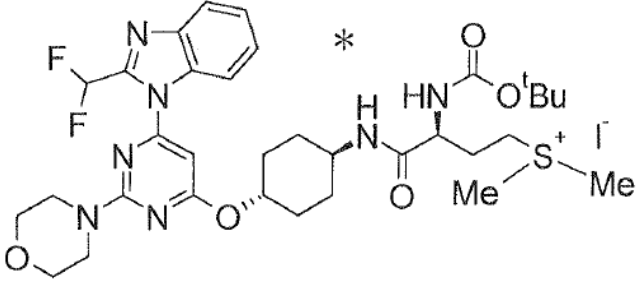
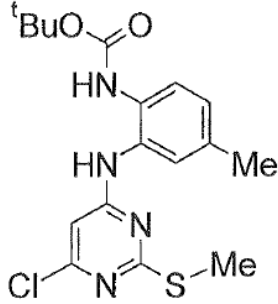
Las fórmulas estructurales químicas, los procedimientos de preparación y los datos fisicoquímicos de los compuestos de los ejemplos de preparación se muestran en las tablas 4 a 34. Además, las fórmulas estructurales químicas de los compuestos de los ejemplos se muestran en las tablas 35 a 139, y los procedimientos de preparación y los datos fisicoquímicos de los compuestos de los ejemplos se muestran en las tablas 140 a 161.

Además, las estructuras y los datos fisicoquímicos de los compuestos de los ejemplos preparados de la misma manera que el procedimiento del ejemplo A1 se muestran en las tablas 162 a 306, y las estructuras y los datos fisicoquímicos de los compuestos de los ejemplos preparados de la misma manera que el procedimiento del Ejemplo B1 se muestran en las tablas 307 a 337.

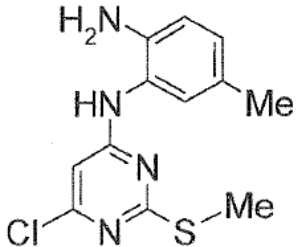
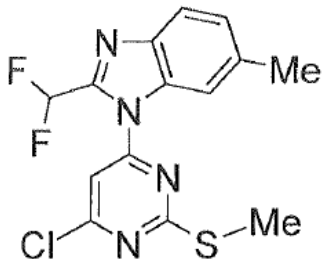
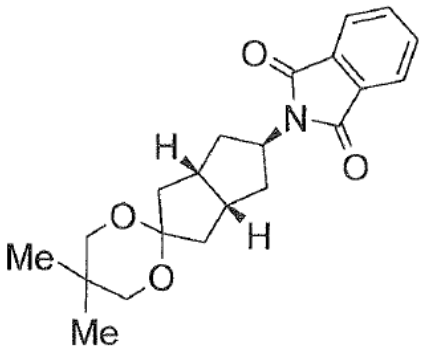
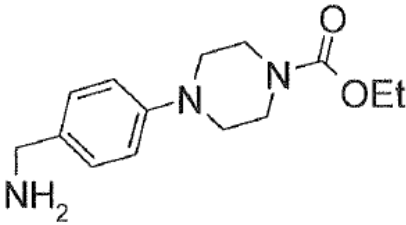
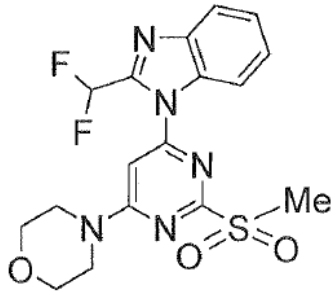
[Tabla 4]

EjP	SinP	Estr	DAT
1	1		ESI+: 327
2	2		ESI+: 378
3	3		ESI+: 394
4	4		ESI+: 410
5	5		ESI+: 506

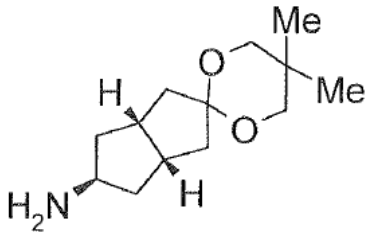
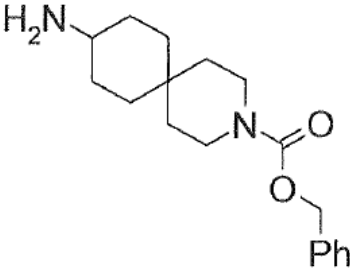
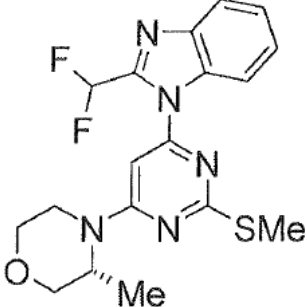
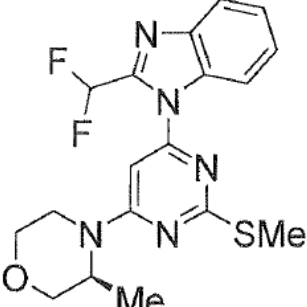
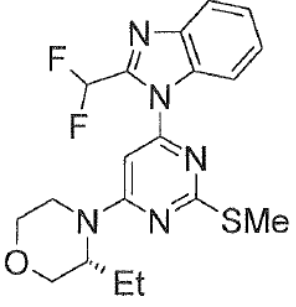
[Tabla 5]

EjP	SinP	Estr	DAT
6	6		ESI+: 281
7	7		ESI+: 362
8	8		ESI+: 332
9	9		ESI+: 690(M+)
10	10		ESI+: 381

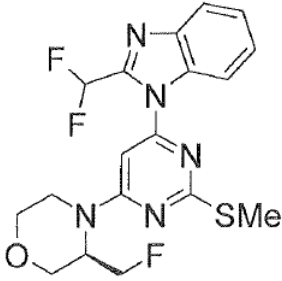
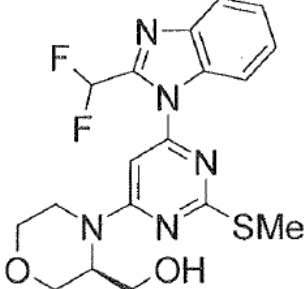
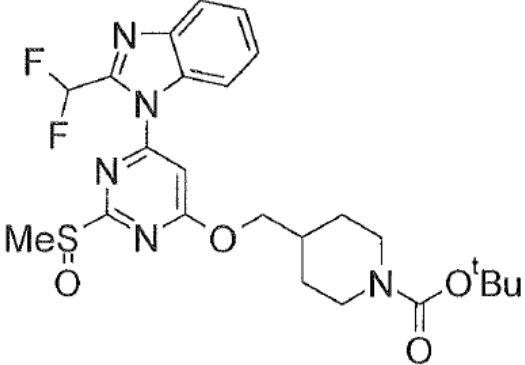
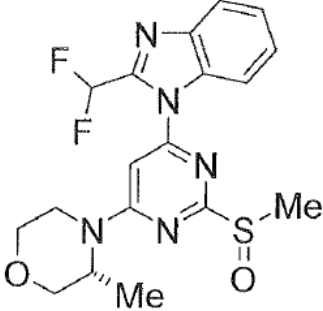
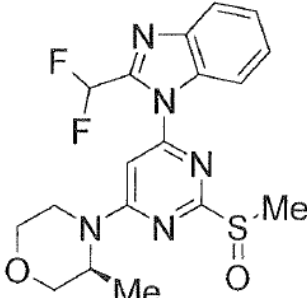
[Tabla 6]

EjP	SinP	Estr	DAT
11	11		ESI+: 281
12	12		ESI+: 341
13	13		ESI+: 356
14	14		ESI+: 264
15	15		ESI+: 410

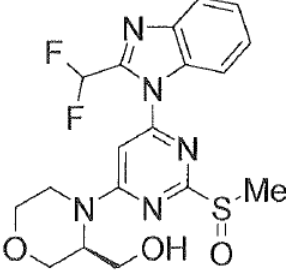
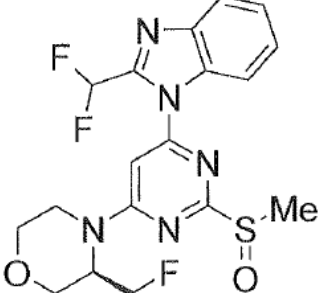
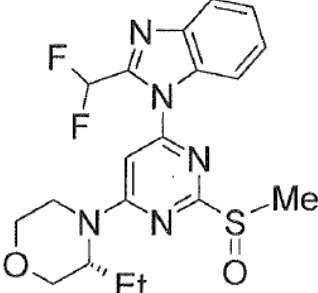
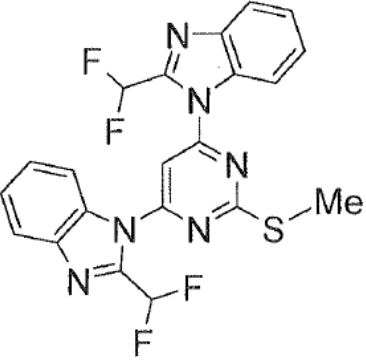
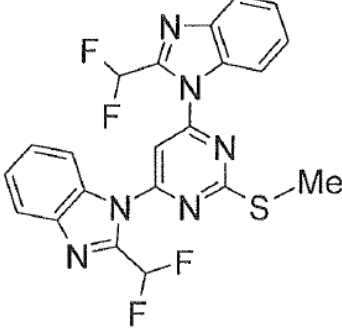
[Tabla 7]

EjP	SinP	Estr	DAT
16	16		ESI+: 226
17	17		ESI+: 303
18	2		ESI+: 392
19	2		ESI+: 392
20	2		ESI+: 406

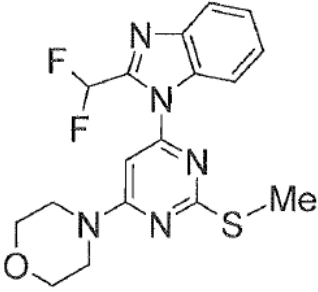
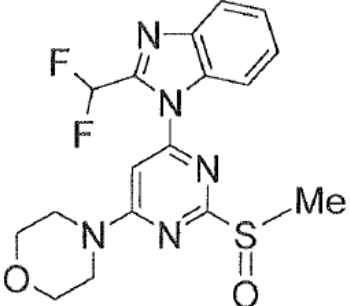
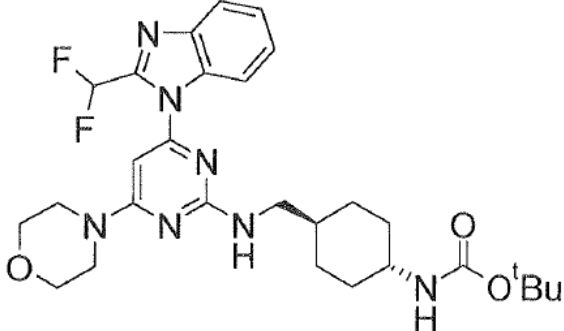
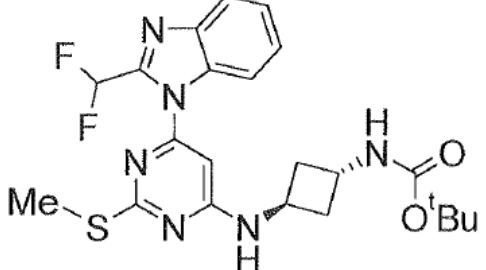
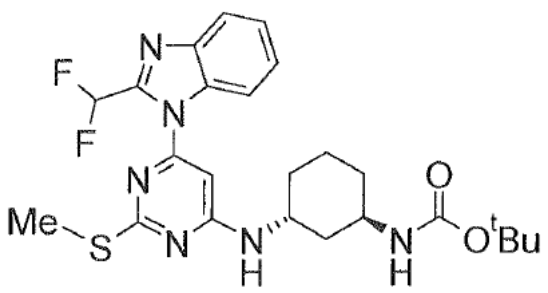
[Tabla 8]

EjP	SinP	Estr	DAT
21	2		ESI+: 410
22	2		ESI+: 408
23	3		ESI+: 522
24	3		ESI+: 408
25	3		ESI+: 408

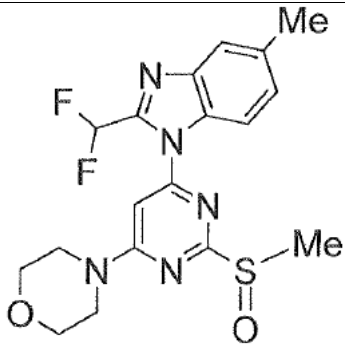
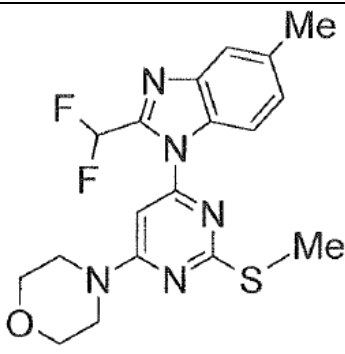
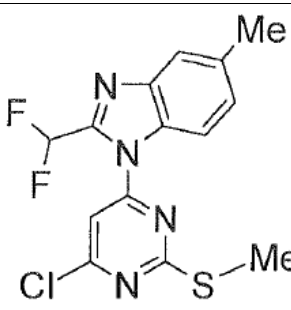
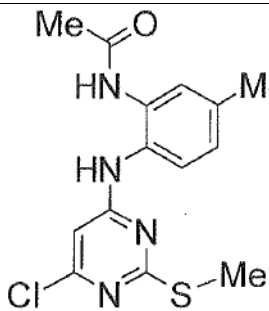
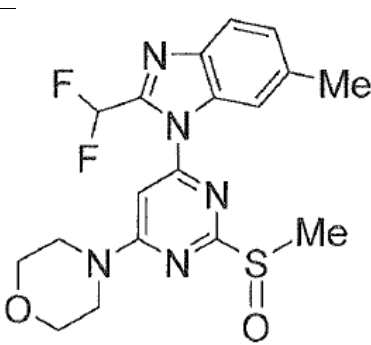
[Tabla 9]

EjP	SinP	Estr	DAT
26	3		ESI+: 424
27	3		ESI+: 426
28	3		ESI+: 422
29	1		ESI+: 459
30	1		ESI+: 459

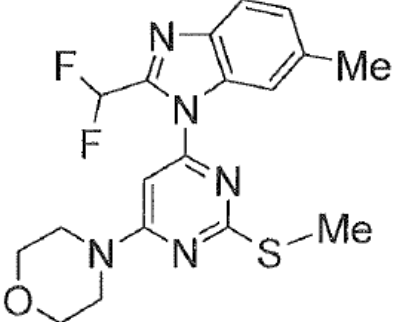
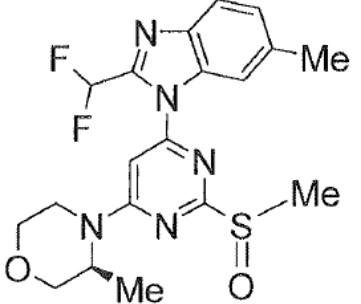
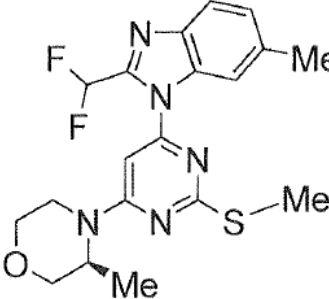
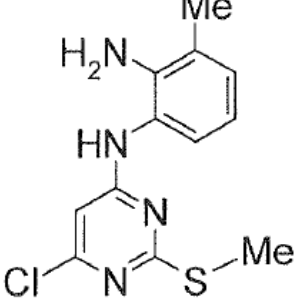
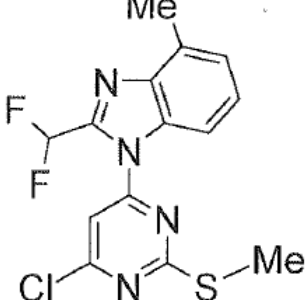
[Tabla 10]

EjP	SinP	Estr	DAT
31	1		ESI+: 378
32	4		ESI+: 394
33	1		ESI+: 580(M+Na)
34	1		ESI+: 477
35	1		ESI+: 505

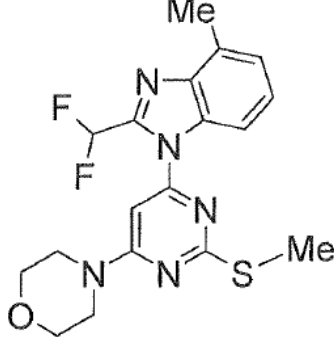
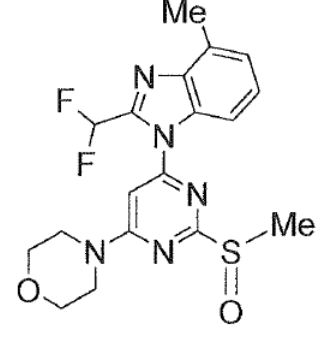
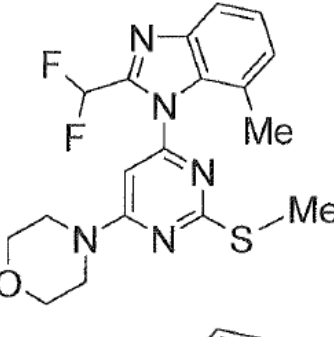
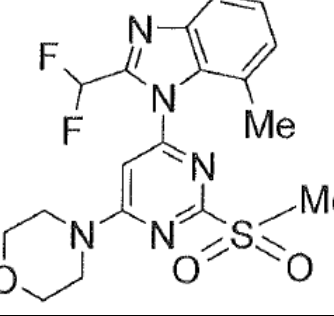
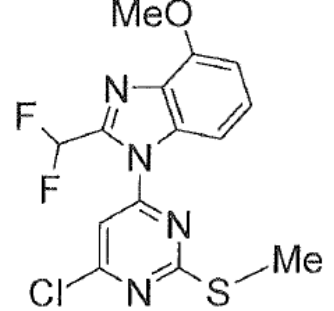
[Tabla 11]

EjP	SinP	Estr	DAT
36	3		ESI+: 408
37	1		ESI+: 392
38	12		ESI+: 341
39	1		ESI+: 323
40	3		ESI+: 408

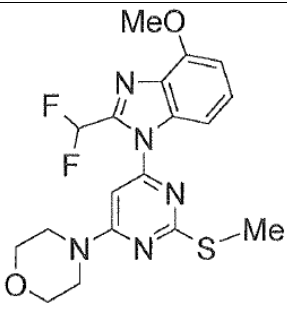
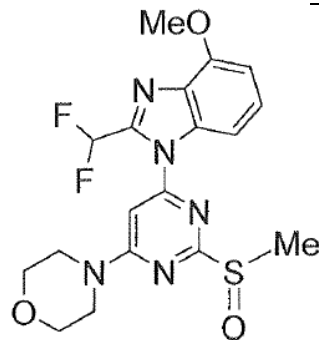
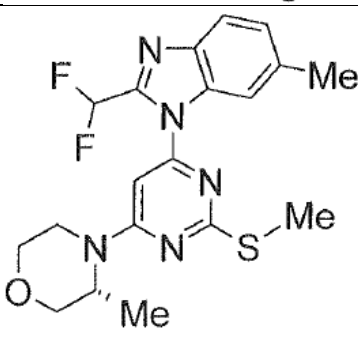
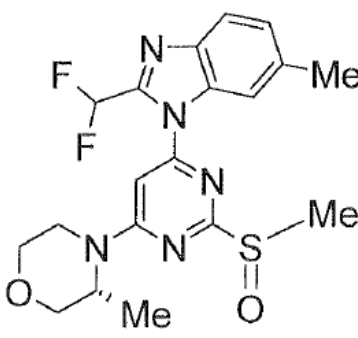
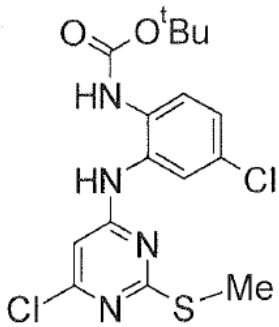
[Tabla 12]

EjP	SinP	Estr	DAT
41	1		ESI+: 392
42	3		ESI+: 422
43	1		ESI+: 406
44	10		ESI+: 281
45	12		ESI+: 341

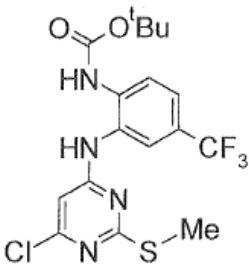
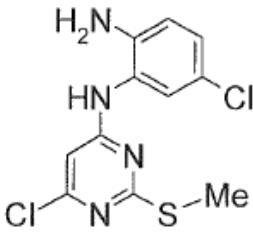
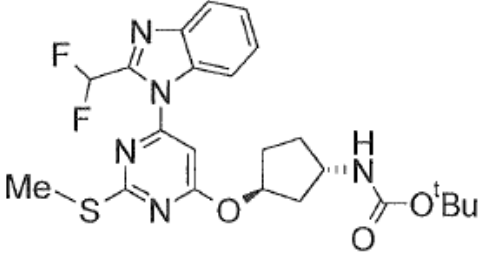
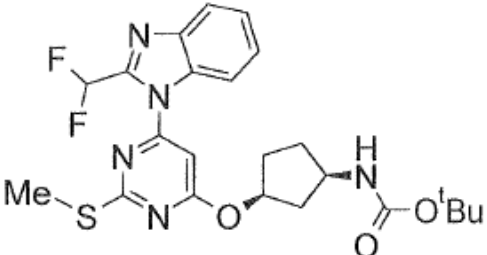
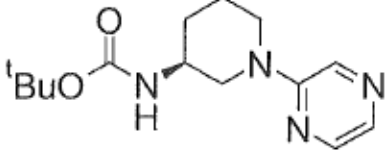
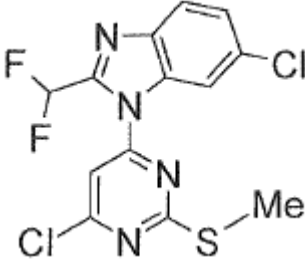
[Tabla 13]

EjP	SinP	Estr	DAT
46	1		ESI+: 392
47	4		ESI+: 408
48	12		ESI+: 392
49	15		ESI+: 424
50	1		ESI+: 357

[Tabla 14]

EjP	SinP	Estr	DAT
51	1		ESI+: 408
52	3		ESI+: 424
53	1		ESI+: 406
54	3		ESI+: 422
55	10		ESI+: 401/403

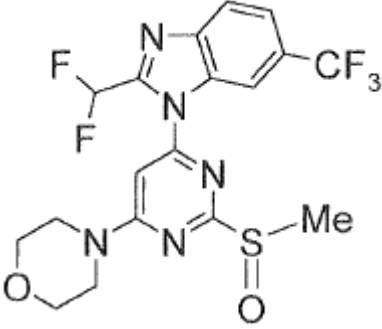
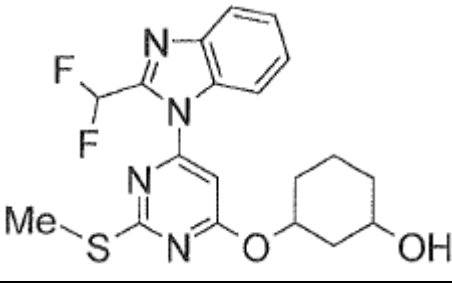
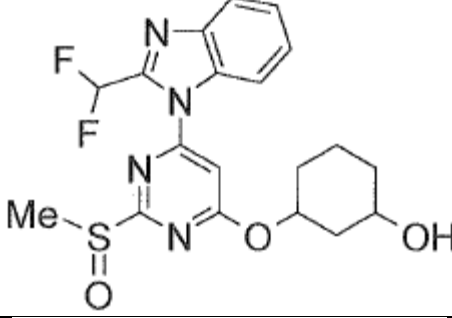
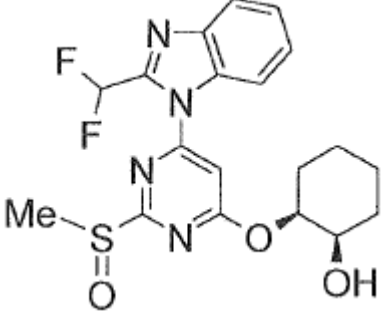
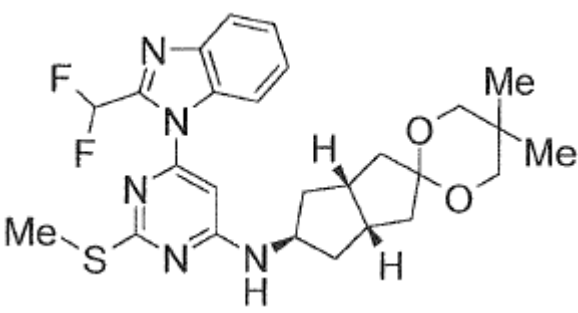
[Tabla 15]

EjP	SinP	Estr	DAT
56	10		ESI+: 435
57	11		ESI+: 301
58	5		ESI+: 492
59	5		ESI+: 492
60	1		ESI+: 279
61	12		ESI+: 361/363

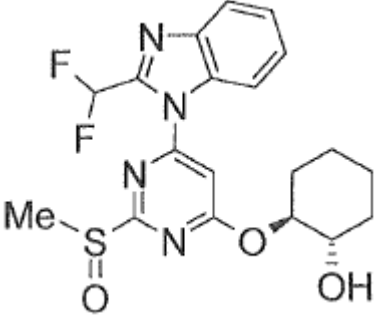
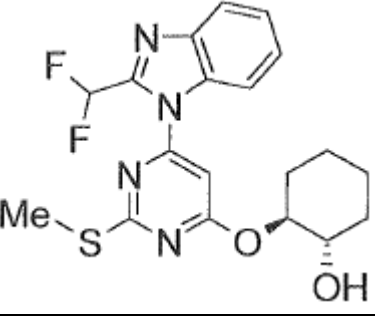
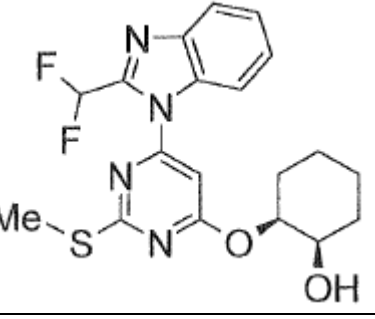
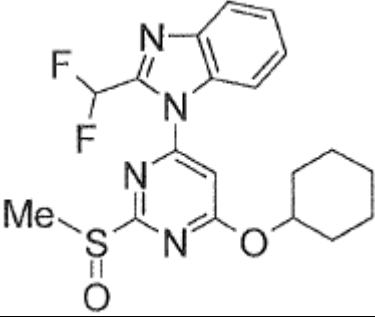
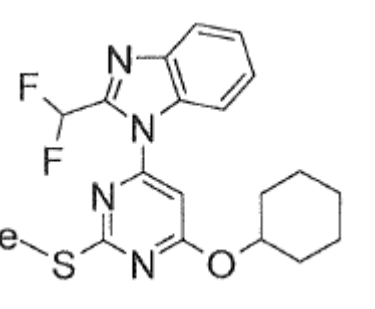
[Tabla 16]

EjP	SinP	Estr	DAT
62	11		ESI+: 335
63	12		ESI+: 395
64	1		ESI+: 412
65	1		ESI+: 446
66	3		ESI+: 428
67	Sin.53		ESI+: 179

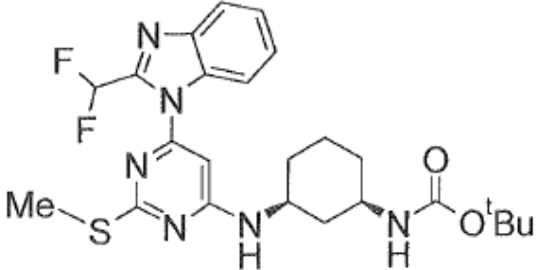
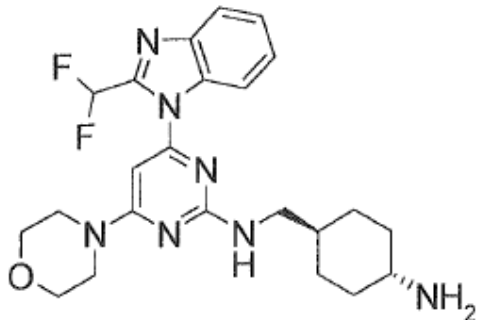
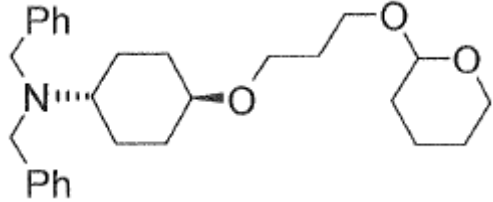
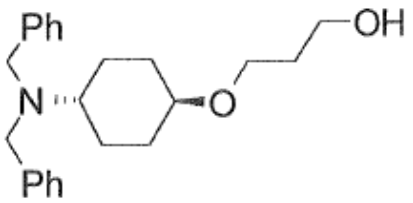
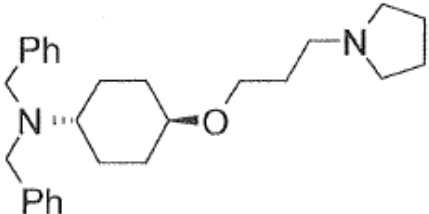
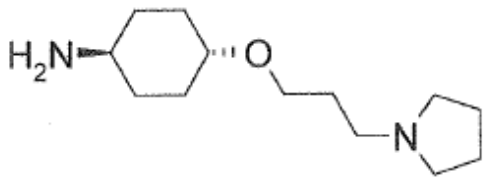
[Tabla 17]

EjP	SinP	Estr	DAT
68	3		ESI+: 462
69	89		ESI+: 407
70	3		ESI+: 423
71	3		ESI+: 423
72	1		ESI+: 516

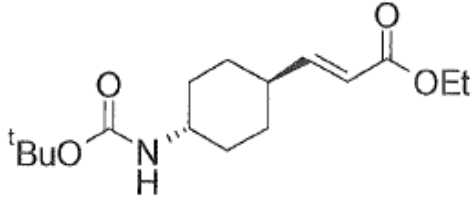
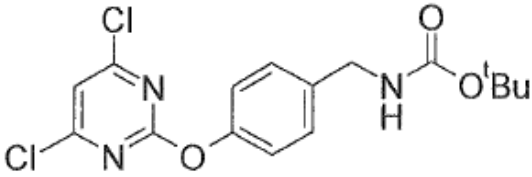
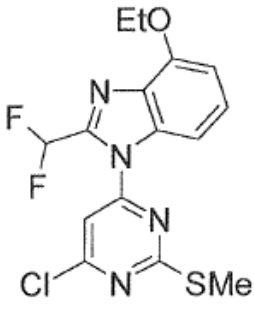
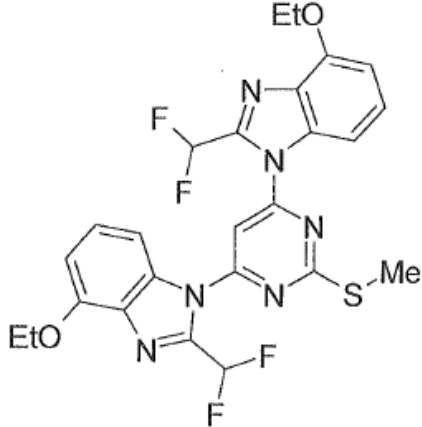
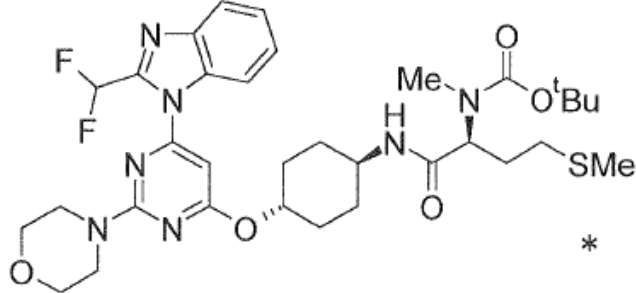
[Tabla 18]

EjP	SinP	Estr	DAT
73	3		ESI+: 423
74	89		ESI+: 407
75	89		ESI+: 407
76	3		ESI+: 407
77	5		ESI+: 391

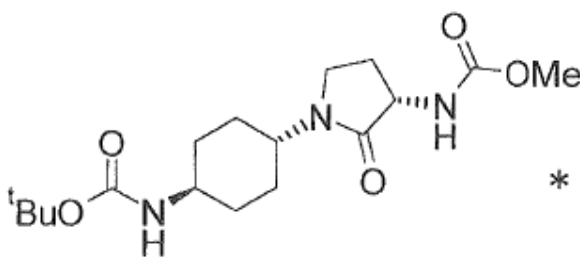
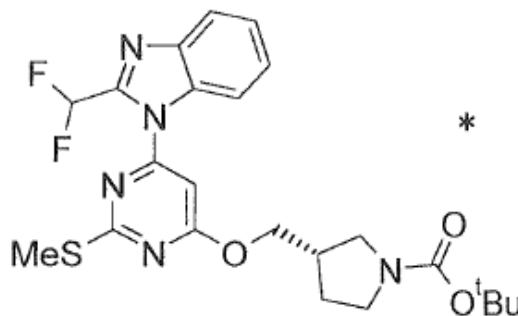
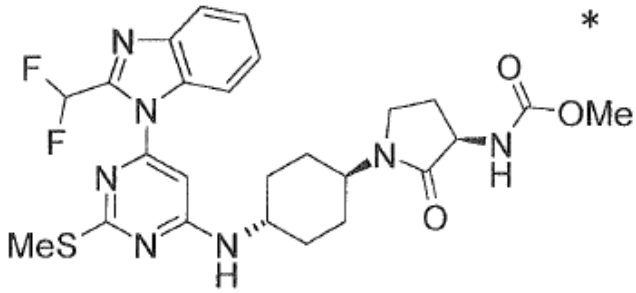
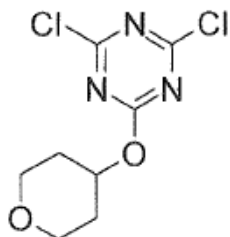
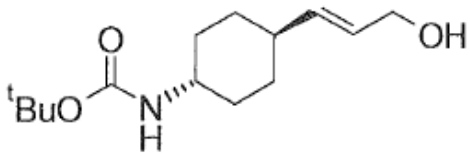
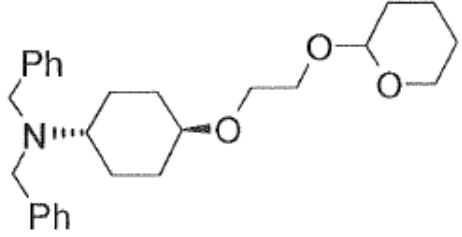
[Tabla 19]

EjP	SinP	Estr	DAT
78	1		ESI+: 505
79	11		ESI+: 458 RMN1:0,82-1,03(4H, m),1,35-2,60(2H, m),1,65-1,82(4H, m),2,99-3,03(2H, m),3,56-3,75(8H, m),6,23-6,37(1H, m),7,09-7,17(1H, m),7,37-7,48(2H, m),7,75-7,79(1H, m),7,82-7,88(1H, m)
80	80		ESI+: 438
81	81		ESI+: 354
82	82		ESI+: 407
83	83		ESI+: 227

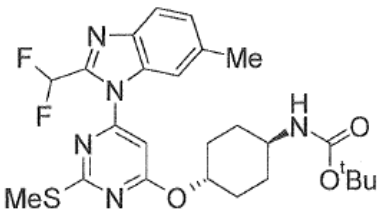
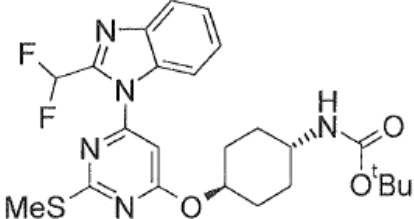
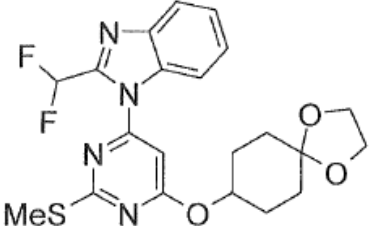
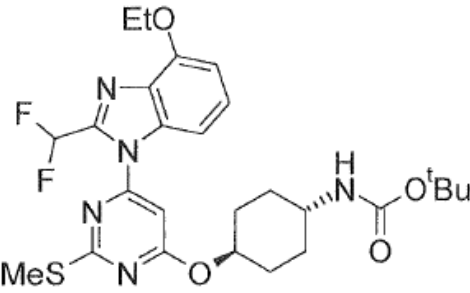
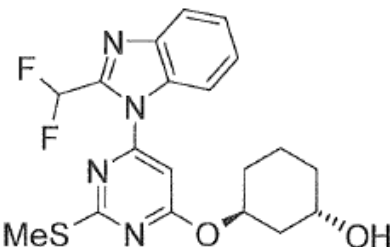
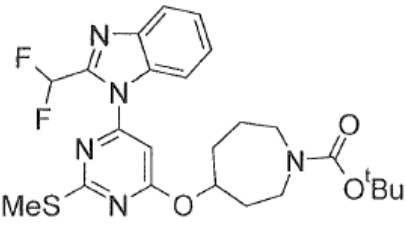
[Tabla 20]

EjP	SinP	Estr	DAT
84	84		ESI+: 320(M+Na)+
85	85		RMN1:1,40(9H, s), 4,08-4,19(2H, m), 7,09-7,34(4H, m), 7,37-7,47(1H, m)
86-1	86		ESI+: 371
86-2	86		ESI+: 547
87	87		ESI+: 690 *

[Tabla 21]

EjP	SinP	Estr	DAT
88	88		ESI+: 356
89	89		ESI+: 492
90	90		ESI+: 546
91	5		RMN2:1,83-1,95(2H,m),2,04-2,14(2H,m),3,58-3,67(2H,m),3.95-4,03(2H,m),5,32-5,40(1H,m)
92	Sin.422		ESI+: 256
93	80		ESI+: 424

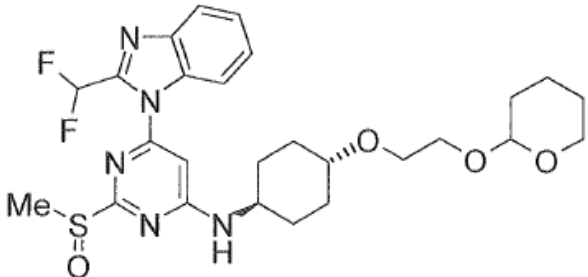
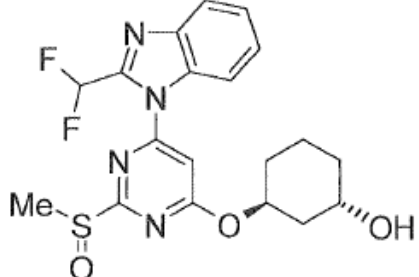
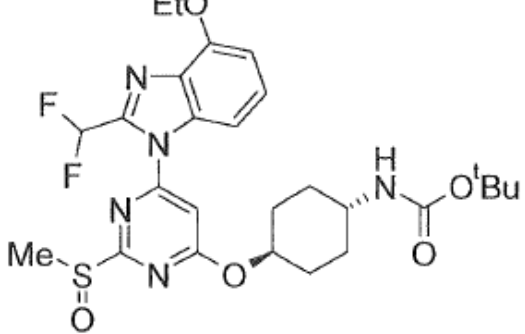
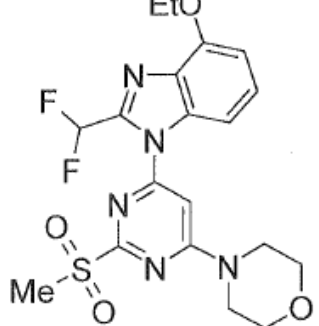
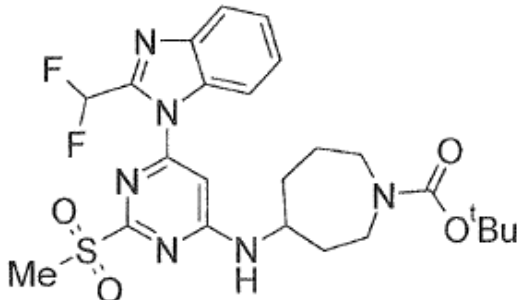
[Tabla 22]

EjP	SinP	Estr	DAT
94	5		no encontrados
95	89		ESI+: 506
96	89		ESI+: 449
97	89		ESI+: 550
98	89		ESI+: 407
99	89		ESI+: 506

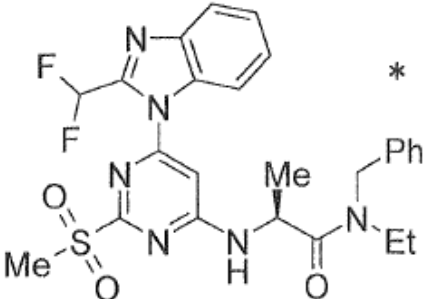
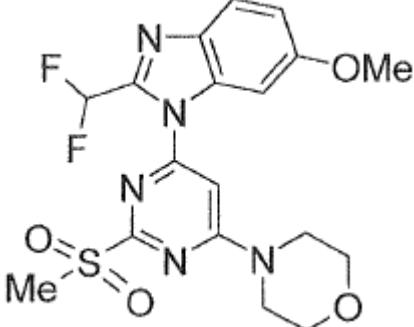
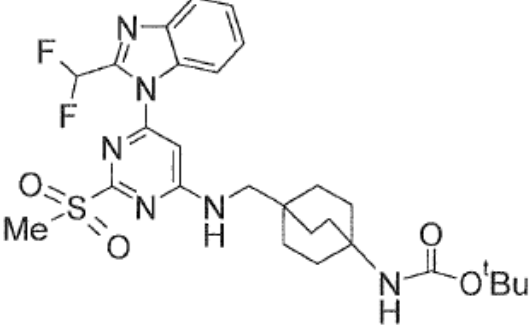
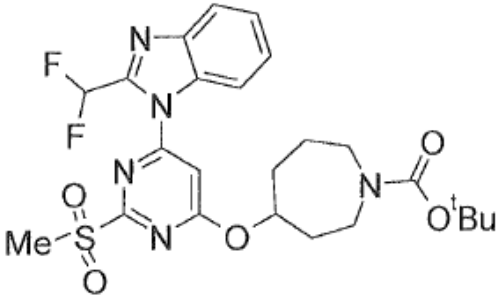
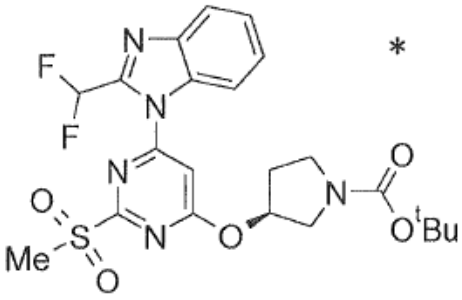
[Tabla 23]

EjP	SinP	Estr	DAT
100	89		ESI+: 478
101	89		ESI+: 407
102	9		ESI+: 690
103	9		ESI+: 704
104	3		ESI+: 564

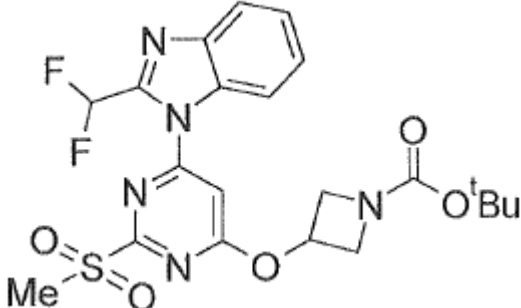
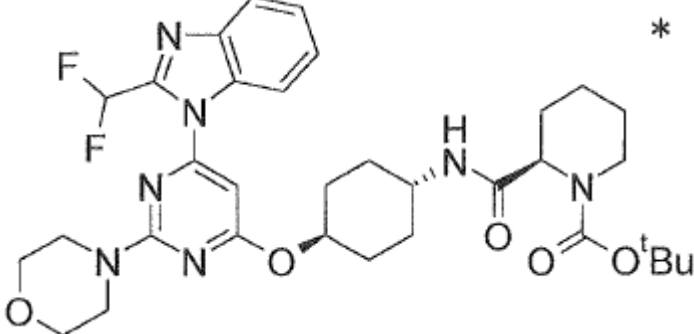
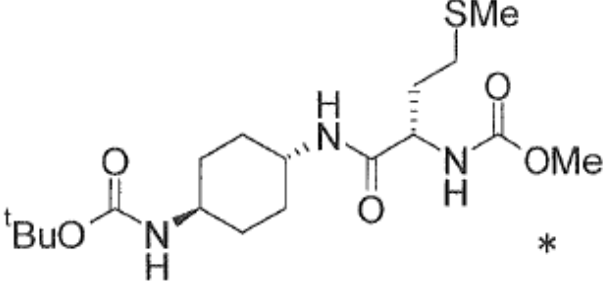
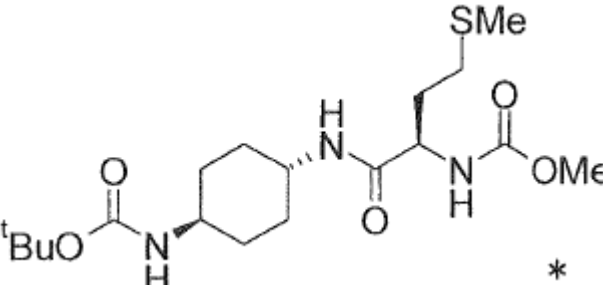
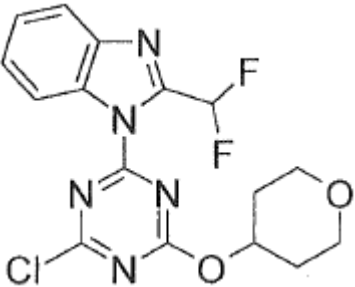
[Tabla 24]

EjP	SinP	Estr	DAT
105	3		ESI+: 550
106	3		ESI+: 423
107	3		ESI+: 566
108	4		ESI+: 454
109	4		ESI+: 537

[Tabla 25]

EjP	SinP	Estr	DAT
110	4		ESI+: 529
111	4		ESI+: 440
112	4		ESI+: 577
113	4		ESI+: 538
114	4		ESI+: 510

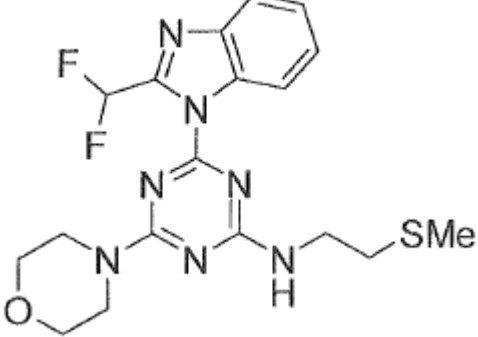
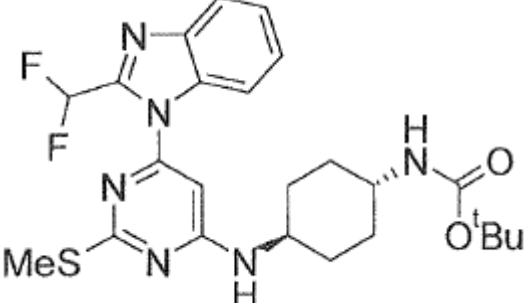
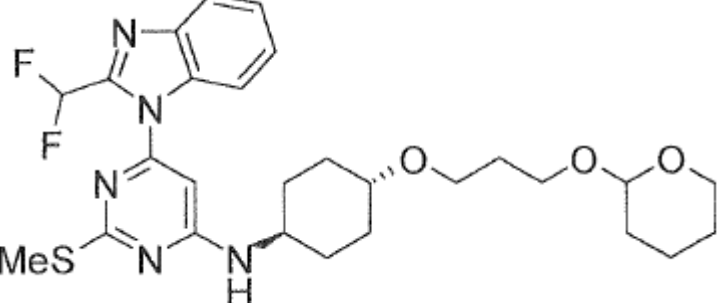
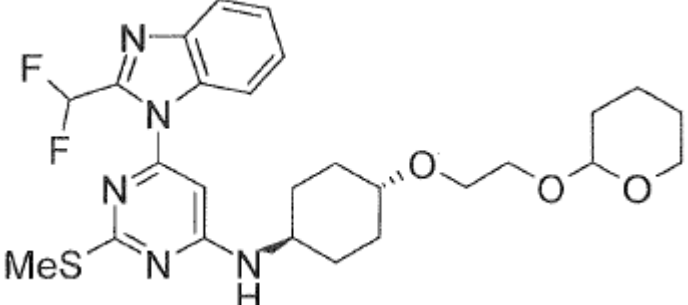
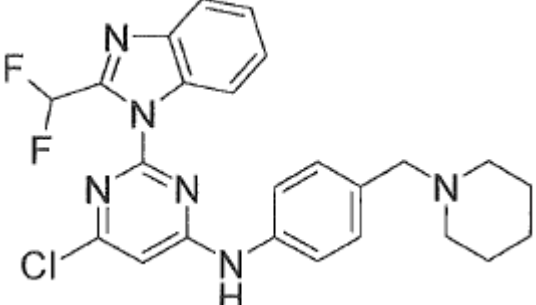
[Tabla 26]

EjP	SinP	Estr	DAT
115	4		ESI+: 496
116	87		ESI+: 656
117	87		ESI+: 404
118	87		ESI+: 404
119	1		ESI+: 382

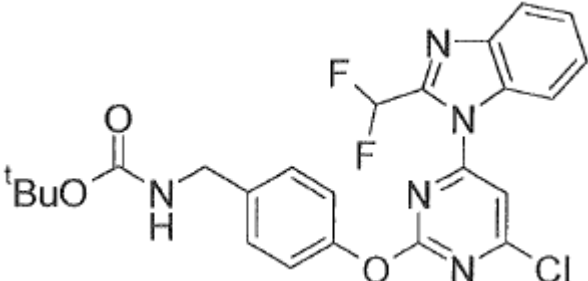
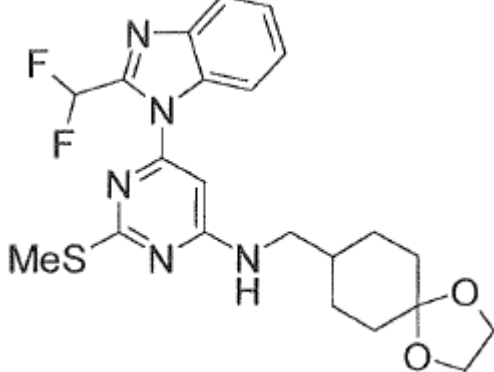
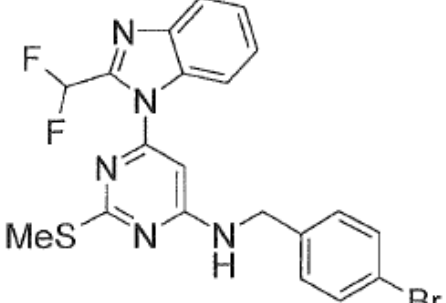
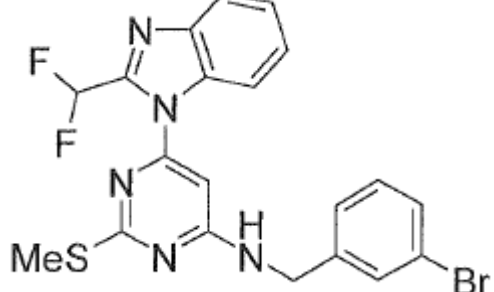
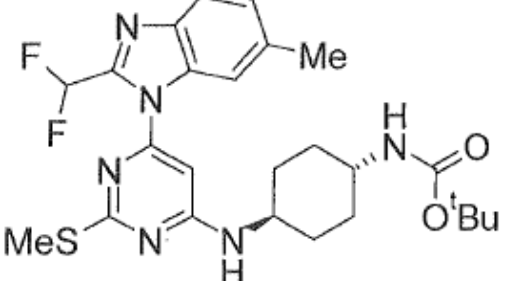
[Tabla 27]

EjP	SinP	Estr	DAT
120	1		ESI+: 367
121	1		RMN1:3,66-3,79(8H, m),7,40-7,69(3H, m),7,8-7,85(1H, d),7,87-7,92(1H,d)
122	1		ESI+: 234
123	1		ESI+: 236
124	1		ESI+: 366

[Tabla 28]

EjP	SinP	Estr	DAT
125	1		ESI+: 422
126	1		ESI+: 527(M+Na)+
127	1		ESI+: 548
128	1		ESI+: 534
129	1		ESI+: 469

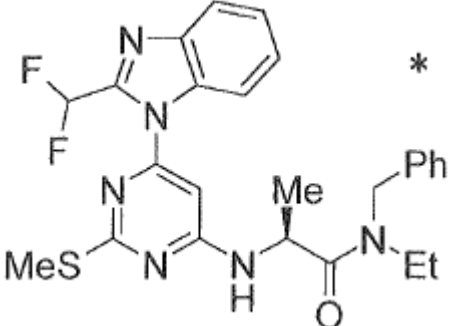
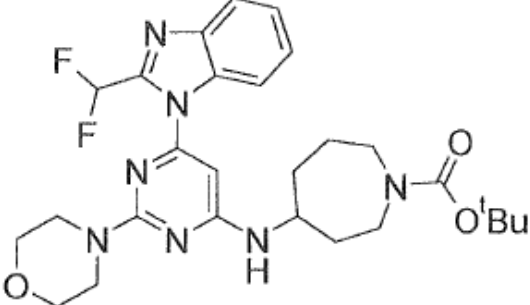
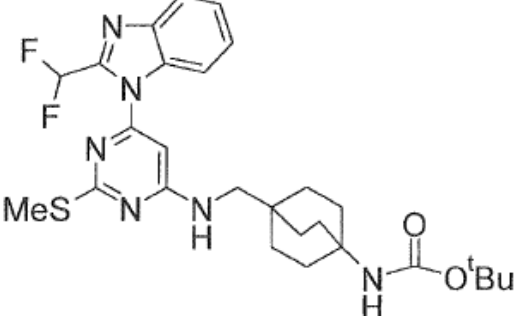
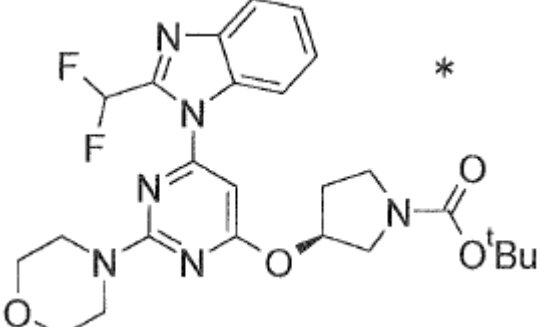
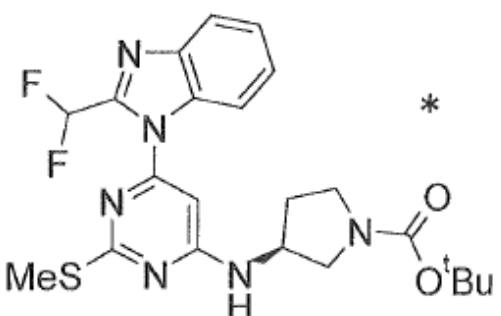
[Tabla 29]

EjP	SinP	Estr	DAT
130	1		no encontrados
131	1		ESI+: 462
132	1		ESI+: 476
133	1		ESI+: 476
134	1		no encontrados

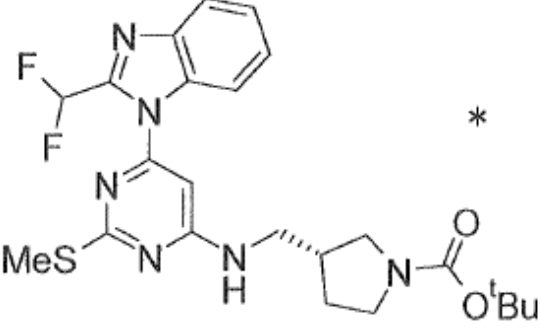
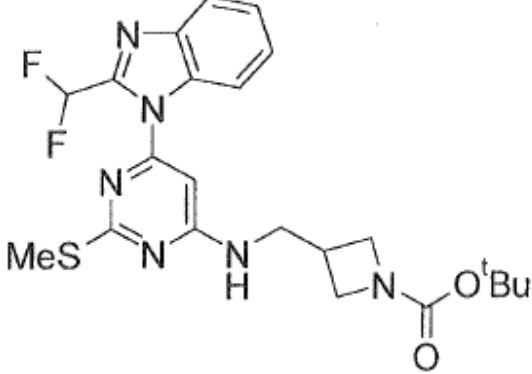
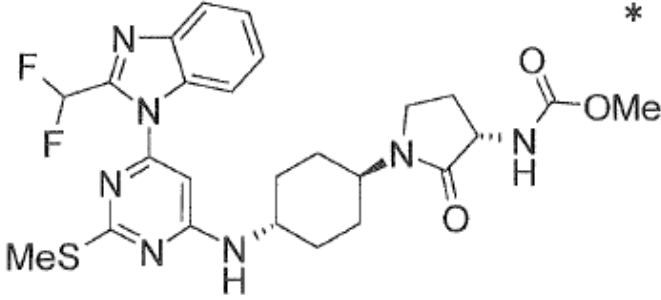
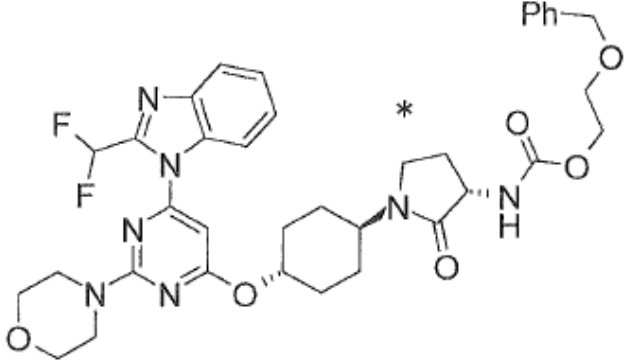
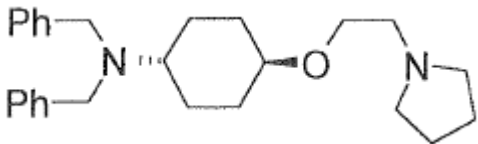
[Tabla 30]

EjP	SinP	Estr	DAT
135	1		ESI+: 490
136	1		ESI+: 516
137	1		ESI+: 422
138	1		ESI+: 505
139	1		ESI+: 505

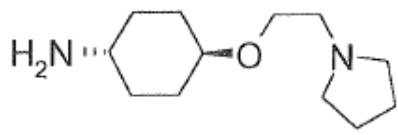
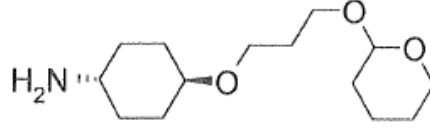
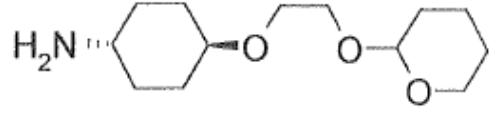
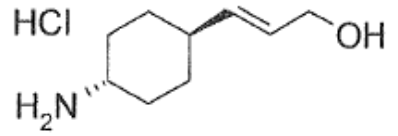
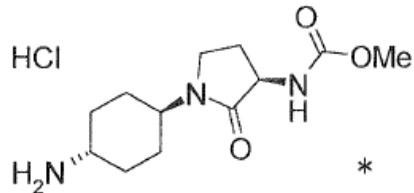
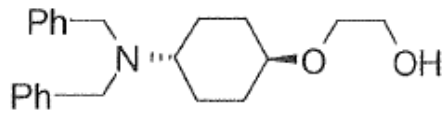
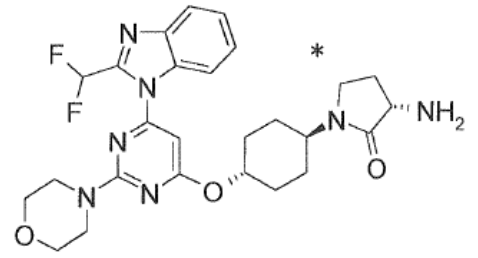
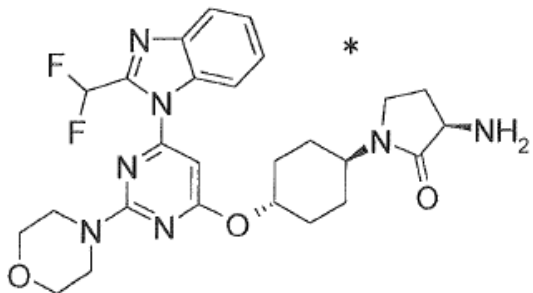
[Tabla 31]

EjP	SinP	Estr	DAT
140	1		ESI+: 497
141	1		ESI+: 544
142	1		ESI+: 545
143	1		ESI+: 517
144	1		ESI+: 477

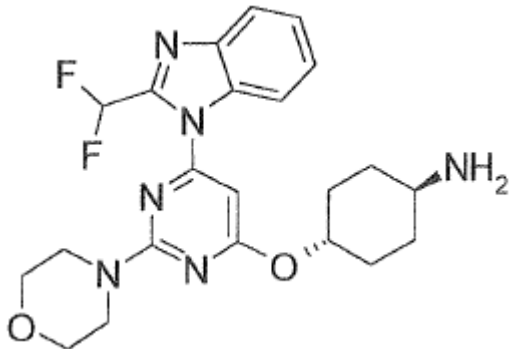
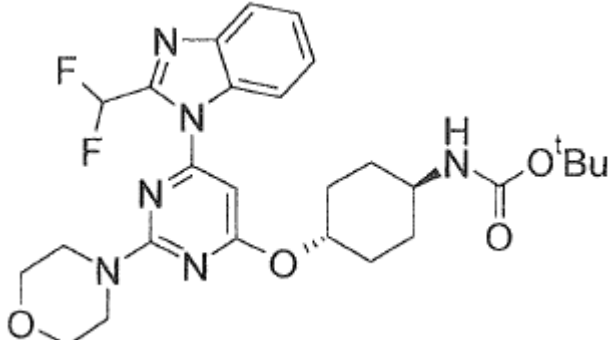
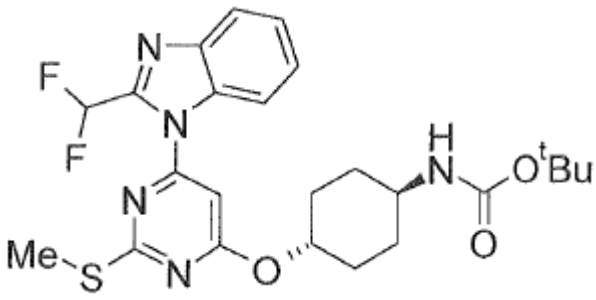
[Tabla 32]

EjP	SinP	Estr	DAT
145	1		ESI+: 491
146	1		ESI+: 477
147	90		ESI+: 546
148	Sin.87		ESI+: 706
149	82		ESI+: 393

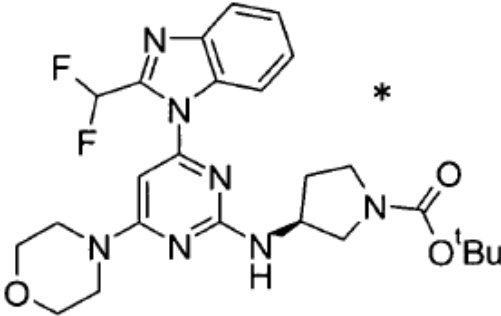
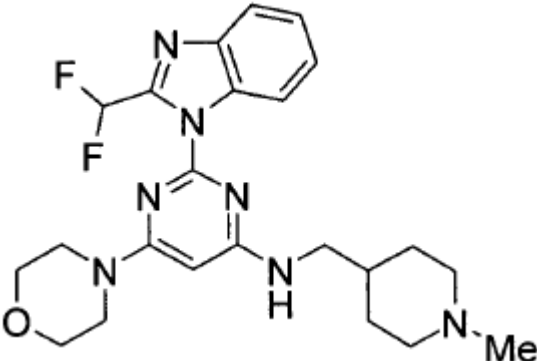
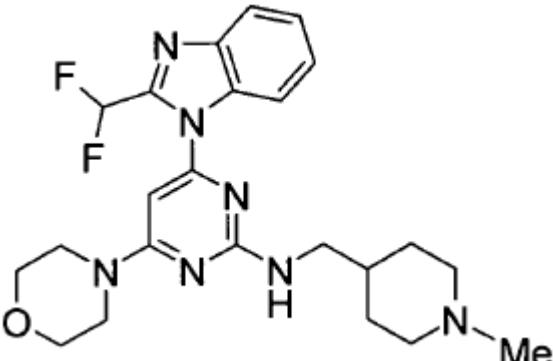
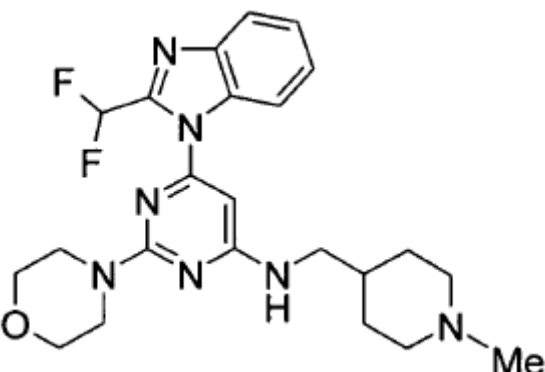
[Tabla 33]

EjP	SinP	Estr	DAT
150	83		ESI+: 213
151	83		ESI+: 258
152	83		ESI+: 244
153	11		ESI+: 156
154	11		ESI+: 256
155	81		ESI+: 340
156	Sin.54		ESI+: 528
157	Sin.54		ESI+: 528

[Tabla 34]

EjP	SinP	Estr	DAT
158	Sin.54		ESI+: 445
159	2		ESI+: 567[M+Na]
160	5		ESI+: 528[M+Na]

[Tabla 35]

Ej	Estr
1#	 <p>Chemical structure 1# shows a pyridine ring substituted with a morpholine group, a 2-fluorophenyl group, and a (1S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl group. An asterisk (*) is placed to the right of the structure.</p>
2#	 <p>Chemical structure 2# shows a pyridine ring substituted with a morpholine group, a 2-fluorophenyl group, and a (1S)-1-(methylamino)ethyl group.</p>
3#	 <p>Chemical structure 3# shows a pyridine ring substituted with a morpholine group, a 2-fluorophenyl group, and a (1S)-1-(methylamino)ethyl group.</p>
4#	 <p>Chemical structure 4# shows a pyridine ring substituted with a morpholine group, a 2-fluorophenyl group, and a (1S)-1-(methylamino)ethyl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 36]

Ej	Estr
5#	<p>Chemical structure 5# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a piperidine ring at the 6-position. The piperidine ring is further substituted with a tert-butyl ester group (-COO^tBu).</p>
6#	<p>Chemical structure 6# is similar to 5#, but the piperidine ring is replaced by a pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl ester group (-COO^tBu) and is marked with an asterisk (*).</p>
7#	<p>Chemical structure 7# is similar to 5#, but the piperidine ring is replaced by a morpholine ring. The morpholine ring is substituted with a tert-butyl ester group (-COO^tBu).</p>
8#	<p>Chemical structure 8# is similar to 5#, but the piperidine ring is replaced by a pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl ester group (-COO^tBu).</p>
9#	<p>Chemical structure 9# is similar to 5#, but the piperidine ring is replaced by a pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl ester group (-COO^tBu).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 37]

Ej	Estr
10#	<p>Chemical structure 10#: A central pyrimidine ring is substituted at the 2-position with a morpholine ring, at the 4-position with a benzimidazole ring substituted with a difluoromethyl group, and at the 6-position with a secondary amine group (-NH-). This secondary amine is further substituted with a propyl chain that ends in a piperidine ring, which is in turn substituted with a morpholine ring.</p>
11#	<p>Chemical structure 11#: Similar to structure 10#, but the piperidine ring is substituted with a tert-butyl ester group (-COO^tBu).</p>
12#	<p>Chemical structure 12#: Similar to structure 11#, but the morpholine ring is substituted with a methyl group (Me) on the carbon adjacent to the nitrogen.</p>
13#	<p>Chemical structure 13#: Similar to structure 12#, but the methyl group (Me) on the morpholine ring is shown with a wedge bond, indicating stereochemistry. An asterisk (*) is placed to the right of the structure.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 38]

Ej	Estr
14#	<p>Chemical structure 14# shows a central pyrimidopyrimidinone core. At position 2, there is a 1H-imidazo[5,1-b]indol-2-yl group substituted with a difluoromethyl group (-CF₂H). At position 4, there is a morpholine ring substituted with an ethyl group (-Et). At position 6, there is a piperidine ring substituted with a tert-butyl ester group (-CO^tBu). An asterisk (*) is placed to the right of the structure.</p>
15#	<p>Chemical structure 15# is identical to structure 14#, but the morpholine ring is substituted with a hydroxymethyl group (-CH₂OH) instead of an ethyl group. An asterisk (*) is placed to the right of the structure.</p>
16#	<p>Chemical structure 16# is identical to structure 14#, but the morpholine ring is substituted with a fluoromethyl group (-CH₂F) instead of an ethyl group. An asterisk (*) is placed to the right of the structure.</p>
17#	<p>Chemical structure 17# is identical to structure 14#, but the piperidine ring is substituted with a fluorine atom (-F) instead of a tert-butyl ester group. An asterisk (*) is placed to the right of the structure.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 39]

Ej	Estr
18#	<p>Chemical structure 18#: A pyrimidopyrimidinone core substituted with a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, a morpholine ring at position 4, and a tert-butyl (1S)-piperidin-4-ylcarbamate group at position 6. An asterisk (*) is placed to the right of the structure.</p>
19#	<p>Chemical structure 19#: A pyrimidopyrimidinone core substituted with a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, a morpholine ring at position 4, and a tert-butyl (1R)-piperidin-4-ylcarbamate group at position 6. An asterisk (*) is placed to the right of the structure.</p>
20#	<p>Chemical structure 20#: A pyrimidopyrimidinone core substituted with a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, a morpholine ring with a methyl group at position 4, and a tert-butyl (1S)-piperidin-4-ylcarbamate group at position 6. An asterisk (*) is placed to the right of the structure.</p>
21#	<p>Chemical structure 21#: A pyrimidopyrimidinone core substituted with a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, a morpholine ring with a methyl group at position 4, and a tert-butyl (1R)-piperidin-4-ylcarbamate group at position 6. An asterisk (*) is placed to the right of the structure.</p>
22#	<p>Chemical structure 22#: A pyrimidopyrimidinone core substituted with a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, a morpholine ring at position 4, a methyl group at position 6, and a (1R)-1-phenylpyrrolidine group at position 7. The structure is shown as a hydrochloride salt (HCl).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 40]

Ej	Estr
23#	<p>Chemical structure 23#: A pyrimidopyrimidinone core substituted with a morpholine ring at position 6, a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, and a (S)-1-phenylpyrrolidin-2-yl group at position 4. The structure is shown as a hydrochloride salt (HCl) and is marked with an asterisk (*).</p>
24#	<p>Chemical structure 24#: A pyrimidopyrimidinone core substituted with a morpholine ring at position 6, a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, and a (R)-1-phenylpyrrolidin-2-yl group at position 4. The structure is shown as a hydrochloride salt (HCl) and is marked with an asterisk (*).</p>
25#	<p>Chemical structure 25#: A pyrimidopyrimidinone core substituted with a morpholine ring at position 6, a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, and a (2-phenylethyl)pyrrolidin-1-yl group at position 4. The structure is shown as a dihydrochloride salt (2HCl).</p>
26#	<p>Chemical structure 26#: A pyrimidopyrimidinone core substituted with a morpholine ring at position 6, a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, and a (S)-1-phenylethylpyrrolidin-2-yl group at position 4. The structure is marked with an asterisk (*).</p>
27	<p>Chemical structure 27: A pyrimidopyrimidinone core substituted with a morpholine ring at position 6, a 2,2-difluoro-1H-benzotriazol-4-yl group at position 2, and a 1-(1,4-dithiane-2-yl)pyrrolidin-2-yl group at position 4.</p>

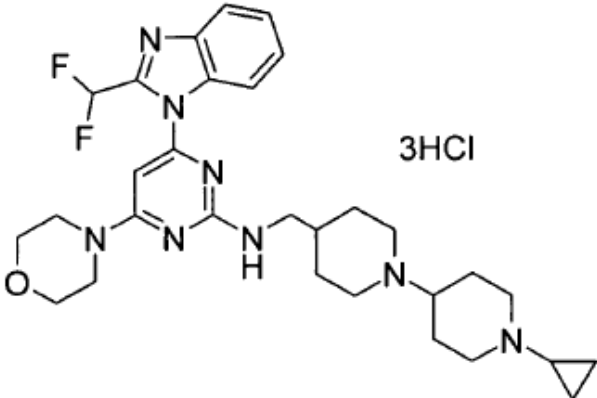
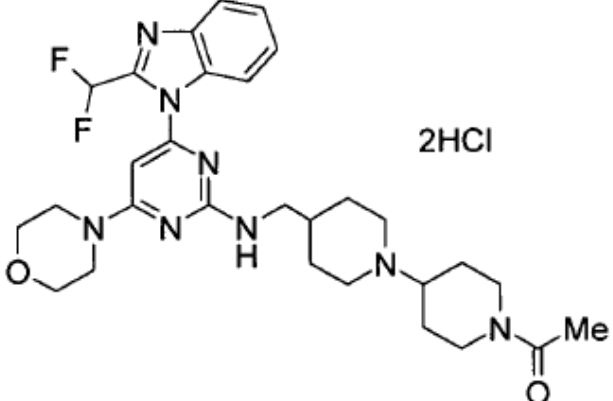
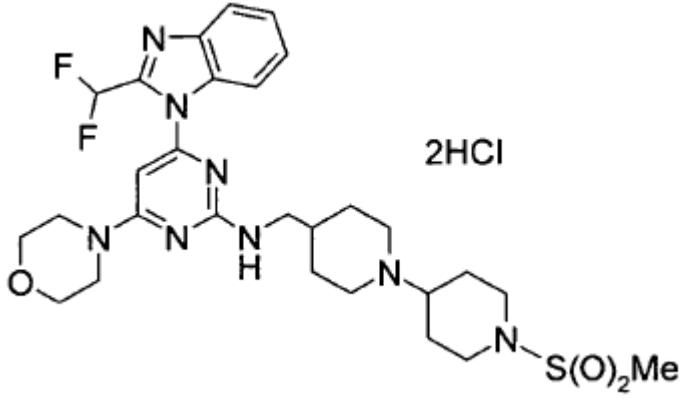
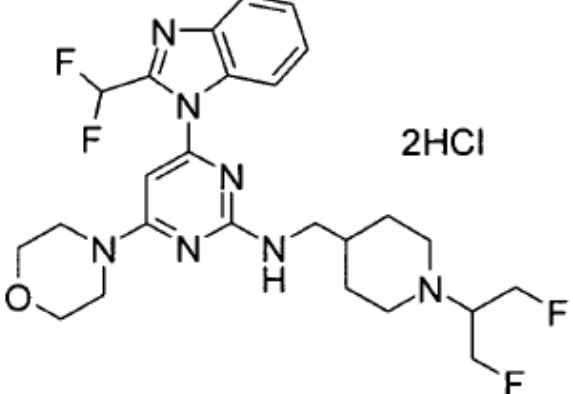
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 41]

Ej	Estr
28#	<p>Chemical structure 28# consists of a central pyrimidine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazo[5,1-b]indole ring system with a difluoromethyl group (-CF₂H) at the 2-position. At the 6-position, there is a secondary amine (-NH-) connected to a methylene group (-CH₂-), which is further connected to another methylene group (-CH₂-) attached to a piperidine ring. This piperidine ring is also connected to a methylene group (-CH₂-) attached to a cyclohexane ring, which has a hydroxyl group (-OH) at the 4-position.</p>
29#	<p>Chemical structure 29# is identical to structure 28#, but the hydroxyl group (-OH) on the cyclohexane ring is attached to a methylene group (-CH₂-), forming a hydroxymethyl group (-CH₂OH).</p>
30#	<p>Chemical structure 30# is identical to structure 28#, but the cyclohexane ring is connected to a methylene group (-CH₂-), which is further connected to another methylene group (-CH₂-) attached to a piperidine ring. This piperidine ring is also connected to a methylene group (-CH₂-) attached to a nitrogen atom, which is part of a tert-butyl carbamate group (-N-C(=O)-O^tBu).</p>
31#	<p>Chemical structure 31# is identical to structure 28#, but the cyclohexane ring is connected to a methylene group (-CH₂-), which is further connected to another methylene group (-CH₂-) attached to a piperidine ring. This piperidine ring is also connected to a methylene group (-CH₂-) attached to a nitrogen atom, which is substituted with a methyl group (-Me). The structure is labeled as 3HCl.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 42]

Ej	Estr
32#	 <p>3HCl</p>
33#	 <p>2HCl</p>
34#	 <p>2HCl</p>
35#	 <p>2HCl</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 43]

Ej	Estr
36#	<p>Chemical structure 36# consists of a central pyrimidopyrimidinone core. At position 2, there is a morpholine ring. At position 4, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At position 6, there is a secondary amine group (-NH-) linked to a piperidine ring, which is further substituted with a difluorocyclohexane ring.</p> <p>2HCl</p>
37#	<p>Chemical structure 37# is similar to 36# but features a morpholine ring with a methyl group (-Me) at the 3-position and a tetrahydropyran ring at the 6-position of the piperidine moiety.</p> <p>* 2HCl</p>
38#	<p>Chemical structure 38# is similar to 37# but has a methyl group (-Me) at the 2-position of the morpholine ring.</p> <p>* 2HCl</p>
39#	<p>Chemical structure 39# is similar to 37# but has a morpholine ring at the 6-position of the piperidine moiety.</p> <p>2HCl</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 44]

Ej	Estr
40#	<p>Chemical structure 40# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a (2-(2-morpholinoethyl)ethyl)oxy group at the 6-position. The structure is labeled with "2HCl".</p>
41#	<p>Chemical structure 41# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a (2-(2-morpholinoethyl)ethyl)amino group at the 6-position. The amino group is shown with a dashed bond to the ethyl chain, indicating a specific stereochemistry. The structure is labeled with "2HCl" and an asterisk (*).</p>
42#	<p>Chemical structure 42# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a (2-(2-morpholinoethyl)ethyl)amino group at the 6-position. The amino group is shown with a solid wedge bond to the ethyl chain, indicating a specific stereochemistry. The structure is labeled with "2HCl" and an asterisk (*).</p>
43-1#	<p>Chemical structure 43-1# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a (2-(2-(2-fluorocyclohexyl)ethyl)ethyl)amino group at the 6-position. The amino group is shown with a solid wedge bond to the ethyl chain, and the cyclohexane ring has a fluorine atom at the 2-position with a dashed bond. The structure is labeled with "2HCl".</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 45]

Ej	Estr
43- 2#	<p>Chemical structure of compound 43-2# is shown. It features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 2-position, and a (1R)-1-(2-fluorocyclohexyl)pyrrolidin-2-ylmethylamino group at the 6-position. The structure is labeled as 2HCl.</p>
44#	<p>Chemical structure of compound 44# is shown. It features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 2-position, and a (1R)-1-phenylpyrrolidin-2-ylmethylamino group at the 6-position. The structure is labeled as 2HCl.</p>
45#	<p>Chemical structure of compound 45# is shown. It features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 2-position, and a (1R)-1-(2-(dimethylamino)ethyl)pyrrolidin-2-ylmethylamino group at the 6-position. The structure is labeled as 2HCl and marked with an asterisk (*).</p>
46#	<p>Chemical structure of compound 46# is shown. It features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 2-position, and a (1R)-1-(2-ethoxycarbonylmethyl)pyrrolidin-2-ylmethylamino group at the 6-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 46]

Ej	Estr
47#	<p>Chemical structure 47# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-(aminomethyl)piperidine ring at the 6-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
48#	<p>Chemical structure 48# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a piperidine ring substituted with a succinimide ring at the 6-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
49#	<p>Chemical structure 49# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-(3-aminopropyl)piperidine ring at the 6-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
50#	<p>Chemical structure 50# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-(4-fluorobutyl)piperidine ring at the 6-position. The structure is shown as a dihydrochloride salt (2HCl).</p>

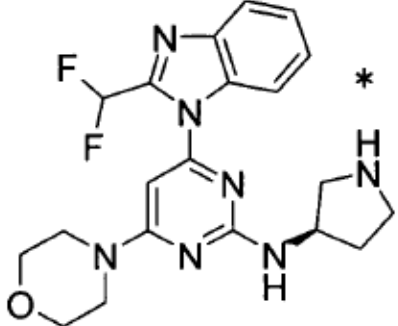
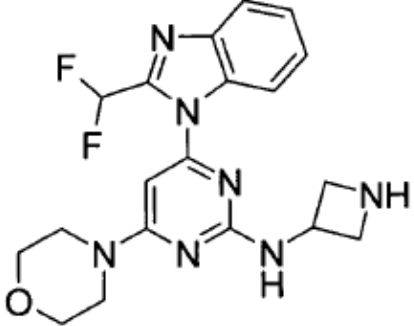
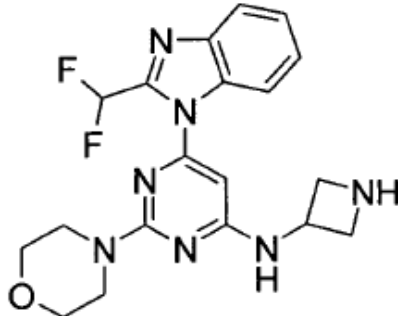
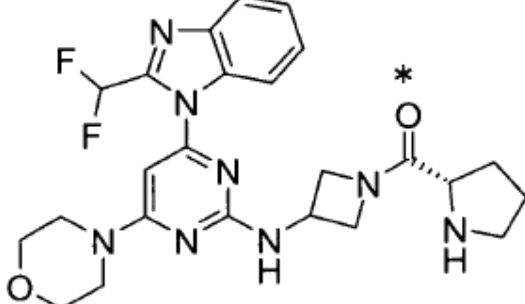
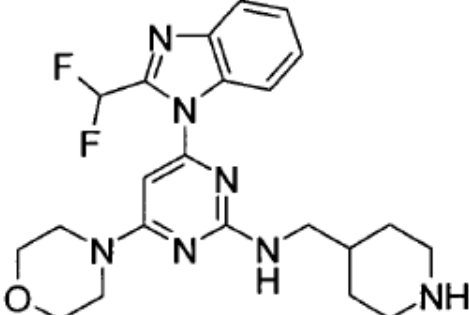
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 47]

Ej	Estr
51#	<p>Chemical structure 51# consists of a central pyrimidopyrimidine core. At the 2-position, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At the 4-position, there is a morpholine ring. At the 6-position, there is a secondary amine group (-NH-) linked to a piperidine ring, which is further substituted with a 4-fluorobutyl chain (-CH₂CH₂CH₂CH₂F). The structure is labeled as a dihydrochloride salt (2HCl).</p>
52#	<p>Chemical structure 52# is similar to 51#, but the piperidine ring is substituted with a 2-fluoroethyl group (-CH₂CH₂F) instead of a 4-fluorobutyl chain. The structure is labeled as a dihydrochloride salt (2HCl).</p>
53	<p>Chemical structure 53 is similar to 51#, but the piperidine ring is replaced by a pyrrolidine ring. The structure is labeled as a dihydrochloride salt (2HCl) with an asterisk (*).</p>
54	<p>Chemical structure 54 is similar to 51#, but the piperidine ring is replaced by a piperazine ring. The structure is labeled as a dihydrochloride salt (2HCl).</p>
55#	<p>Chemical structure 55# is similar to 51#, but the piperidine ring is replaced by a piperazine ring. The structure is labeled as a dihydrochloride salt (2HCl).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 48]

Ej	Estr
56	
57	
58	
59	
60#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 49]

Ej	Estr
61#	<p>Chemical structure 61#: A central pyrimidine ring is substituted at the 2-position with a morpholine ring (with a methyl group on the carbon adjacent to the nitrogen), at the 4-position with a 1H-piperidin-2-ylmethylamino group, and at the 6-position with a 1H-benzotriazol-2-ylidene group. The benzotriazol-2-ylidene group has a difluoromethyl group (-CF₂H) attached to its 4-position. An asterisk (*) is placed to the right of the structure.</p>
62#	<p>Chemical structure 62#: Similar to 61#, but the methyl group on the morpholine ring is shown with a wedge bond, indicating a specific stereochemistry. An asterisk (*) is placed to the right of the structure.</p>
63#	<p>Chemical structure 63#: Similar to 61#, but the piperidine ring is connected to the pyrimidine ring via an ether linkage (-O-CH₂-) instead of an amine linkage. An asterisk (*) is placed to the right of the structure.</p>
64#	<p>Chemical structure 64#: Similar to 61#, but the piperidine ring is connected to the pyrimidine ring via a methylene bridge (-CH₂-) instead of an amine linkage. An asterisk (*) is placed to the right of the structure.</p>
65#	<p>Chemical structure 65#: Similar to 61#, but the piperidine ring is connected to the pyrimidine ring via a methylene bridge (-CH₂-) and the bond to the piperidine ring is shown with a dashed bond, indicating a specific stereochemistry. An asterisk (*) is placed to the right of the structure.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 50]

Ej	Estr
66#	<p>Chemical structure 66#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a piperidine ring. The piperidine ring is further substituted with a dimethylacetamide group.</p>
67#	<p>Chemical structure 67#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a piperidine ring. The piperidine ring is further substituted with a dimethylacetamide group.</p>
68#	<p>Chemical structure 68#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a pyrrolidine ring. The pyrrolidine ring is further substituted with a dimethylacetamide group. An asterisk (*) is placed above the dimethylacetamide group, indicating it is not included in the claims.</p>
69#	<p>Chemical structure 69#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a pyrrolidine ring. The pyrrolidine ring is further substituted with a dimethylacetamide group.</p>
70	<p>Chemical structure 70: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a pyrrolidine ring. The pyrrolidine ring is further substituted with a dimethylacetamide group and a tert-butyl ester group. An asterisk (*) is placed above the dimethylacetamide group, indicating it is not included in the claims.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 51]

Ej	Estr
71#	<p>Chemical structure 71# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a (1-methylpiperidin-4-yl)methylamino group at the 6-position.</p>
72#	<p>Chemical structure 72# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a (1-(dimethylamino)acetamido)piperidin-4-ylmethylamino group at the 6-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
73#	<p>Chemical structure 73# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a (1-(dimethylamino)propanamido)piperidin-4-ylmethylamino group at the 6-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
74#	<p>Chemical structure 74# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a (1-phenylpiperidin-4-yl)methylamino group at the 6-position.</p>

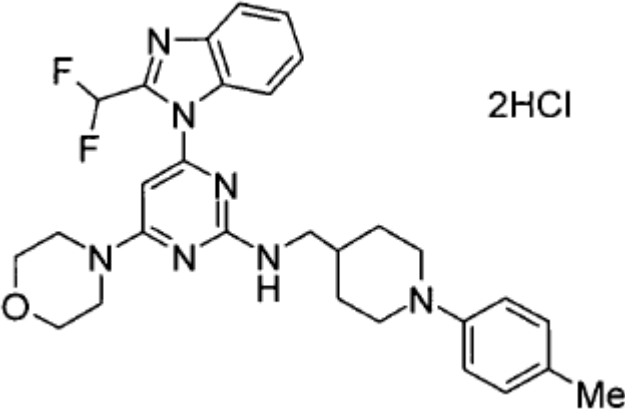
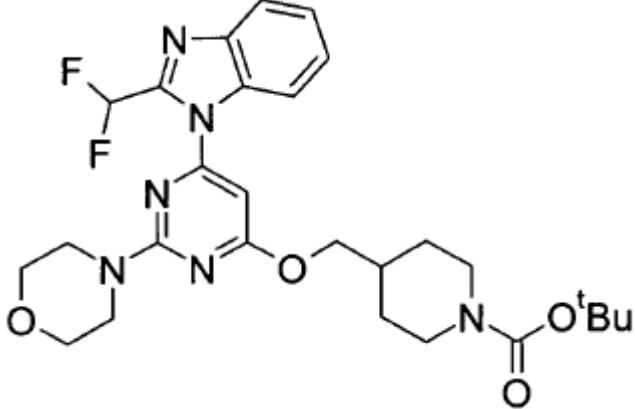
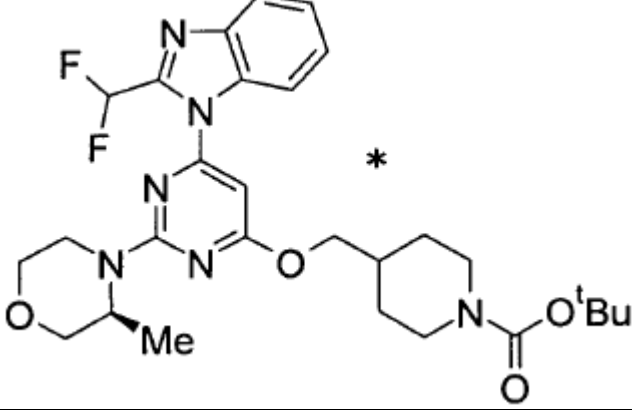
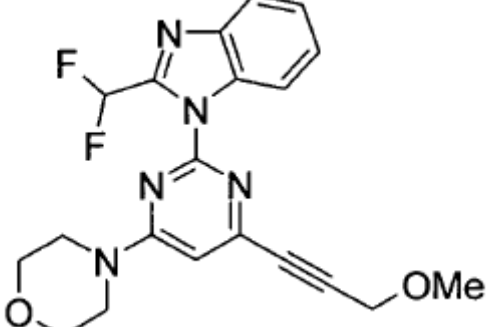
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 52]

Ej	Estr
75#	<p>Chemical structure 75# consists of a central pyrimidine ring. At the 2-position of the pyrimidine, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At the 6-position, there is a secondary amine group (-NH-) linked to a piperidine ring, which is further substituted with a 4-fluorophenyl group. The structure is shown as a dihydrochloride salt (2HCl).</p>
76#	<p>Chemical structure 76# is identical to structure 75#, but the fluorine atom on the phenyl ring is at the 3-position instead of the 4-position. It is shown as a dihydrochloride salt (2HCl).</p>
77#	<p>Chemical structure 77# is identical to structure 76#, but the fluorine atom on the phenyl ring is at the 2-position instead of the 3-position. It is shown as a dihydrochloride salt (2HCl).</p>
78#	<p>Chemical structure 78# is identical to structure 75#, but the phenyl ring is substituted with a methoxy group (-OMe) at the 4-position instead of a fluorine atom. It is shown as a dihydrochloride salt (2HCl).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 53]

Ej	Estr
79#	 <p style="text-align: right;">2HCl</p>
80#	
81#	
82#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 54]

Ej	Estr
83#	<p>Chemical structure 83# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1H-imidazole-2-ylmethyl group at the 2-position. The imidazole ring is further substituted with a difluoromethyl group. The pyrimidine ring is also substituted at the 6-position with a (1S,2S)-2-(2-hydroxycyclohexyl)ethylamino group.</p>
84#	<p>Chemical structure 84# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1H-imidazole-2-ylmethyl group at the 2-position. The imidazole ring is further substituted with a difluoromethyl group. The pyrimidine ring is also substituted at the 6-position with a (1S,2S)-2-(2-(tert-butylcarbamoyl)pyrrolidin-1-yl)cyclohexyl group. An asterisk (*) is placed above the pyrrolidine ring.</p>
85#	<p>Chemical structure 85# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1H-imidazole-2-ylmethyl group at the 2-position. The imidazole ring is further substituted with a difluoromethyl group. The pyrimidine ring is also substituted at the 6-position with a (1S,2S)-2-(2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)cyclohexyl group.</p>
86#	<p>Chemical structure 86# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1H-imidazole-2-ylmethyl group at the 2-position. The imidazole ring is further substituted with a difluoromethyl group and a methyl group at the 5-position. The pyrimidine ring is also substituted at the 6-position with a (1S,2S)-2-(2-(2,2-dimethyl-1,3-dioxol-5-yl)cyclohexyl)ethylamino group. An asterisk (*) is placed above the dioxolane ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 55]

Ej	Estr
87#	<p>Chemical structure 87# features a central pyrimidine ring substituted with a morpholine group, a 2,6-difluorophenyl group, and a 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group. The pyrimidine ring is also linked via an oxygen atom to a cyclohexane ring, which is further substituted with a morpholine group and a 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group. An asterisk (*) is placed near the pyrimidine ring.</p>
88#	<p>Chemical structure 88# is similar to 87# but the 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group is substituted with a methylsulfonamide group (-NH-SO₂-Me). An asterisk (*) is placed near the pyrimidine ring.</p>
89#	<p>Chemical structure 89# is similar to 87# but the 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group is substituted with a cyclobutylmethylamide group (-NH-CH₂-N(cyclobutyl)-C(=O)-). An asterisk (*) is placed near the pyrimidine ring.</p>
90#	<p>Chemical structure 90# features a central pyrimidine ring substituted with a morpholine group, a 2,6-difluoro-3-methylphenyl group, and a 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group. The pyrimidine ring is also linked via an oxygen atom to a cyclohexane ring, which is further substituted with a morpholine group and a 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group. A methyl group (Me) is attached to the morpholine ring. An asterisk (*) is placed near the pyrimidine ring.</p>
91#	<p>Chemical structure 91# features a central pyrimidine ring substituted with a morpholine group, a 2,6-difluorophenyl group, and a 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group. The pyrimidine ring is also linked via an oxygen atom to a cyclohexane ring, which is further substituted with a morpholine group and a 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group. The 2-oxo-1,2,3,4-tetrahydropyridin-5-yl group is substituted with a cyclopentylsulfonamide group (-NH-CH₂-CH₂-S(=O)-cyclopentyl). An asterisk (*) is placed near the pyrimidine ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 56]

Ej	Estr
92#	<p>Chemical structure 92# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring system at the 6-position. A (2-oxo-1,4-dioxane-6-yl)methoxy group is attached to the 5-position of the pyrimidine ring.</p>
93#	<p>Chemical structure 93# is similar to 92#, but the (2-oxo-1,4-dioxane-6-yl)methoxy group is replaced by a cyclohexanone ring attached via its methylene group.</p>
94#	<p>Chemical structure 94# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring system at the 6-position. A cyclopentane ring is attached to the 5-position of the pyrimidine ring via a methylene group, which is further substituted with a sulfonyl group (-SO₂-).</p>
95#	<p>Chemical structure 95# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring system at the 6-position. A cyclopentane ring is attached to the 5-position of the pyrimidine ring via an oxygen atom, and the cyclopentane ring is further substituted with a tert-butyl carbamate group (-NHCO^tBu).</p>
96#	<p>Chemical structure 96# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring system at the 6-position. A cyclobutane ring is attached to the 5-position of the pyrimidine ring via a nitrogen atom, and the cyclobutane ring is further substituted with a tert-butyl carbamate group (-NHCO^tBu).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 57]

Ej	Estr
97#	<p>Chemical structure 97# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-indolizol-5-ylidene group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a tert-butyl carbamate group. The indolizolone ring has a difluoromethyl group at the 3-position.</p>
98#	<p>Chemical structure 98# is similar to 97# but the cyclohexane ring is replaced by a cyclopentane ring, which is substituted with a tert-butyl carbamate group.</p>
99#	<p>Chemical structure 99# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-indolizol-5-ylidene group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a pyrrolidine ring, which is substituted with a methyl carbamate group. An asterisk (*) is placed above the pyrrolidine ring.</p>
100#	<p>Chemical structure 100# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-indolizol-5-ylidene group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a dimethylacetamide group. The word "HCl" is written above the structure.</p>
101#	<p>Chemical structure 101# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-indolizol-5-ylidene group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a propyl chain, which is substituted with a tert-butyl carbamate group and a methylsulfanyl group (SMe). An asterisk (*) is placed above the propyl chain.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 58]

Ej	Estr
102#	<p>Chemical structure 102# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 1H-benzotriazol-2-ylidene group with a difluoromethyl substituent at the 4-position, and a 4-methoxyphenyl group at the 6-position. The 4-position of the pyrimidine ring is linked via an oxygen atom to a cyclohexane ring. This cyclohexane ring is further substituted with an amide group (-NH-CO-CH2-CH2-SMe) and a tert-butyl ester group (-NH-CO-O^tBu). An asterisk (*) is placed above the amide group.</p>
103#	<p>Chemical structure 103# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 1H-benzotriazol-2-ylidene group with a difluoromethyl substituent at the 4-position, and a 4-methoxyphenyl group at the 6-position. The 4-position of the pyrimidine ring is linked via an oxygen atom to a cyclopentane ring. This cyclopentane ring is further substituted with an amide group (-NH-CO-CH2-N(Me)₂).</p>
104#	<p>Chemical structure 104# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 1H-benzotriazol-2-ylidene group with a difluoromethyl substituent at the 4-position, and a 4-methoxyphenyl group at the 6-position. The 4-position of the pyrimidine ring is linked via an oxygen atom to a cyclopentane ring. This cyclopentane ring is further substituted with an amide group (-NH-CO-CH2-N(Me)₂).</p>
105#	<p>Chemical structure 105# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 1H-benzotriazol-2-ylidene group with a difluoromethyl substituent at the 4-position, and a 4-methoxyphenyl group at the 6-position. The 4-position of the pyrimidine ring is linked via an oxygen atom to a cyclopentane ring. This cyclopentane ring is further substituted with an amide group (-NH-CO-CH2-N(Et)₂).</p>
106#	<p>Chemical structure 106# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 1H-benzotriazol-2-ylidene group with a difluoromethyl substituent at the 4-position, and a 4-methoxyphenyl group at the 6-position. The 4-position of the pyrimidine ring is linked via an oxygen atom to a cyclopentane ring. This cyclopentane ring is further substituted with an amide group (-NH-CO-CH2-N(Et)₂).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 59]

Ej	Estr
107	
108	
109	
110#	
111#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 60]

Ej	Estr
112#	<p>Chemical structure 112# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-indazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a cyclopropylamino group (-NH-Cyclopropyl) where the cyclopropyl ring is further substituted with a phenyl group (-Ph).</p>
113#	<p>Chemical structure 113# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-indazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a cyclohexylamino group (-NH-Cyclohexyl) where the cyclohexyl ring is further substituted with a dimethylacetamide group (-NH-CO-CH₂-N(Me)₂).</p>
114#	<p>Chemical structure 114# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-indazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a cyclohexylamino group (-NH-Cyclohexyl) where the cyclohexyl ring is further substituted with a dimethylacetamide group (-NH-CO-CH₂-N(Me)₂).</p>
115#	<p>Chemical structure 115# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-indazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a cyclohexylamino group (-NH-Cyclohexyl) where the cyclohexyl ring is further substituted with a morpholine-4-carbonyl group (-CO-N-morpholine).</p>

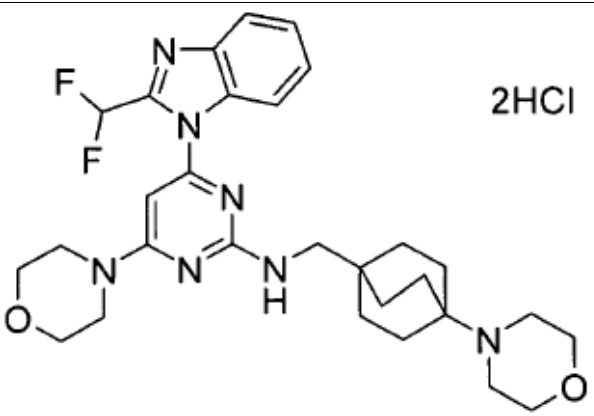
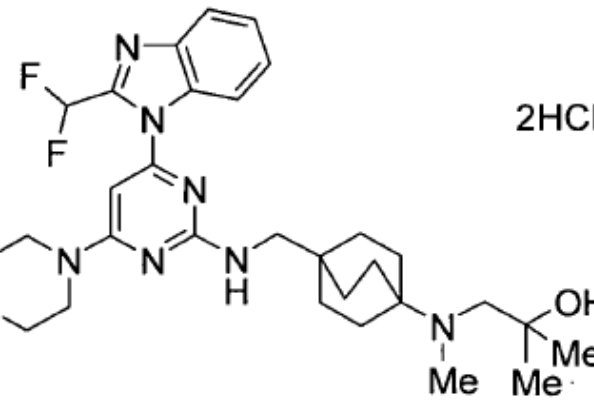
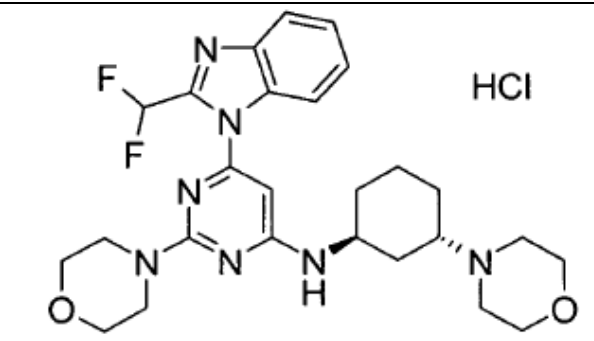
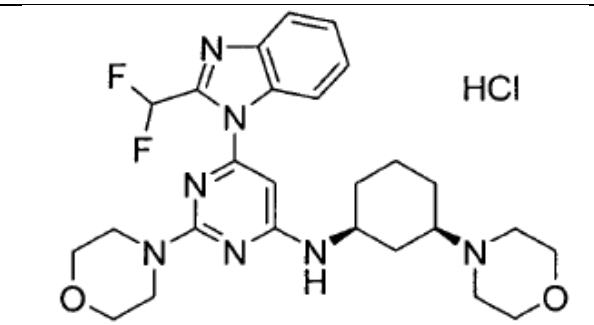
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 61]

Ej	Estr
116#	<p>Chemical structure 116# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. The 5-position is linked to a cyclohexane ring, which is further substituted with a dimethylacetamide group and a cyclopropylmethyl group.</p>
117#	<p>Chemical structure 117# is similar to 116#, but the cyclohexane ring is substituted with a dimethylacetamide group and an isopropylmethyl group.</p>
118#	<p>Chemical structure 118# is similar to 116#, but the cyclohexane ring is substituted with two dimethylacetamide groups. The structure is shown as a hydrochloride salt (HCl).</p>
119#	<p>Chemical structure 119# is similar to 116#, but the cyclohexane ring is replaced by a cyclobutane ring. The structure is shown as a hydrochloride salt (HCl).</p>

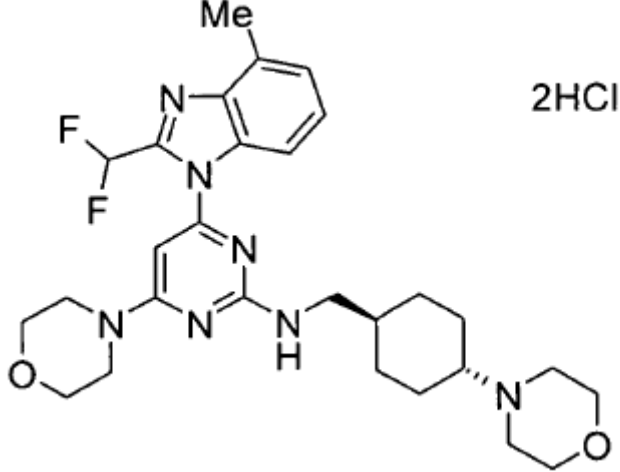
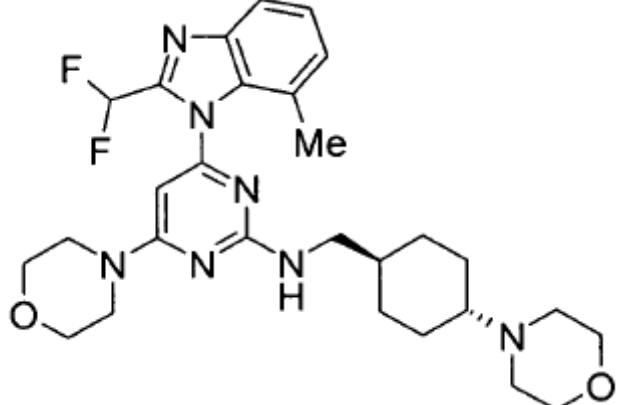
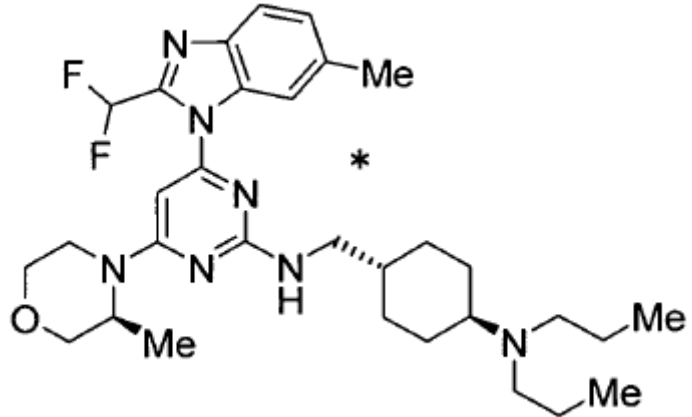
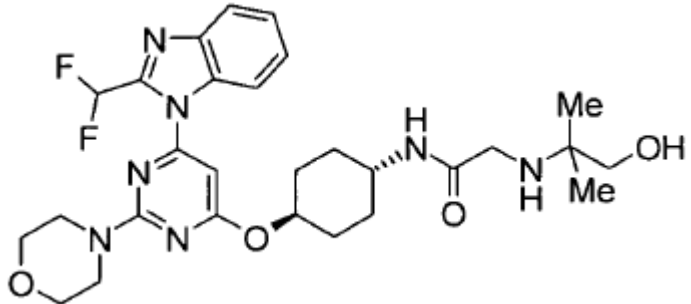
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 62]

Ej	Estr
120#	 <p style="text-align: right;">2HCl</p>
121#	 <p style="text-align: right;">2HCl</p>
122#	 <p style="text-align: right;">HCl</p>
123#	 <p style="text-align: right;">HCl</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 63]

Ej	Estr
124#	 <p style="text-align: right;">2HCl</p>
125#	
126#	
127#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 64]

Ej	Estr
128#	<p>Chemical structure 128# is a complex molecule featuring a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring, a 2,6-difluorophenyl group, and a 4-hydroxycyclohexyl group. The cyclohexane ring is further linked to a chain containing a secondary amide and a primary amide.</p>
129#	<p>Chemical structure 129# is similar to 128#, but the hydroxyl group on the cyclohexane ring is shown with a different stereochemistry (dashed bond).</p>
130#	<p>Chemical structure 130# features a central pyrimidopyrimidine ring system substituted with a morpholine ring, a 2,6-difluorophenyl group, a cyclopropylmethyl group, and a cyclohexane ring. The cyclohexane ring is linked to a tert-butyl carbamate group.</p>
131#	<p>Chemical structure 131# is a complex molecule featuring a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring, a 2,6-difluorophenyl group, a 4-methylphenyl group, and a cyclohexane ring. The cyclohexane ring is linked to a morpholine ring. The structure is shown as a dihydrochloride salt (2HCl).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 65]

Ej	Estr
132#	<p>Chemical structure 132# is a dihydroquinazolinone derivative. It features a 2,2-difluoroethyl group at the 4-position of the quinazolinone ring, a methyl group at the 6-position, and a morpholine ring at the 2-position. The 3-position is substituted with a (1R,2S)-2-(2-morpholinoethyl)cyclohexylamino group. The structure is shown as a dihydrochloride salt (2HCl).</p>
133#	<p>Chemical structure 133# is a dihydroquinazolinone derivative. It features a 2,2-difluoroethyl group at the 4-position of the quinazolinone ring, a phenyl group at the 6-position, and a morpholine ring at the 2-position. The 3-position is substituted with a (1R,2S)-2-(2-(cyclopropylamino)ethyl)cyclohexyloxy group.</p>
134#	<p>Chemical structure 134# is a dihydroquinazolinone derivative. It features a 2,2-difluoroethyl group at the 4-position of the quinazolinone ring, a phenyl group at the 6-position, and a morpholine ring at the 2-position. The 3-position is substituted with a (1R,2S)-2-(2-(cyclopentylamino)ethyl)cyclohexyloxy group.</p>
135#	<p>Chemical structure 135# is a dihydroquinazolinone derivative. It features a 2,2-difluoroethyl group at the 4-position of the quinazolinone ring, a phenyl group at the 6-position, and a morpholine ring at the 2-position. The 3-position is substituted with a (1R,2S)-2-(2-(cyclohexylamino)ethyl)cyclohexyloxy group.</p>
136#	<p>Chemical structure 136# is a dihydroquinazolinone derivative. It features a 2,2-difluoroethyl group at the 4-position of the quinazolinone ring, a phenyl group at the 6-position, and a morpholine ring at the 2-position. The 3-position is substituted with a (1R,2S)-2-(2-(4-morpholinylethyl)cyclohexyloxy group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 66]

Ej	Estr
137#	<p>Chemical structure 137# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a 4-(2-(2-methylpropylamino)acetyl)cyclohexyloxy group at the 6-position.</p>
138#	<p>Chemical structure 138# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a 4-(2-(2-(oxolan-2-ylamino)acetyl)cyclohexyloxy group at the 6-position.</p>
139#	<p>Chemical structure 139# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a 4-(2-(2-(oxolan-3-ylamino)acetyl)cyclohexyloxy group at the 6-position.</p>
140#	<p>Chemical structure 140# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a 4-(2-(2-(bicyclo[2.2.1]heptan-2-ylamino)acetyl)cyclohexyloxy group at the 6-position.</p>
141#	<p>Chemical structure 141# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a 4-(2-(2-(bicyclo[2.2.2]octan-2-ylamino)acetyl)cyclohexyloxy group at the 6-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 67]

Ej	Estr
142#	<p>Chemical structure 142# features a central pyrimidopyridine ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-phenyl-1H-imidazole-2-yl group at the 6-position. The 5-position is linked via an oxygen atom to a cyclohexane ring. This cyclohexane ring is further substituted with an amide group (-NH-) and a 2-hydroxy-1-adamantylethyl group.</p>
143#	<p>Chemical structure 143# is similar to 142#, but the cyclohexane ring is substituted with a methyl group and a hydroxyl group instead of the adamantane derivative.</p>
144#	<p>Chemical structure 144# is similar to 143#, but the methyl and hydroxyl groups on the cyclohexane ring are in different relative positions.</p>
145#	<p>Chemical structure 145# features a central pyrimidopyridine ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-(4-methylphenyl)-1H-imidazole-2-yl group at the 6-position. The 5-position is linked via an oxygen atom to a cyclohexane ring. This cyclohexane ring is further substituted with an amide group (-NH-) and a 2-hydroxy-2-methylpropyl group. An asterisk (*) is placed near the amide group.</p>
146#	<p>Chemical structure 146# features a central pyrimidopyridine ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-(3-methylphenyl)-1H-imidazole-2-yl group at the 6-position. The 5-position is linked via an oxygen atom to a cyclohexane ring. This cyclohexane ring is further substituted with an amide group (-NH-) and a tert-butyl ester group (-COO^tBu).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 68]

Ej	Estr
147#	<p>Chemical structure 147# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-methyl-1H-benzotriazol-5-yl group at the 6-position. The 8-position of the core is linked via a methylene bridge to a cyclohexane ring, which is further substituted with a tert-butyl carbamate group.</p>
148#	<p>Chemical structure 148# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 4-methyl-1H-benzotriazol-5-yl group at the 6-position. The 8-position of the core is linked via a methylene bridge to a piperidine ring, which is further substituted with a tert-butyl carbamate group.</p>
149#	<p>Chemical structure 149# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1H-benzotriazol-5-yl group at the 6-position. The 8-position of the core is linked via a methylene bridge to a pyrrolidine ring, which is further substituted with a tert-butyl carbamate group. An asterisk (*) is placed to the right of the structure, indicating it is not included in the claims.</p>
150#	<p>Chemical structure 150# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1H-benzotriazol-5-yl group at the 6-position. The 8-position of the core is linked via a methylene bridge to a benzamide group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 69]

Ej	Estr
151#	<p>Chemical structure 151# shows a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1H-pyrrolidin-2-ylmethyl group at the 2-position. The pyrimidine ring is also substituted at the 6-position with a 1H-benzotriazol-2-yl group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H). An asterisk (*) is placed to the right of the benzotriazole moiety.</p>
152#	<p>Chemical structure 152# is similar to 151#, but the 1H-pyrrolidin-2-ylmethyl group is replaced by a 1H-bicyclo[2.2.1]heptan-2-ylmethyl group.</p>
153#	<p>Chemical structure 153# is similar to 151#, but the benzotriazole ring is substituted at the 5-position with a methoxy group (-MeO). The difluoromethyl group is at the 4-position.</p>
154#	<p>Chemical structure 154# is similar to 151#, but the benzotriazole ring is substituted at the 5-position with a trifluoromethyl group (-CF₃). The difluoromethyl group is at the 4-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 70]

Ej	Estr
155#	<p>Chemical structure 155# consists of a central pyrimidine ring. At the 2-position of the pyrimidine, there is a morpholine ring. At the 4-position, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a methylene group (-CH₂-) connected to a pyridine ring, which has a methyl group (-Me) at the 3-position.</p>
156#	<p>Chemical structure 156# consists of a central pyrimidine ring. At the 2-position of the pyrimidine, there is a morpholine ring. At the 4-position, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a methylene group (-CH₂-) connected to a pyridine ring, which has a morpholine ring attached at the 3-position.</p>
157#	<p>Chemical structure 157# consists of a central pyrimidine ring. At the 2-position of the pyrimidine, there is a morpholine ring. At the 4-position, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a methylene group (-CH₂-) connected to a pyridine ring, which has a N-methylpiperazine ring attached at the 3-position.</p>
158#	<p>Chemical structure 158# consists of a central pyrimidine ring. At the 2-position of the pyrimidine, there is a morpholine ring. At the 4-position, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a methylene group (-CH₂-) connected to a benzene ring, which has a N-ethylcarbamoylpiperazine ring attached at the para position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 71]

Ej	Estr
159#	<p>Chemical structure 159# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a 2-phenylacetamido group at the 6-position. The 2-phenylacetamido group is marked with an asterisk (*).</p>
160#	<p>Chemical structure 160# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a (1-(4-chlorophenyl)ethyl)amino group at the 6-position.</p>
161#	<p>Chemical structure 161# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a (1H-imidazol-2-yl)pyrrolidine-2-ylamino group at the 6-position. The 1H-imidazo[5,1-b]indol-2-yl group is marked with an asterisk (*).</p>
162#	<p>Chemical structure 162# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a (1-morpholin-4-ylmethyl)amino group at the 6-position.</p>
163#	<p>Chemical structure 163# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a cyclohexyl ether group at the 6-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 72]

Ej	Estr
164#	<p>Chemical structure 164# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 1-phenyl-2-(difluoromethyl)-1H-imidazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring has a hydroxyl group (-OH) at the 1-position, shown with a wedge bond.</p>
165#	<p>Chemical structure 165# is identical to 164#, but the hydroxyl group (-OH) on the cyclohexane ring is shown with a dashed bond, indicating a different stereochemistry.</p>
166#	<p>Chemical structure 166# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 1-phenyl-2-(difluoromethyl)-1H-imidazol-5-yl group at the 4-position, and a 2,2,4,4-tetramethylpiperidin-1-yl group at the 6-position.</p>
167#	<p>Chemical structure 167# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 1-phenyl-2-(difluoromethyl)-1H-imidazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring has a hydroxyl group (-OH) at the 1-position.</p>
168#	<p>Chemical structure 168# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 1-phenyl-2-(difluoromethyl)-1H-imidazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring has a hydroxyl group (-OH) and a methyl group (-Me) at the 1-position, both shown with wedge bonds.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 73]

Ej	Estr
169#	<p>Chemical structure 169# features a central 1,3,5-triazine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At the 6-position, there is a cyclohexane ring with a methyl group and a hydroxyl group in a trans configuration.</p>
170#	<p>Chemical structure 170# features a central 1,3,5-triazine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At the 6-position, there is a bicyclic decalin system with a hydroxyl group.</p>
171#	<p>Chemical structure 171# features a central 1,3,5-triazine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At the 6-position, there is a cyclopentane ring with an oxygen atom, forming a tetrahydrofuran-like structure.</p>
172#	<p>Chemical structure 172# features a central 1,3,5-triazine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At the 6-position, there is a cyclohexane ring.</p>
173#	<p>Chemical structure 173# features a central 1,3,5-triazine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At the 6-position, there is a propyl chain ending in a cyclopentane ring with a sulfur atom.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 74]

Ej	Estr
174#	<p>Chemical structure 174# features a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a 4-tert-butylamino phenoxy group. At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>
175#	<p>Chemical structure 175# features a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a cyclohexane ring bearing an amino group (-NH₂) at the 1-position. At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>
176#	<p>Chemical structure 176# features a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a cyclohexane ring bearing an amino group (-NH₂) at the 1-position. At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>
177#	<p>Chemical structure 177# features a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a cyclohexane ring bearing a methoxyethyl group (-OCH₂CH₂OMe) at the 1-position. At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>
178#	<p>Chemical structure 178# features a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a bicyclic system (bicyclo[2.2.1]heptane) bearing a hydroxyl group (-OH) at the 1-position. At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 75]

Ej	Estr
179#	<p>Chemical structure 179# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a methyl ester group (-COOMe).</p>
180#	<p>Chemical structure 180# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a dimethylamide group (-CONMe₂).</p>
181#	<p>Chemical structure 181# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a propylpyrrolidine ether group (-OCH₂CH₂CH₂N(CH₂)₂).</p> <p>2HCl</p>
182#	<p>Chemical structure 182# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a (2-morpholinyl)ethylamino group (-NHCH₂CH₂N(CH₂)₂O).</p>
183#	<p>Chemical structure 183# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a piperidine ring, which is in turn substituted with a benzyl carbamate group (-COOCH₂Ph).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 76]

Ej	Estr
184#	<p>Chemical structure 184# features a central pyrimidine ring substituted with a piperazine ring at the 4-position, a 1H-imidazole ring at the 2-position, and a (1R)-2-(2-methoxycarbonylcyclohexyl)ethylamino group at the 6-position. The imidazole ring is further substituted with a 1,1-difluoroethyl group at the 2-position.</p>
185#	<p>Chemical structure 185# is similar to 184# but includes a methyl group (Me) at the 5-position of the imidazole ring. The cyclohexane ring is substituted with a tert-butyl carbamate group (-NHCOO^tBu) at the 1-position.</p>
186#	<p>Chemical structure 186# is similar to 184# but features a 1H-imidazole ring with a different ring fusion pattern. The cyclohexane ring is substituted with a tert-butyl carbamate group (-NHCOO^tBu) at the 1-position.</p>
187#	<p>Chemical structure 187# is similar to 185# but features a 1H-imidazole ring with a different ring fusion pattern. The cyclohexane ring is substituted with a tert-butyl carbamate group (-NHCOO^tBu) at the 1-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 77]

Ej	Estr
188#	<p>Chemical structure of compound 188# showing a central pyrimidopyrimidine core. The core is substituted with a morpholine ring, a 2,2-difluoroethyl group, a benzimidazole ring, and a 3-(pyridin-2-yl)propanamide chain. The structure is labeled with "2HCl".</p>
189#	<p>Chemical structure of compound 189# showing a central pyrimidopyrimidine core. The core is substituted with a morpholine ring, a 2,2-difluoroethyl group, a benzimidazole ring, and a 2-((1R,2S,4S)-2-oxocyclopentane-1-yl)ethanamide chain.</p>
190#	<p>Chemical structure of compound 190# showing a central pyrimidopyrimidine core. The core is substituted with a morpholine ring, a 2,2-difluoroethyl group, a benzimidazole ring, and a cyclohexane ring with a carboxylic acid group.</p>
191#	<p>Chemical structure of compound 191# showing a central pyrimidopyrimidine core. The core is substituted with a morpholine ring, a 2,2-difluoroethyl group, a 4-methylbenzimidazole ring, and a 2-(2-(2-methylmorpholino)ethyl)ethanamide chain. The structure is marked with an asterisk (*).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 78]

Ej	Estr
192#	<p>Chemical structure 192# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a secondary amine at the 2-position. The secondary amine is linked to a piperidine ring, which is further substituted with a morpholine group. The pyrimidine ring is also substituted at the 6-position with a benzimidazole ring system. The benzimidazole ring has a methoxy group (MeO) at the 2-position and a difluoromethyl group (CF₂H) at the 4-position.</p>
193#	<p>Chemical structure 193# is similar to 192# but lacks the methoxy group on the benzimidazole ring. It features a central pyrimidine ring substituted with a morpholine group at the 4-position and a secondary amine at the 2-position. The secondary amine is linked to a piperidine ring, which is further substituted with a cyclohexane ring. The pyrimidine ring is also substituted at the 6-position with a benzimidazole ring system that has a difluoromethyl group (CF₂H) at the 4-position.</p>
194#	<p>Chemical structure 194# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a secondary amine at the 2-position. The secondary amine is linked to a piperidine ring, which is further substituted with a morpholine ring. This morpholine ring has two methyl groups (Me) attached to its carbon atoms. The pyrimidine ring is also substituted at the 6-position with a benzimidazole ring system that has a difluoromethyl group (CF₂H) at the 4-position.</p>
195#	<p>Chemical structure 195# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a secondary amine at the 2-position. The secondary amine is linked to a bicyclic system (8-membered ring fused to a 5-membered ring). The bicyclic system has a morpholine group attached to the 5-membered ring. The pyrimidine ring is also substituted at the 6-position with a benzimidazole ring system that has a difluoromethyl group (CF₂H) at the 4-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 79]

Ej	Estr
196#	<p>Chemical structure of compound 196#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with an amide group linked to a methyl group and a cyclobutane ring.</p>
197#	<p>Chemical structure of compound 197#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a secondary amine group. The secondary amine is linked to a cyclohexane ring via a methylene bridge.</p>
198#	<p>Chemical structure of compound 198#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with an amide group linked to a dimethylamino group. The structure is shown as a hydrochloride salt (HCl).</p>
199#	<p>Chemical structure of compound 199#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with an amide group linked to a methyl group and a cyclohexane ring.</p>
200#	<p>Chemical structure of compound 200#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a secondary amine group. The secondary amine is linked to a cyclohexane ring via a methylene bridge. The structure is shown as a dihydrochloride salt (2HCl).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 80]

Ej	Estr
201#	<p>Chemical structure 201# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-phenyl-1H-imidazole-2-ylmethyl group at the 6-position. The core is linked via an ether bridge to a cyclohexane ring, which is further substituted with a proline ring. An asterisk (*) is placed near the proline ring, indicating it is not included in the claims.</p>
202#	<p>Chemical structure 202# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 4-(trifluoromethyl)phenyl group at the 6-position. The core is linked via an amine bridge to a piperidine ring, which is further substituted with a morpholine ring. The structure is shown as a dihydrochloride salt (2HCl).</p>
203#	<p>Chemical structure 203# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-phenyl-1H-imidazole-2-ylmethyl group at the 6-position. The core is linked via an amine bridge to a piperidine ring, which is further substituted with a morpholine ring and a methyl group (Me). The structure is shown as a hydrochloride salt (HCl).</p>
204#	<p>Chemical structure 204# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-phenyl-1H-imidazole-2-ylmethyl group at the 6-position. The core is linked via an amine bridge to a pyrrolidine ring, which is further substituted with a morpholine ring. The structure is shown as a hydrochloride salt (HCl).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 81]

Ej	Estr
205#	<p>Chemical structure of compound 205#: A central pyrimidine ring is substituted at the 2-position with a morpholine group, at the 4-position with a 1H-imidazole ring, and at the 6-position with an NH group. The imidazole ring is further substituted at the 2-position with a 1,1-difluoroethyl group and at the 4-position with a 2-methylphenyl group. The NH group is connected via a methylene bridge to a cyclohexane ring, which has an amino group (NH₂) at the 4-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
206#	<p>Chemical structure of compound 206#: Similar to 205#, but the cyclohexane ring is replaced by a piperidine ring. The structure is shown as a dihydrochloride salt (2HCl).</p>
207#	<p>Chemical structure of compound 207#: Similar to 205#, but the cyclohexane ring is replaced by a pyrrolidine ring. The structure is marked with an asterisk (*) and shown as a dihydrochloride salt (2HCl).</p>
208#	<p>Chemical structure of compound 208#: Similar to 206#, but the phenyl ring of the imidazole group is substituted with a methoxy group (MeO) at the 3-position. The structure is shown as a dihydrochloride salt (2HCl).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 82]

Ej	Estr
209#	<p>Chemical structure 209# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,1-difluoroethyl group at the 4-position, and a cyclopropylmethyl group at the 6-position. The 5-position of the core is linked to a cyclohexane ring via a nitrogen atom, which also has an amino group (-NH₂) attached to the cyclohexane ring. The structure is labeled as a dihydrochloride salt (2HCl).</p>
210#	<p>Chemical structure 210# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,1-difluoroethyl group at the 4-position, and a methyl group at the 7-position. The 5-position of the core is linked to a cyclohexane ring via a nitrogen atom, which also has an amino group (-NH₂) attached to the cyclohexane ring. The structure is labeled as a dihydrochloride salt (2HCl).</p>
211#	<p>Chemical structure 211# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,1-difluoroethyl group at the 4-position, and a methyl group at the 7-position. The 5-position of the core is linked to a cyclohexane ring via a nitrogen atom, which also has an amino group (-NH₂) attached to the cyclohexane ring. The structure is labeled as a dihydrochloride salt (2HCl).</p>
212#	<p>Chemical structure 212# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,1-difluoroethyl group at the 4-position, and a bicyclic amine group at the 6-position. The structure is labeled as a dihydrochloride salt (2HCl).</p>

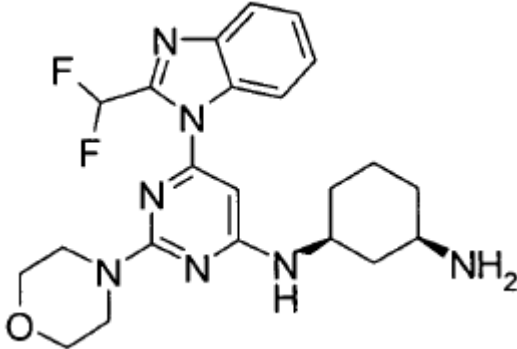
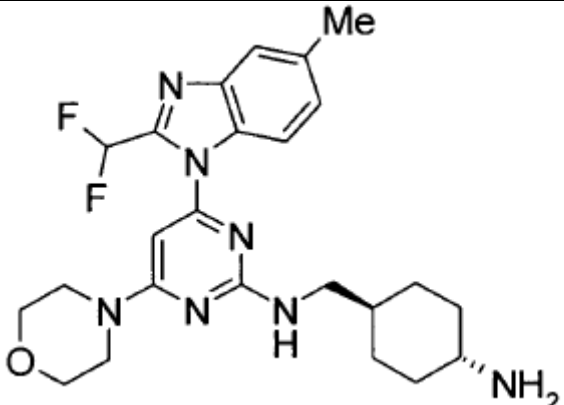
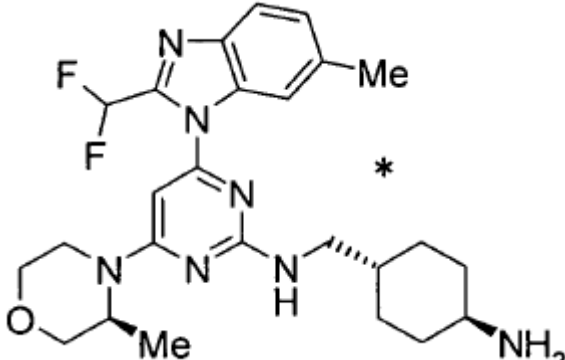
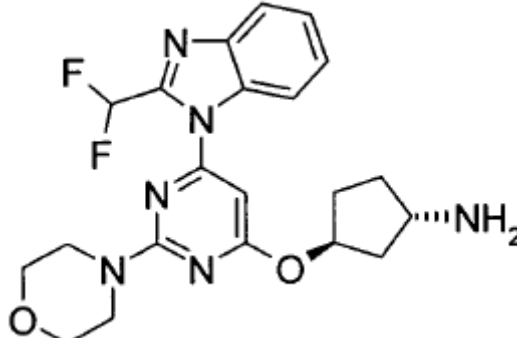
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 83]

Ej	Estr
213#	<p>Chemical structure 213# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a secondary amine group (-NH-) connected to a cyclohexane ring. At the 6-position, there is a benzimidazole ring system. The benzimidazole ring has a chlorine atom at the 5-position and a difluoromethyl group (-CH₂F₂) at the 2-position.</p>
214#	<p>Chemical structure 214# is similar to 213#, but the benzimidazole ring has a trifluoromethyl group (-CF₃) at the 5-position instead of a chlorine atom.</p>
215#	<p>Chemical structure 215# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a secondary amine group (-NH-) connected to a cyclohexane ring, which is further substituted with a cyclopropylcarbamoyl group (-NH-CO-C₃H₅-NH₂). At the 6-position, there is a benzimidazole ring system with a difluoromethyl group (-CH₂F₂) at the 2-position.</p>
216#	<p>Chemical structure 216# is similar to 215#, but the cyclohexane ring is substituted with a cyclopentylcarbamoyl group (-NH-CO-C₅H₉-NH₂) instead of a cyclopropylcarbamoyl group.</p>
217#	<p>Chemical structure 217# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a secondary amine group (-NH-) connected to a cyclohexane ring, which is substituted with an amino group (-NH₂). At the 6-position, there is a benzimidazole ring system with a difluoromethyl group (-CH₂F₂) at the 2-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 84]

Ej	Estr
218#	
219#	
220#	
221#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 85]

Ej	Estr
222#	<p>Chemical structure 222# features a central pyrimidopyrimidinone ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-aminocyclopentyl ether group at the 6-position.</p>
223#	<p>Chemical structure 223# features a central pyrimidopyrimidinone ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-butyl-2-(aminocyclohexyl)amino group at the 6-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
224#	<p>Chemical structure 224# features a central pyrimidopyrimidinone ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-((2S,4S)-2,4-dimethylpiperidin-1-yl)ethan-1-ylamino group at the 6-position.</p>
225#	<p>Chemical structure 225# features a central pyrimidopyrimidinone ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-((2S,4S)-2-((tert-butoxycarbonyl)amino)piperidin-1-yl)ethan-1-ylamino group at the 6-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 86]

Ej	Estr
226#	<p>Chemical structure 226# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a piperidine ring. The piperidine ring is further substituted with a 2,2-dimethyl-1,3-dioxolane ring.</p>
227#	<p>Chemical structure 227# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a piperidine ring. The piperidine ring is further substituted with a tert-butyl carbamate group.</p>
228#	<p>Chemical structure 228# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a piperidine ring. The piperidine ring is further substituted with a tert-butyl carbamate group.</p>
229#	<p>Chemical structure 229# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, a methyl group, and a piperidine ring. The piperidine ring is further substituted with a tert-butyl carbamate group. An asterisk (*) is placed near the structure, indicating it is not claimed.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 87]

Ej	Estr
230#	<p>Chemical structure 230# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1-(2-fluorophenyl)imidazole-2-yl group at the 2-position. The 6-position of the pyrimidine ring is substituted with a 1-(tert-butyl)pyrrolidine-3-ylmethyl group, which is marked with an asterisk (*). The morpholine ring has a methyl group attached to its nitrogen atom.</p>
231#	<p>Chemical structure 231# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1-(2-fluorophenyl)imidazole-2-yl group at the 2-position. The 6-position of the pyrimidine ring is substituted with a 1-(tert-butyl)pyrrolidine-3-ylmethyl group.</p>
232#	<p>Chemical structure 232# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1-(2-fluorophenyl)imidazole-2-yl group at the 2-position. The 6-position of the pyrimidine ring is substituted with a 1-(tert-butyl)pyrrolidine-3-ylmethyl group, where the pyrrolidine ring is shown with a specific stereochemistry.</p>
233#	<p>Chemical structure 233# features a central pyrimidine ring substituted with a morpholine group at the 4-position and a 1-(2-fluorophenyl)imidazole-2-yl group at the 2-position. The 6-position of the pyrimidine ring is substituted with a pyrrolidine-3-ylmethyl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 88]

Ej	Estr
234#	<p>Chemical structure 234# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a cyclobutylamino group at the 6-position. The cyclobutyl ring is attached to the core via its nitrogen atom, which is also bonded to a hydrogen atom.</p>
235#	<p>Chemical structure 235# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-methylpiperidin-4-ylamino group at the 6-position. The piperidine ring is attached to the core via its nitrogen atom, which is also bonded to a hydrogen atom and a methyl group.</p>
236#	<p>Chemical structure 236# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-methyl-4-(tert-butoxycarbonyl)piperidin-4-ylamino group at the 6-position. The piperidine ring is attached to the core via its nitrogen atom, which is also bonded to a hydrogen atom and a methyl group. The piperidine ring is further substituted with a tert-butoxycarbonyl group.</p>
237#	<p>Chemical structure 237# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-(4-oxocyclohexyl)pyrrolidin-2-ylamino group at the 6-position. The pyrrolidine ring is attached to the core via its nitrogen atom, which is also bonded to a hydrogen atom. The pyrrolidine ring is further substituted with a 4-oxocyclohexyl group.</p>
238#	<p>Chemical structure 238# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 4-(morpholin-2-ylmethyl)benzenesulfonamido group at the 6-position. The sulfonamide group is attached to the core via its nitrogen atom, which is also bonded to a hydrogen atom. The sulfonamide group is further substituted with a 4-(morpholin-2-ylmethyl)phenyl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 89]

Ej	Estr
239#	<p>Chemical structure of compound 239#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a cyclohexane ring with an amino group.</p>
240#	<p>Chemical structure of compound 240#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a cyclohexane ring with a morpholine ring. Labeled as 2HCl.</p>
241#	<p>Chemical structure of compound 241#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a cyclohexane ring with a benzamide group.</p>
242-1#	<p>Chemical structure of compound 242-1#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoroethyl group, a methyl group, and a cyclohexane ring with a methylamino group. Labeled as 2HCl.</p>
242-2#	<p>Chemical structure of compound 242-2#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoroethyl group, a methyl group, and a cyclohexane ring with a dimethylamino group. Labeled as 2HCl.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 90]

Ej	Estr
243#	<p>Chemical structure 243# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 4-methyl-5-(difluoromethyl)-1H-imidazole ring at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a pyrrolidine-2-one ring.</p>
244#	<p>Chemical structure 244# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 5-(difluoromethyl)-1H-imidazole ring at the 4-position, and a propanoic acid group at the 6-position. The structure is marked with an asterisk and 'HCl', indicating it is a hydrochloride salt.</p>
245#	<p>Chemical structure 245# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 5-(difluoromethyl)-1H-imidazole ring at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a pyrrolidine-2-one ring, which is in turn substituted with a 2-hydroxyethyl ester group. The structure is marked with an asterisk.</p>
246#	<p>Chemical structure 246# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 5-(difluoromethyl)-1H-imidazole ring at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a piperidine ring, which is in turn substituted with a cyclopentane ring bearing two methyl groups and a hydroxyl group.</p>
247#	<p>Chemical structure 247# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 5-(difluoromethyl)-1H-imidazole ring at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a guanidino group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 91]

Ej	Estr
248#	<p>Chemical structure of compound 248#: A central pyrimidopyrimidine core is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with a proline ring, which is in turn substituted with a methyl ester group (-COOMe).</p>
249-1	<p>Chemical structure of compound 249-1: A central pyrimidopyrimidine core is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with a proline ring, which is in turn substituted with a methoxy group (-OMe).</p>
249-2	<p>Chemical structure of compound 249-2: A central pyrimidopyrimidine core is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with a proline ring, which is in turn substituted with a methoxy group (-OMe).</p>
250#	<p>Chemical structure of compound 250#: A central pyrimidopyrimidine core is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a benzyl group (-CH₂Ph).</p>
251#	<p>Chemical structure of compound 251#: A central pyrimidopyrimidine core is substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a 2-pyridylmethyl group (-CH₂pyridine).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 92]

Ej	Estr
252#	<p>Chemical structure of compound 252#: A central 1,3,5-triazine ring is substituted at the 2, 4, and 6 positions. At position 2, there is a morpholine ring. At position 4, there is a 2-(2,2-difluoroethyl)-1H-benzotriazol-5-yl group. At position 6, there is a (pyridin-2-yl)methylamino group.</p>
253#	<p>Chemical structure of compound 253#: A central 1,3,5-triazine ring is substituted at the 2, 4, and 6 positions. At position 2, there is a morpholine ring. At position 4, there is a 2-(2,2-difluoroethyl)-1H-benzotriazol-5-yl group. At position 6, there is a (pyridin-2-yl)methylamino group.</p>
254#	<p>Chemical structure of compound 254#: A central 1,3,5-triazine ring is substituted at the 2, 4, and 6 positions. At position 2, there is a morpholine ring. At position 4, there is a 2-(2,2-difluoroethyl)-1H-benzotriazol-5-yl group. At position 6, there is a (1-phenylethyl)amino group.</p>
255#	<p>Chemical structure of compound 255#: A central 1,3,5-triazine ring is substituted at the 2, 4, and 6 positions. At position 2, there is a morpholine ring. At position 4, there is a 2-(2,2-difluoroethyl)-1H-benzotriazol-5-yl group. At position 6, there is a (1-hydroxyadamantan-1-yl)amino group.</p>
256#	<p>Chemical structure of compound 256#: A central 1,3,5-triazine ring is substituted at the 2, 4, and 6 positions. At position 2, there is a morpholine ring. At position 4, there is a 2-(2,2-difluoroethyl)-1H-benzotriazol-5-yl group. At position 6, there is a (tetrahydro-2H-pyran-2-yl)amino group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 93]

Ej	Estr
257#	<p>Chemical structure 257# is a 1,2,4,5-tetrazine derivative. It features a morpholine ring attached to the 2-position of the tetrazine core. The 4-position is substituted with a phenyl group (Ph). The 5-position is substituted with a benzimidazole ring system, which has a difluoromethyl group (-CH₂F₂) attached to its 2-position.</p>
258#	<p>Chemical structure 258# is a 1,2,4,5-tetrazine derivative. It features a morpholine ring attached to the 2-position of the tetrazine core. The 4-position is substituted with a 3-methoxyphenyl group (-NH-C₆H₄-OMe). The 5-position is substituted with a benzimidazole ring system, which has a difluoromethyl group (-CH₂F₂) attached to its 2-position.</p>
259#	<p>Chemical structure 259# is a 1,2,4,5-tetrazine derivative. It features a morpholine ring attached to the 2-position of the tetrazine core. The 4-position is substituted with a 4-pyridinyl group (-O-C₅H₄N). The 5-position is substituted with a benzimidazole ring system, which has a difluoromethyl group (-CH₂F₂) attached to its 2-position.</p>
260#	<p>Chemical structure 260# is a 1,2,4,5-tetrazine derivative. It features a morpholine ring attached to the 2-position of the tetrazine core. The 4-position is substituted with a 3-pyridinyl group (-NH-C₅H₄N). The 5-position is substituted with a benzimidazole ring system, which has a difluoromethyl group (-CH₂F₂) attached to its 2-position.</p>
261#	<p>Chemical structure 261# is a 1,2,4,5-tetrazine derivative. It features a morpholine ring attached to the 2-position of the tetrazine core. The 4-position is substituted with a 4-morpholinyl group (-O-C₄H₈O). The 5-position is substituted with a benzimidazole ring system, which has a difluoromethyl group (-CH₂F₂) attached to its 2-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 94]

Ej	Estr
262#	<p>Chemical structure 262# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a hydrogen atom. At the 6-position, it is substituted with a 1-(2,2,2-trifluoroethyl)-1H-benzotriazol-5-yl group. At the 5-position, it is substituted with a hydrogen atom. Additionally, a norbornane ring is attached to the 4-position of the triazine ring via its nitrogen atom.</p>
263#	<p>Chemical structure 263# is identical to structure 262#.</p>
264#	<p>Chemical structure 264# features a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a hydrogen atom. At the 6-position, it is substituted with a 1-(2,2,2-trifluoroethyl)-1H-benzotriazol-5-yl group. At the 5-position, it is substituted with a hydrogen atom. Additionally, a cyclohexane ring is attached to the 4-position of the triazine ring via its nitrogen atom, with a hydroxyl group (-OH) attached to the cyclohexane ring.</p>
265#	<p>Chemical structure 265# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a hydrogen atom. At the 6-position, it is substituted with a 1-(2,2,2-trifluoroethyl)-1H-benzotriazol-5-yl group. At the 5-position, it is substituted with a hydrogen atom. Additionally, a norbornane ring is attached to the 4-position of the triazine ring via its nitrogen atom.</p>
266#	<p>Chemical structure 266# features a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a hydrogen atom. At the 6-position, it is substituted with a 1-(2,2,2-trifluoroethyl)-1H-benzotriazol-5-yl group. At the 5-position, it is substituted with a hydrogen atom. Additionally, a cyclohexane ring is attached to the 4-position of the triazine ring via its nitrogen atom, with a hydroxyl group (-OH) attached to the cyclohexane ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 95]

Ej	Estr
267#	<p>Chemical structure 267# features a central pyrimidine ring substituted at the 2-position with a morpholine group, at the 4-position with a 1H-cyclohexylamino group, and at the 6-position with a 1H-benzotriazol-2-ylidene group. The benzotriazol-2-ylidene group is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>
268#	<p>Chemical structure 268# is identical to 267# but with the cyclohexane ring in the amino group substituted with a hydroxyl group (-OH) at the 1-position.</p>
269#	<p>Chemical structure 269# is identical to 268# but with the cyclohexane ring in the amino group substituted with a hydroxyl group (-OH) at the 2-position.</p>
270#	<p>Chemical structure 270# features a central pyrimidine ring substituted at the 2-position with a morpholine group, at the 4-position with a 1H-piperidin-2-ylamino group, and at the 6-position with a 1H-benzotriazol-2-ylidene group. The benzotriazol-2-ylidene group is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>
271#	<p>Chemical structure 271# is identical to 269# but with the bicyclic ring in the amino group substituted with a hydroxyl group (-OH) at the 1-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 96]

Ej	Estr
272#	<p>Chemical structure 272# shows a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 1H-cyclohexylamino group at the 4-position, and a 1H-benzotriazol-2-ylidene group at the 6-position. The benzotriazol-2-ylidene group is further substituted with a difluoromethyl group (-CF₂H).</p>
273#	<p>Chemical structure 273# is identical to 272#, but the cyclohexane ring is substituted with a methyl group (-Me) and a hydroxyl group (-OH) at the 1-position, with the methyl group shown with a dashed bond and the hydroxyl group with a wedged bond.</p>
274#	<p>Chemical structure 274# is identical to 272#, but the cyclohexane ring is unsubstituted.</p>
275#	<p>Chemical structure 275# is identical to 272#, but the cyclohexane ring is substituted with a propylsulfonamide group (-NHCH₂CH₂SO₂N) at the 1-position.</p>
276#	<p>Chemical structure 276# is identical to 272#, but the cyclohexane ring is substituted with a bicyclic system (bicyclo[2.2.1]heptane) at the 1-position, which has a hydroxyl group (-OH) attached to one of the bridgehead carbons.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 97]

Ej	Estr
277#	<p>Chemical structure 277# shows a central 1,2,4,5-tetrazine ring. At position 2, there is a morpholine ring. At position 4, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At position 6, there is a primary amide group (-NH-CH₂-CH₂-SO₂-N-morpholine).</p>
278#	<p>Chemical structure 278# is similar to 277#, but the morpholine ring is attached to the benzimidazole ring at position 2 instead of the tetrazine ring.</p>
279#	<p>Chemical structure 279# is similar to 277#, but the morpholine ring is attached to the tetrazine ring at position 2, and the primary amide group is substituted with a benzyl group (-NH-CH₂-Ph).</p>
280#	<p>Chemical structure 280# is similar to 277#, but the primary amide group is substituted with a methyl group (-NH-CH₂-SO₂-Me).</p>
281#	<p>Chemical structure 281# is similar to 277#, but the primary amide group is substituted with a 4-aminophenoxy group (-NH-CH₂-O-C₆H₄-NH₂).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 98]

Ej	Estr
282#	<p>Chemical structure 282# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a pyridin-2-ylsulfanyl group. At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H).</p>
283#	<p>Chemical structure 283# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H). At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group.</p>
284#	<p>Chemical structure 284# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H). At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group.</p>
285#	<p>Chemical structure 285# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H). At the 6-position, it is substituted with a 1H-benzotriazol-2-ylidene group.</p>
286#	<p>Chemical structure 286# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a 1H-benzotriazol-2-ylidene group, which is further substituted at the 4-position with a difluoromethyl group (-CF₂H). At the 6-position, it is substituted with a 1,2,4-thiazol-5-yl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 99]

Ej	Estr
287#	<p>Chemical structure 287# consists of a central 1,3,5-triazine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a 2-aminothiazole ring. At the 6-position, it is substituted with a benzimidazole ring that has a difluoromethyl group (-CH₂F₂) attached to its 2-position.</p>
288#	<p>Chemical structure 288# is similar to 287#, but the 2-aminothiazole ring is replaced by a 2,4,5-triazole ring.</p>
289#	<p>Chemical structure 289# is similar to 287#, but the 2-aminothiazole ring is replaced by a 4-(piperidin-2-ylmethyl)aniline ring.</p>
290#	<p>Chemical structure 290# is similar to 287#, but the 2-aminothiazole ring is replaced by a 2-methyl-2,4,5-triazole ring.</p>
291#	<p>Chemical structure 291# is similar to 287#, but the 2-aminothiazole ring is replaced by a 4-(piperidin-2-ylmethyl)aniline ring.</p>

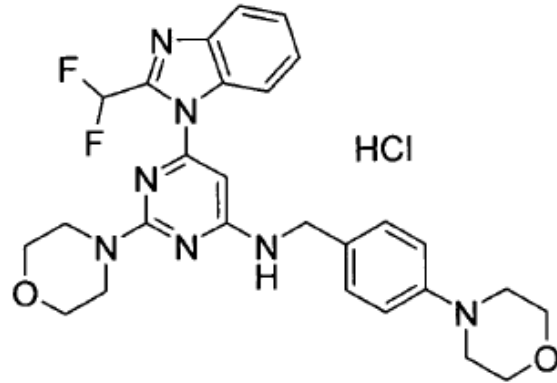
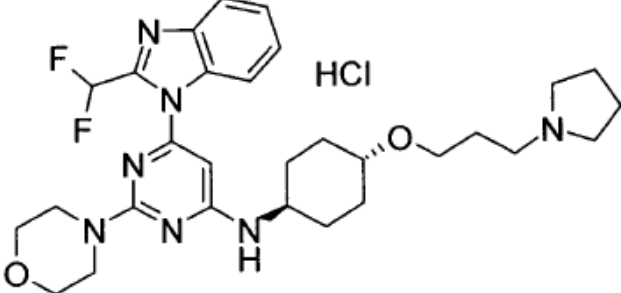
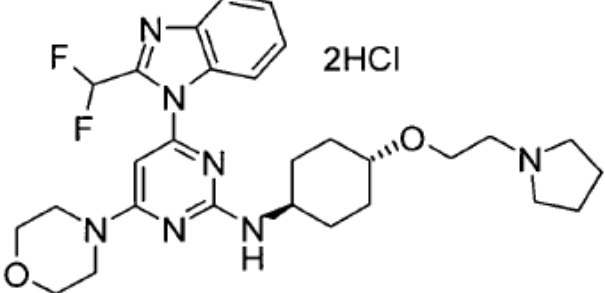
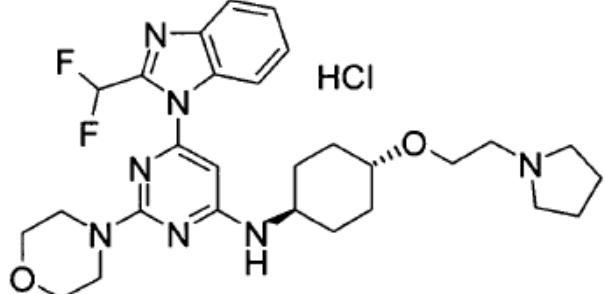
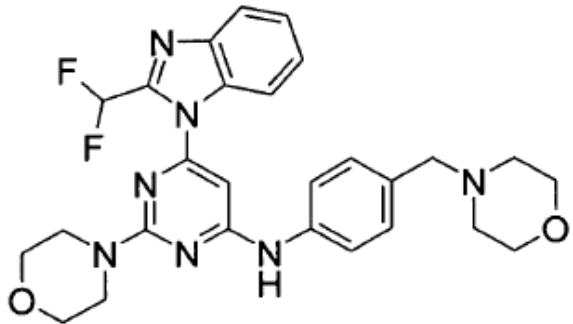
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 100]

Ej	Estr
292#	<p>Chemical structure of compound 292# is shown. It features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. The 5-position of the core is substituted with a cyclobutane ring, which is further substituted with a propylamine group. The structure is labeled as HCl.</p>
293#	<p>Chemical structure of compound 293# is shown. It features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. The 5-position of the core is substituted with a benzene ring, which is further substituted with a methylene group connected to a piperazine ring. The piperazine ring is substituted with a sulfonyl group.</p>
294#	<p>Chemical structure of compound 294# is shown. It features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. The 5-position of the core is substituted with a methylene group connected to a benzene ring. The benzene ring is substituted with a nitro group (NO₂).</p>
295#	<p>Chemical structure of compound 295# is shown. It features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. The 5-position of the core is substituted with a methylene group connected to a benzene ring. The benzene ring is substituted with an amino group (NH₂).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 101]

Ej	Estr
296#	
297#	
298#	
299#	
300#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 102]

Ej	Estr
301#	<p>Chemical structure 301# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a 4-(dimethylaminomethyl)phenylamino group at the 6-position.</p>
302#	<p>Chemical structure 302# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a 4-(piperidin-1-ylmethyl)phenylamino group at the 6-position.</p>
303#	<p>Chemical structure 303# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a 4-(tert-butylcarbamoyl)cyclohexylamino group at the 6-position.</p>
304#	<p>Chemical structure 304# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a cyclohexylamino group at the 6-position.</p>
305#	<p>Chemical structure 305# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 4-position, and a cyclohexylamino group at the 6-position. The cyclohexane ring is further substituted with a morpholine ring via an ether linkage.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 103]

Ej	Estr
306#	<p>Chemical structure 306# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a 3-(tetrahydro-2H-pyran-2-yl)propoxy group.</p>
307#	<p>Chemical structure 307# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a dimethylacetamide group. The structure is shown as a dihydrochloride salt (2HCl).</p>
308#	<p>Chemical structure 308# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a 2-hydroxyethoxy group.</p>
309#	<p>Chemical structure 309# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a 3-hydroxypropoxy group.</p>
310#	<p>Chemical structure 310# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a 3,4-dimethoxybenzyl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 104]

Ej	Estr
311#	<p>Chemical structure 311# consists of a central pyrimidine ring. At the 2-position, it is substituted with a morpholine ring. At the 4-position, it is substituted with a benzimidazole ring that has a difluoromethyl group (-CH₂F₂) attached to its 2-position. At the 6-position, it is substituted with an amino group (-NH-) which is further attached to a 4-methoxyphenyl ring.</p>
312#	<p>Chemical structure 312# is similar to 311#, but the 4-methoxyphenyl ring is replaced by a 2-methoxy-5-pyridyl ring.</p>
313#	<p>Chemical structure 313# is identical to structure 311#.</p>
314#	<p>Chemical structure 314# is similar to 311#, but the 4-methoxyphenyl ring is replaced by a 2-(piperidin-2-ylmethyl)pyridine ring.</p>
315#	<p>Chemical structure 315# is similar to 311#, but the 4-methoxyphenyl ring is replaced by a 4-(pyrrolidin-1-yl)benzoyl ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 105]

Ej	Estr
316#	<p>Chemical structure 316# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-imidazo[5,1-b]indol-3-yl group substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a 4-(tert-butylcarbamoyl)phenoxy group (-O-C₆H₄-CH₂-NH-C(=O)-O^tBu).</p>
317#	<p>Chemical structure 317# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-imidazo[5,1-b]indol-3-yl group substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a 4-aminophenoxy group (-O-C₆H₄-CH₂-NH₂).</p>
318#	<p>Chemical structure 318# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-imidazo[5,1-b]indol-3-yl group substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a 4-(morpholinomethyl)phenoxy group (-O-C₆H₄-CH₂-N(morpholine)). The structure is shown as a dihydrochloride salt (2HCl).</p>
319#	<p>Chemical structure 319# features a central pyrimidine ring. At the 2-position, there is a morpholine group. At the 4-position, there is a 1H-imidazo[5,1-b]indol-3-yl group substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a (1R,4S)-4-(2-hydroxyethylidene)cyclohexylamino group (-NH-CH(cyclohexane)-CH=CH-OH).</p>
320#	<p>Chemical structure 320# features a central pyrimidine ring. At the 2-position, there is a morpholine group substituted with a methyl group (-Me). At the 4-position, there is a 1H-imidazo[5,1-b]indol-3-yl group substituted with a difluoromethyl group (-CF₂H). At the 6-position, there is a (1S,4S)-4-(piperidin-1-yl)cyclohexylamino group (-NH-CH(cyclohexane)-NH(piperidine)). An asterisk (*) is present next to the structure.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 106]

Ej	Estr
321#	<p>Chemical structure 321# features a central pyrimidine ring. At the 2-position, there is a 1H-imidazo[5,1-b]indol-3-ylidene group substituted with a difluoromethyl group (-CF₂H). At the 4-position, there is a morpholine ring. At the 6-position, there is a piperidine ring connected via its nitrogen atom to the pyrimidine ring. A methyl group (-Me) is attached to the morpholine ring. An asterisk (*) is placed to the right of the structure.</p>
322#	<p>Chemical structure 322# is similar to 321# but the piperidine ring is substituted with a tetrahydro-2H-pyran ring at the 4-position. An asterisk (*) is placed to the right of the structure.</p>
323#	<p>Chemical structure 323# is identical to 322# but the methyl group (-Me) on the morpholine ring is shown with a dashed bond, indicating it is not in the claims. An asterisk (*) is placed to the right of the structure.</p>
324#	<p>Chemical structure 324# is identical to 322# but the methyl group (-Me) on the morpholine ring is shown with a dashed bond, indicating it is not in the claims. An asterisk (*) is placed to the right of the structure.</p>
325#	<p>Chemical structure 325# is similar to 321# but the piperidine ring is substituted with a 2-phenylpiperidine ring at the 4-position. An asterisk (*) is placed to the right of the structure.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 107]

Ej	Estr
326#	<p>Chemical structure 326# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 4-position, and a piperidine ring at the 6-position. The piperidine ring is further substituted with a dimethylacetamide group (-C(=O)CH₂NMe₂). A fluorinated group (-CF₂) is attached to the imidazole ring. An asterisk (*) is placed to the right of the structure, indicating it is not claimed.</p>
327#	<p>Chemical structure 327# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 4-position, and a piperidine ring at the 6-position. The piperidine ring is further substituted with a benzyl group (-CH₂Ph). A fluorinated group (-CF₂) is attached to the imidazole ring. An asterisk (*) is placed to the right of the structure, indicating it is not claimed.</p>
328#	<p>Chemical structure 328# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 4-position, and a piperidine ring at the 6-position. The piperidine ring is further substituted with a benzyl group (-CH₂Ph). A fluorinated group (-CF₂) is attached to the imidazole ring. An asterisk (*) is placed to the right of the structure, indicating it is not claimed.</p>
329#	<p>Chemical structure 329# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 4-position, and a pyrrolidine ring at the 6-position. The pyrrolidine ring is further substituted with a dimethylacetamide group (-C(=O)CH₂NMe₂). A fluorinated group (-CF₂) is attached to the imidazole ring. An asterisk (*) is placed to the right of the structure, indicating it is not claimed.</p>
330#	<p>Chemical structure 330# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 4-position, and a pyrrolidine ring at the 6-position. The pyrrolidine ring is further substituted with an ethyl ester group (-C(=O)OEt). A fluorinated group (-CF₂) is attached to the imidazole ring. An asterisk (*) is placed to the right of the structure, indicating it is not claimed.</p>

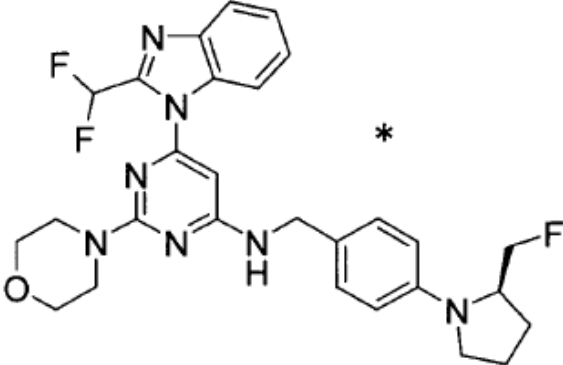
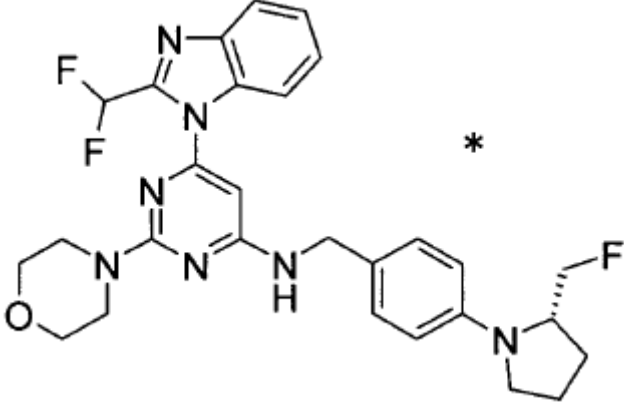
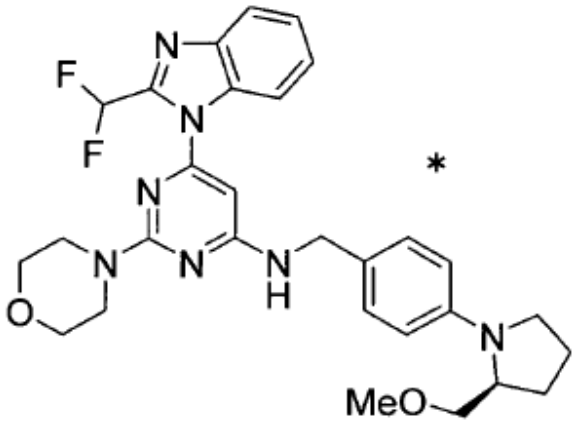
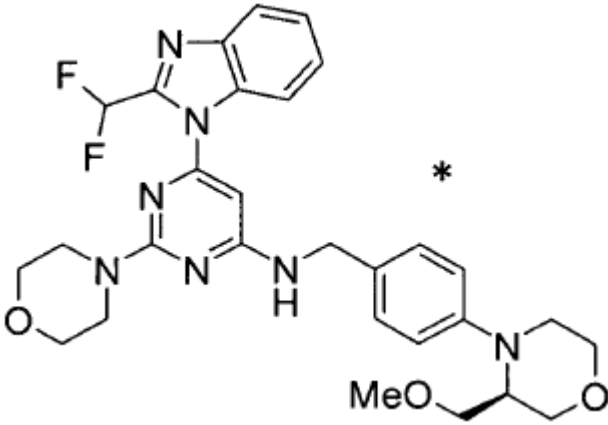
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 108]

Ej	Estr
331#	<p>Chemical structure 331# shows a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1H-pyrazolo[4,3-b]pyridine ring at the 6-position. The core is further substituted at the 8-position with a piperidine ring, which is in turn substituted with a 2-methylbenzamide group. An asterisk (*) is placed above the piperidine ring, indicating it is not included in the claims.</p>
332#	<p>Chemical structure 332# is identical to 331#, but the benzamide group is substituted with a 3-methylphenyl group. An asterisk (*) is placed above the piperidine ring, indicating it is not included in the claims.</p>
333#	<p>Chemical structure 333# is identical to 331#, but the benzamide group is substituted with a 4-methylphenyl group. An asterisk (*) is placed above the piperidine ring, indicating it is not included in the claims.</p>
334#	<p>Chemical structure 334# is identical to 331#, but the piperidine ring is substituted with a 4-(pyrrolidin-1-yl)phenyl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 109]

Ej	Estr
335#	
336#	
337#	
338#	

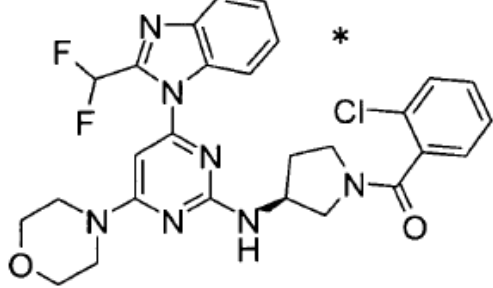
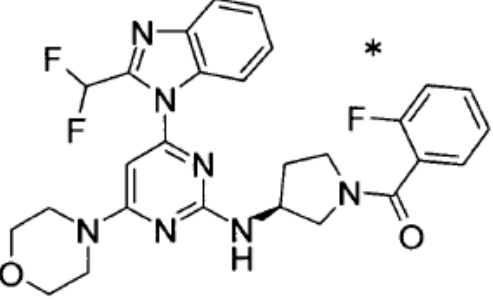
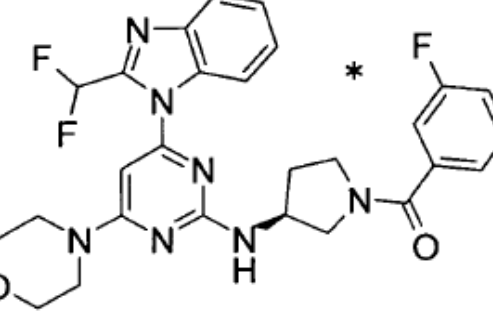
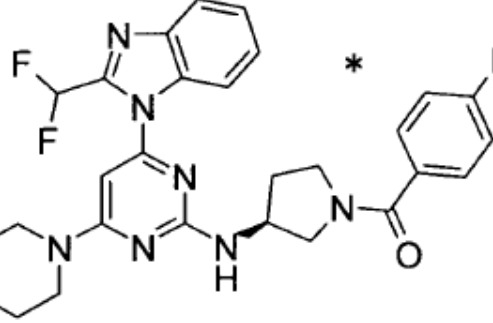
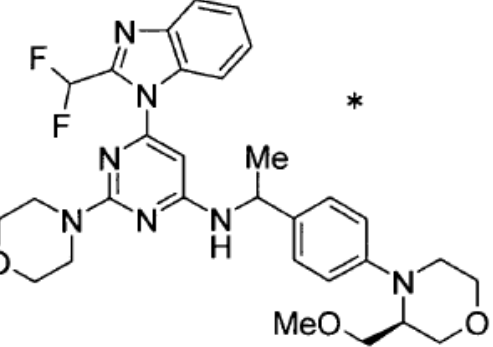
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 110]

Ej	Estr
339#	<p>Chemical structure 339# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a 4-(2-methoxyethyl)phenylamino group at the 6-position. The structure is labeled as a hydrochloride salt (HCl).</p>
340#	<p>Chemical structure 340# is similar to 339#, but the 4-(2-methoxyethyl)phenylamino group is replaced by a 4-bromophenylamino group.</p>
341#	<p>Chemical structure 341# features the same core as 339#, but with a 4-(tert-butylcarbamoyl)pyrrolidine ring attached to the 6-position of the pyrimidopyrimidine core via an ether linkage. An asterisk (*) is placed near the pyrrolidine ring.</p>
342	<p>Chemical structure 342 features the same core as 339#, but with a morpholine ring attached to the 6-position of the pyrimidopyrimidine core via an amine linkage. An asterisk (*) is placed near the morpholine ring.</p>
343#	<p>Chemical structure 343# features the same core as 339#, but with a 2-methoxyphenyl ring attached to the 6-position of the pyrimidopyrimidine core via an amine linkage. An asterisk (*) is placed near the phenyl ring.</p>

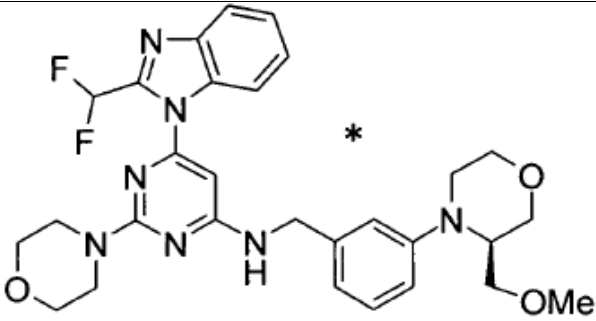
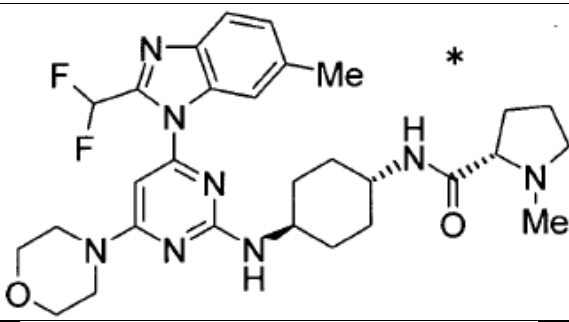
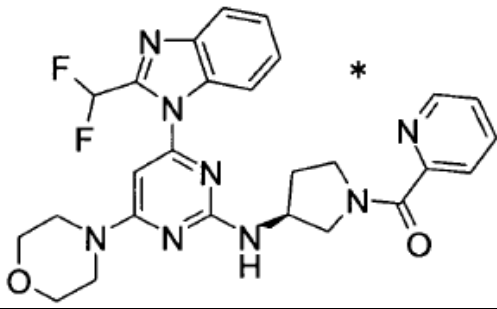
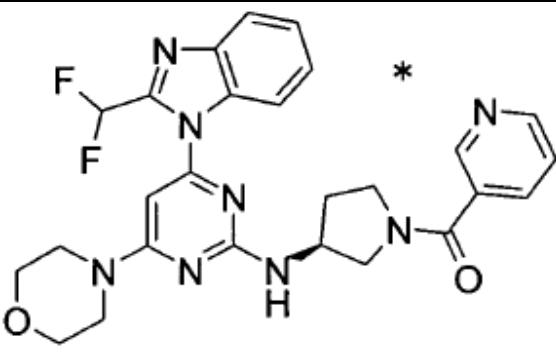
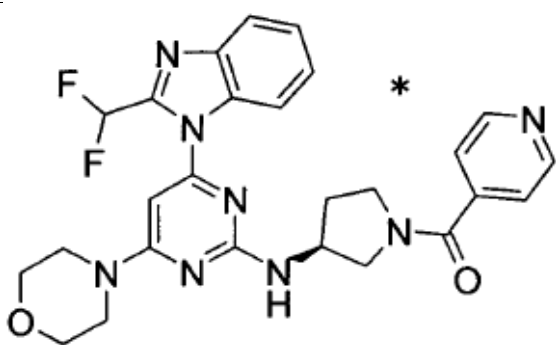
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 111]

Ej	Estr
344#	
345#	
346#	
347#	
348#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 112]

Ej	Estr
349#	
350#	
351#	
352#	
353#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 113]

Ej	Estr
354#	<p>Chemical structure of compound 354#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-pyrrolidin-2-ylmethyl group. The structure is marked with an asterisk (*) and labeled as 2HCl.</p>
355#	<p>Chemical structure of compound 355#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (R)-N-benzyloxymethylpyrrolidin-2-ylmethyl group. The structure is marked with an asterisk (*).</p>
356#	<p>Chemical structure of compound 356#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-N-benzyloxymethylpyrrolidin-2-ylmethyl group. The structure is marked with an asterisk (*).</p>
357#	<p>Chemical structure of compound 357#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-N-(2-fluoro-4-methylphenyl)pyrrolidin-2-ylmethyl group. The structure is marked with an asterisk (*).</p>
358#	<p>Chemical structure of compound 358#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-N-ethyl-N-(1-ethyl-2-hydroxypropan-2-yl)pyrrolidin-2-ylmethyl group. The structure is marked with an asterisk (*) and labeled as 2HCl.</p>

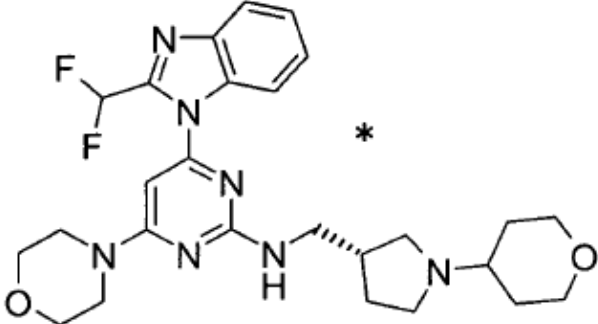
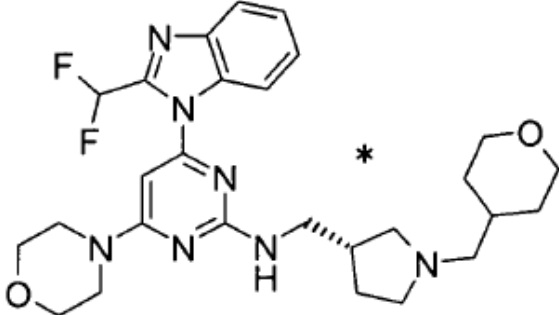
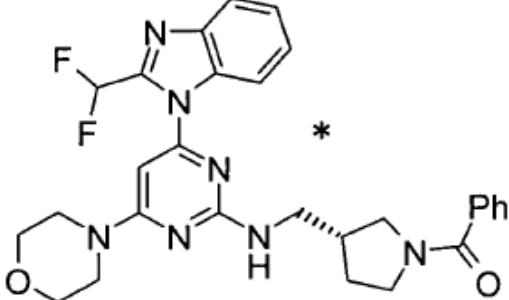
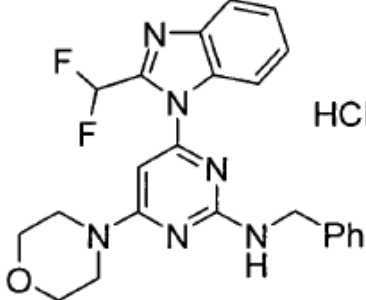
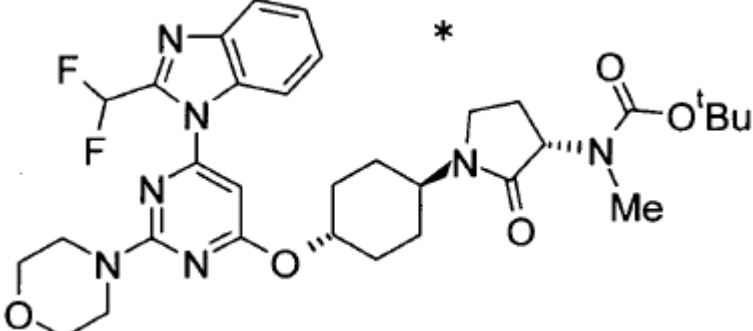
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 114]

Ej	Estr
359#	<p>Chemical structure 359# shows a central pyrimidopyrimidine core. It features a morpholine ring attached to the 2-position of the pyrimidine ring. The 4-position of the pyrimidine ring is linked via an oxygen atom to a bicyclic system consisting of a cyclopentane ring fused to a tetrahydrofuran ring. The bicyclic system has two methyl groups (Me) attached to the tetrahydrofuran ring. The 6-position of the pyrimidine ring is substituted with a benzimidazole ring system, which has a difluoromethyl group (-CF₂H) attached to its 2-position.</p>
360#	<p>Chemical structure 360# is similar to 359#, but the oxygen atom at the 4-position of the pyrimidine ring is replaced by a hydrogen atom. The bicyclic system is attached to the 6-position of the pyrimidine ring via its nitrogen atom.</p>
361#	<p>Chemical structure 361# is similar to 360#, but the bicyclic system is attached to the 6-position of the pyrimidine ring via its nitrogen atom, and the tetrahydrofuran ring of the bicyclic system has a carbonyl group (=O) attached to its 2-position.</p>
362#	<p>Chemical structure 362# is similar to 360#, but the bicyclic system is attached to the 6-position of the pyrimidine ring via its nitrogen atom, and the tetrahydrofuran ring of the bicyclic system has a morpholine ring attached to its 2-position. The structure is shown as a dihydrochloride salt (2HCl).</p>
363#	<p>Chemical structure 363# is similar to 359#, but the bicyclic system is replaced by a cyclohexane ring fused to a tetrahydrofuran ring. The tetrahydrofuran ring has two methyl groups (Me) attached to its 2-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 115]

Ej	Estr
364#	
365#	
366#	
367#	
368#	

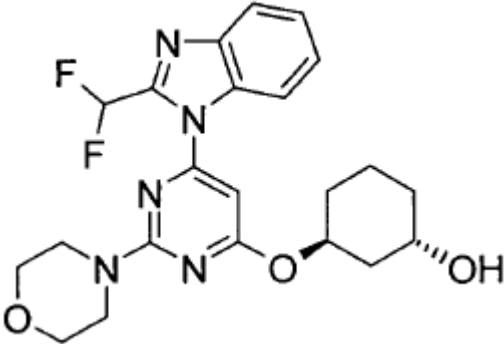
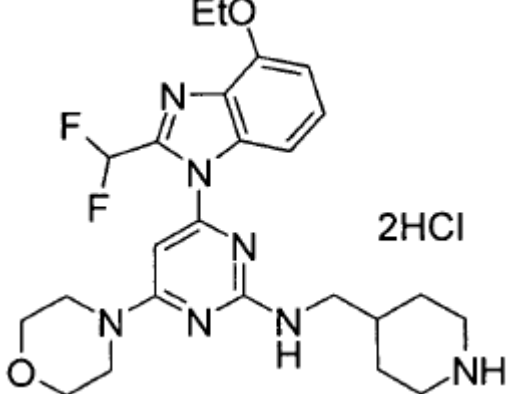
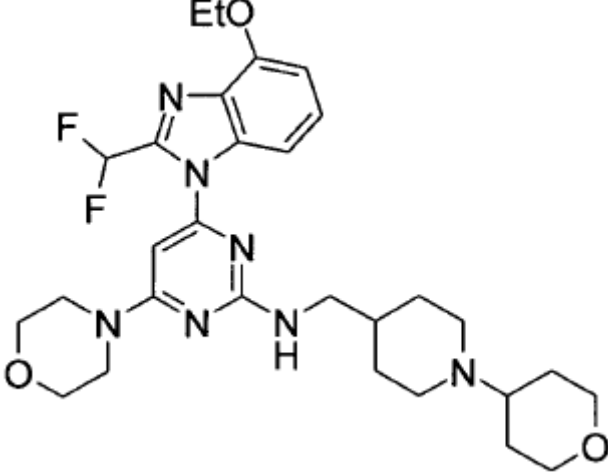
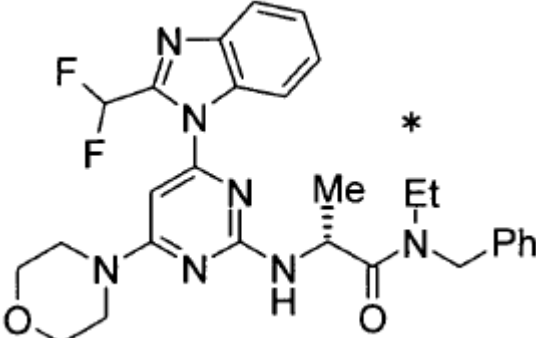
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 116]

Ej	Estr
369#	<p>Chemical structure 369# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazole ring at the 4-position, and a 1-phenylethylamino group at the 6-position. The imidazole ring is further substituted with a 1,1-difluoroethyl group. The ethylamino group is marked with an asterisk (*).</p>
370#	<p>Chemical structure 370# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazole ring at the 4-position, and a cyclohexylamino group at the 6-position. The imidazole ring is further substituted with a 1,1-difluoroethyl group. The cyclohexylamino group is connected to a 2-methoxycarbonylpyrrolidine ring, which is marked with an asterisk (*).</p>
371#	<p>Chemical structure 371# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazole ring at the 4-position, and a cyclohexylamino group at the 6-position. The imidazole ring is further substituted with a 1,1-difluoroethyl group. The cyclohexylamino group is connected to a 2-methoxycarbonylpyrrolidine ring, which is marked with an asterisk (*).</p>
372#	<p>Chemical structure 372# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazole ring at the 4-position, and a (2-ethoxyphenyl)amino group at the 6-position. The imidazole ring is further substituted with a 1,1-difluoroethyl group. The (2-ethoxyphenyl)amino group is marked with an asterisk (*).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 117]

Ej	Estr
373#	
374#	
375#	
376#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 118]

Ej	Estr
377#	<p>Chemical structure 377# is a complex molecule. It features a central pyrimidine ring. At the 2-position of the pyrimidine, there is a morpholine ring. At the 4-position, there is a hydrogen atom. At the 6-position, there is a nitrogen atom bonded to a 7-membered azepane ring, which is further substituted with a tert-butyl ester group (-COO^tBu). At the 5-position of the pyrimidine, there is a nitrogen atom bonded to a benzimidazole ring system. The benzimidazole ring has a 2,2-difluoroethyl group (-CH₂(F)₂) attached to its 2-position.</p>
378#	<p>Chemical structure 378# is similar to 377#, but the tert-butyl ester group is absent. The 7-membered azepane ring is a secondary amine (-NH-).</p>
379#	<p>Chemical structure 379# is similar to 377#, but the 7-membered azepane ring is replaced by a 6-membered piperidine ring, which is substituted with a tert-butyl ester group (-COO^tBu).</p>
380#	<p>Chemical structure 380# is similar to 379#, but the tert-butyl ester group is absent. The 6-membered piperidine ring is a secondary amine (-NH-).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 119]

Ej	Estr
381#	<p>Chemical structure 381# features a central pyrimidopyrimidinone core. The core is substituted with a 2,2-difluoroethyl group at the 2-position, a phenyl ring at the 4-position, a morpholine ring at the 6-position, and a (2-(morpholin-2-yl)ethyl)amino group at the 5-position.</p>
382#	<p>Chemical structure 382# features a central pyrimidopyrimidinone core. The core is substituted with a 2,2-difluoroethyl group at the 2-position, a phenyl ring at the 4-position, a morpholine ring at the 6-position, and a (7-(dimethylamino)heptan-1-yl)amino group at the 5-position.</p>
383	<p>Chemical structure 383 features a central pyrimidopyrimidinone core. The core is substituted with a 2,2-difluoroethyl group at the 2-position, a phenyl ring at the 4-position, a morpholine ring at the 6-position, and a (7-(morpholin-2-yl)heptan-1-yl)amino group at the 5-position.</p>
384#	<p>Chemical structure 384# features a central pyrimidopyrimidinone core. The core is substituted with a 2,2-difluoroethyl group at the 2-position, a phenyl ring at the 4-position, a morpholine ring at the 6-position, and a (2-(4,4-difluorophenyl)ethyl)amino group at the 5-position.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 120]

Ej	Estr
385#	<p>Chemical structure 385# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazole ring with a 2,2-difluoroethyl group at the 4-position, and a 2-(2-(2-methyl-2,3-dihydro-1H-pyridin-1-yl)ethyl)amino group at the 6-position. The pyrimidine ring also has a methyl group at the 5-position.</p>
386#	<p>Chemical structure 386# is identical to structure 385#.</p>
387#	<p>Chemical structure 387# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazole ring with a 2,2-difluoroethyl group at the 4-position, and a 2-(2-(2-(2-((cyclopropyl)sulfonyl)amino)ethyl)ethyl)oxy group at the 6-position. The pyrimidine ring also has a methyl group at the 5-position. An asterisk (*) is placed above the structure.</p>
388#	<p>Chemical structure 388# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-imidazole ring with a 2,2-difluoroethyl group at the 4-position, and a 2-(2-(2-(2-(2-hydroxypropan-2-yl)amino)ethyl)ethyl)oxy group at the 6-position. The pyrimidine ring also has a methyl group at the 5-position. An asterisk (*) is placed above the structure.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 121]

Ej	Estr
389#	<p>Chemical structure 389# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-benzotriazol-2-ylidene group at the 4-position, and a 2,2-difluoroethyl group at the 5-position. The pyrimidine ring is further substituted at the 6-position with a cyclohexane ring, which is in turn linked to a 2-methoxy-N-methylpyrrolidine-3-carboxamide moiety. An asterisk (*) is placed above the pyrrolidine ring to indicate a stereocenter.</p>
390#	<p>Chemical structure 390# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-benzotriazol-2-ylidene group at the 4-position, and a 2,2-difluoroethyl group at the 5-position. The pyrimidine ring is further substituted at the 6-position with an amide group (-NH-), which is linked to a chiral center (marked with an asterisk *) bearing an ethyl group and a benzyl group, and is also connected to another ethyl group.</p>
391#	<p>Chemical structure 391# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-benzotriazol-2-ylidene group at the 4-position, and a 2,2-difluoroethyl group at the 5-position. The pyrimidine ring is further substituted at the 6-position with an amide group (-NH-), which is linked to a chiral center (marked with an asterisk *) bearing an ethyl group and a benzyl group, and is also connected to a methyl group.</p>
392	<p>Chemical structure 392 features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-benzotriazol-2-ylidene group at the 4-position, and a 2,2-difluoroethyl group at the 5-position. The pyrimidine ring is further substituted at the 6-position with an amide group (-NH-), which is linked to a 7-membered azepane ring, which is in turn connected to an ethylpiperidine ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 122]

Ej	Estr
393#	<p>Chemical structure 393# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1H-pyrazolo[5,1-b]pyridine ring system at the 6-position. The core is further substituted at the 5-position with a secondary amine group (-NH-) that is linked via a methylene bridge to a piperidine ring. This piperidine ring is in turn substituted at the 4-position with another methylene bridge leading to a cyclohexane ring. The cyclohexane ring is substituted with a methyl group (Me) and a hydroxyl group (OH) at the 1-position.</p>
394#	<p>Chemical structure 394# is identical to structure 393#, but the hydroxyl group (OH) on the cyclohexane ring is replaced by a methoxy group (OMe).</p>
395#	<p>Chemical structure 395# is identical to structure 393#, but the cyclohexane ring is replaced by a four-membered oxetane ring.</p>
396#	<p>Chemical structure 396# is identical to structure 393#, but the cyclohexane ring is substituted at the 1-position with a hydroxymethyl group (-CH₂OH) and an ethyl ester group (-COOEt).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 123]

Ej	Estr
397#	<p>Chemical structure 397# features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 2-position, and a 1-(tert-butyl (S)-1-methylamino)propan-1-yl group at the 6-position. The imidazole ring of the indole system is substituted with a difluoromethyl group. An asterisk (*) is placed to the right of the structure.</p>
398#	<p>Chemical structure 398# features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 2-position, and a 1-(N-ethyl-N-phenylamino)propan-1-yl group at the 6-position. The imidazole ring of the indole system is substituted with a difluoromethyl group.</p>
399#	<p>Chemical structure 399# features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 2-position, and a 1-(N-ethyl-N-(4-pyridylmethyl)amino)propan-1-yl group at the 6-position. The imidazole ring of the indole system is substituted with a difluoromethyl group. An asterisk (*) is placed to the right of the structure.</p>
400#	<p>Chemical structure 400# features a central pyrimidine ring substituted with a morpholine group at the 4-position, a 1H-imidazo[5,1-b]indol-2-yl group at the 2-position, and a 1-(2-(2-hydroxyethoxy)ethyl)propan-1-yl group at the 6-position. The imidazole ring of the indole system is substituted with a difluoromethyl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 124]

Ej	Estr
401#	<p>Chemical structure 401# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a (2-hydroxyethyl)amino group at the 6-position. The amino group is further substituted with a piperidine ring, which is in turn substituted with a tetrahydro-2H-pyran-2-yl group.</p>
402#	<p>Chemical structure 402# is similar to 401#, but the hydroxyl group on the tetrahydro-2H-pyran ring is replaced by a fluorine atom.</p>
403#	<p>Chemical structure 403# is similar to 401#, but the hydroxyl group on the tetrahydro-2H-pyran ring is replaced by a sulfonyl group (-SO₂-).</p>
404#	<p>Chemical structure 404# is similar to 401#, but the hydroxyl group on the tetrahydro-2H-pyran ring is replaced by a morpholine ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 125]

Ej	Estr
405#	<p>Chemical structure 405# consists of a central pyrimidopyrimidine ring system. At the 2-position, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At the 4-position, there is a morpholine ring. At the 6-position, there is a secondary amine group (-NH-) connected to a piperidine ring, which is further connected to a morpholine ring.</p>
406#	<p>Chemical structure 406# features a central pyrimidopyrimidine ring system. At the 2-position, there is a benzimidazole ring with a difluoromethyl group (-CF₂H). At the 4-position, there is a morpholine ring. At the 6-position, there is a secondary amine group (-NH-) connected to a 7-membered azepane ring.</p>
407#	<p>Chemical structure 407# has a central pyrimidopyrimidine ring system. At the 2-position, there is a benzimidazole ring with a difluoromethyl group (-CF₂H). At the 4-position, there is a morpholine ring. At the 6-position, there is a secondary amine group (-NH-) connected to a piperidine ring, which is further connected to another piperidine ring substituted with a methyl carbonyl group (-N-C(=O)-Me). The structure is shown as a dihydrochloride salt (2HCl).</p>
408	<p>Chemical structure 408 is similar to 406#, featuring a central pyrimidopyrimidine ring system with a benzimidazole ring at the 2-position substituted with a difluoromethyl group (-CF₂H). At the 4-position, there is a morpholine ring. At the 6-position, there is a secondary amine group (-NH-) connected to a 7-membered azepane ring, which is further connected to a morpholine ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 126]

Ej	Estr
409#	<p>Chemical structure 409# features a central pyrimidine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 4-methoxyphenyl group and a difluoromethyl group. At the 6-position, there is a secondary amine group (-NH-) connected via a methylene bridge to a piperidine ring, which is further substituted with a morpholine ring.</p>
410#	<p>Chemical structure 410# features a central pyrimidine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a phenyl group and a difluoromethyl group. At the 6-position, there is a secondary amine group (-NH-) connected via a methylene bridge to a bicyclic decalin system, which is further substituted with a tert-butyl carbamate group (-NHCOO^tBu).</p>
411#	<p>Chemical structure 411# features a central pyrimidine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a phenyl group and a difluoromethyl group. At the 6-position, there is a secondary amine group (-NH-) connected via a methylene bridge to a bicyclic decalin system, which is further substituted with an amino group (-NH₂).</p>
412#	<p>Chemical structure 412# features a central pyrimidine ring. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a phenyl group and a difluoromethyl group. At the 6-position, there is a secondary amine group (-NH-) connected via a methylene bridge to a bicyclic decalin system, which is further substituted with a 2-hydroxypropan-2-yl group (-NHCH₂CMe₂OH).</p>

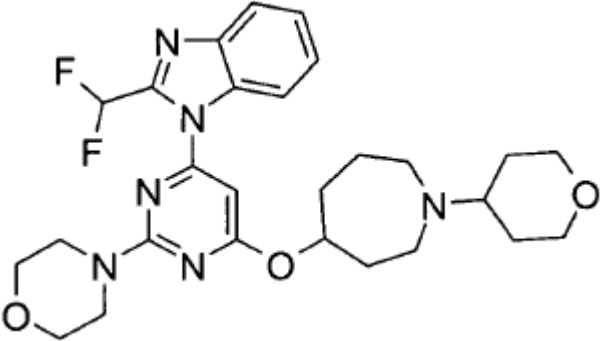
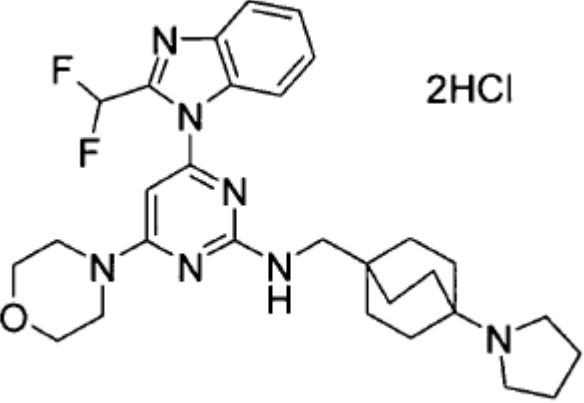
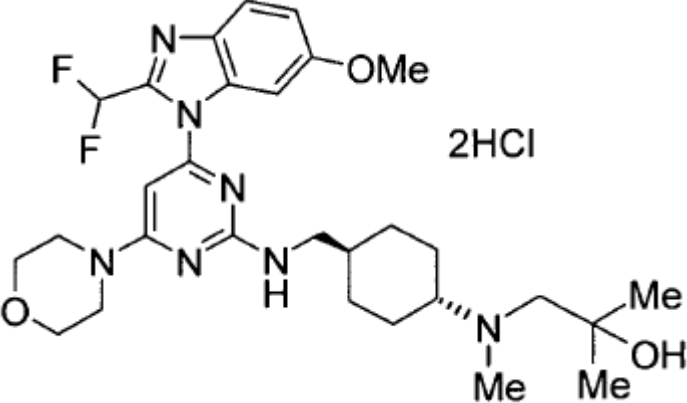
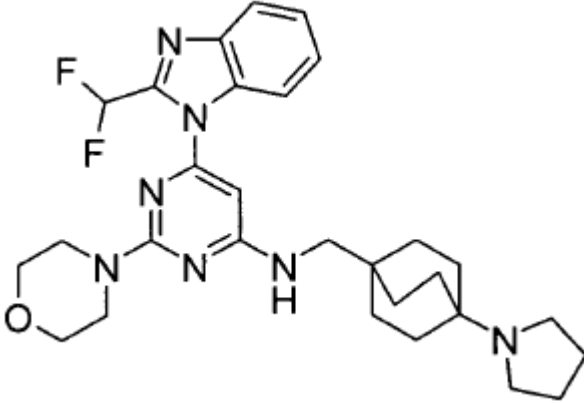
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 127]

Ej	Estr
413#	<p>Chemical structure 413# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-indazole ring at the 4-position, and a 2,2-difluoroethyl group at the 6-position. The 5-position of the core is linked via an amide bond to a bicyclic decalin system, which is further substituted with a dimethylamino group and a 2-hydroxypropan-2-yl group.</p>
414#	<p>Chemical structure 414# is similar to 413#, but the dimethylamino group on the decalin system is replaced by a diethylamino group.</p>
415#	<p>Chemical structure 415# features the same pyrimidopyrimidine core as 413# and 414#, but the 5-position is substituted with a tert-butyl carbamate group attached to a 7-membered azepane ring.</p>
416	<p>Chemical structure 416 is similar to 415#, but the carbamate group is replaced by a secondary amine group on the 7-membered azepane ring.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 128]

Ej	Estr
417	
418#	
419#	
420#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 129]

Ej	Estr
421#	<p>Chemical structure 421# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 4-position, and a (2-methoxycarbonyl)cyclopentylamino group at the 6-position.</p>
422#	<p>Chemical structure 422# is similar to 421#, but the cyclopentane ring is substituted with a hydroxymethyl group (-CH₂OH) instead of a methoxycarbonyl group.</p>
423#	<p>Chemical structure 423# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[5,1-b]indol-2-ylidene group at the 4-position, and a (1-ethoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridin-5-yl)cyclohexyloxy group at the 6-position. An asterisk (*) is placed above the structure.</p>
424#	<p>Chemical structure 424# is similar to 423#, but the cyclohexane ring is substituted with a (1-ethoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridin-5-yl) group instead of an ethoxycarbonyl group. An asterisk (*) is placed above the structure.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 130]

Ej	Estr
425#	<p>Chemical structure 425# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 1H-benzotriazol-2-ylidene group at the 4-position, and a 2-(2-oxocyclohexyl)oxy group at the 6-position. The cyclohexane ring is shown with a wedged bond to the oxygen atom and a carboxylic acid group (-COOH) at the 1-position.</p>
426#	<p>Chemical structure 426# is similar to 425# but features a 1-(tert-butyl)pyrrolidine-3-yl group instead of the cyclohexane ring. An asterisk (*) is placed to the right of the structure, indicating it is not included in the claims.</p>
427#	<p>Chemical structure 427# is similar to 426# but features a 1-(tert-butyl)pyrrolidine-2-yl group instead of the 3-yl group.</p>
428#	<p>Chemical structure 428# is similar to 426# but features a 1-(tert-butyl)pyrrolidine-3-ylmethyl group instead of the 3-yl group.</p>
429#	<p>Chemical structure 429# is similar to 428# but features a pyrrolidine ring instead of the 1-(tert-butyl)pyrrolidine group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 131]

Ej	Estr
430#	<p>Chemical structure 430# shows a central pyrimidine ring substituted with a morpholine group at position 2, a 1H-imidazo[5,1-b]indol-2-yl group at position 4, and a (S)-pyrrolidin-2-yl group at position 6. The imidazo[5,1-b]indol-2-yl group is further substituted with a difluoromethyl group at position 2. An asterisk (*) is placed next to the pyrrolidine group, indicating it is not included in the claims.</p>
431	<p>Chemical structure 431 is similar to 430#, but the pyrrolidine group is replaced by a pyrrolidine ring. The asterisk (*) is placed next to the pyrrolidine group, indicating it is not included in the claims.</p>
432-1	<p>Chemical structure 432-1 features a central pyrimidine ring substituted with a morpholine group at position 2, a 1H-imidazo[5,1-b]indol-2-yl group at position 4, and a (S)-piperidin-2-yl group at position 6. The imidazo[5,1-b]indol-2-yl group is further substituted with a difluoromethyl group at position 2.</p>
432-2	<p>Chemical structure 432-2 is identical to 432-1, but the piperidine ring is substituted with a morpholine group at the 4-position.</p>
433	<p>Chemical structure 433 is similar to 430#, but the pyrrolidine group is replaced by a piperidine ring. The asterisk (*) is placed next to the piperidine group, indicating it is not included in the claims.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 132]

Ej	Estr
434#	<p>Chemical structure 434# shows a central pyrimidopyrimidine core. It features a morpholine ring attached to the 2-position, a 1H-imidazo[5,1-b]pyridine ring system with a difluoromethyl group at the 2-position, and a cyclohexane ring with a hydroxyl group at the 4-position, connected via an oxygen atom at the 6-position of the pyrimidine ring.</p>
435#	<p>Chemical structure 435# is similar to 434# but with a tert-butyl carbamate group attached to the 4-position of the cyclohexane ring. An asterisk (*) is placed to the right of the structure.</p>
436	<p>Chemical structure 436 is similar to 435# but with a secondary amine group (-NH-) attached to the 4-position of the cyclohexane ring. An asterisk (*) is placed to the right of the structure.</p>
437#	<p>Chemical structure 437# is similar to 435# but with a dashed bond connecting the cyclohexane ring to the pyrimidine core. An asterisk (*) is placed to the right of the structure.</p>
438#	<p>Chemical structure 438# is similar to 436 but with a dashed bond connecting the cyclohexane ring to the pyrimidine core. An asterisk (*) is placed to the right of the structure.</p>

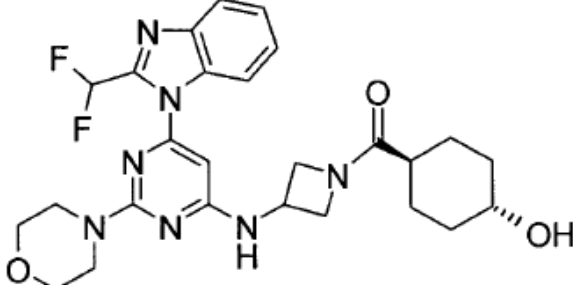
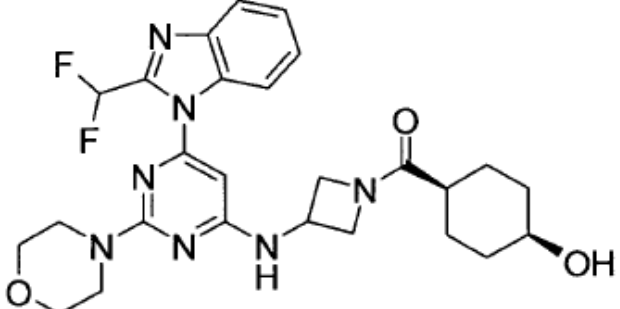
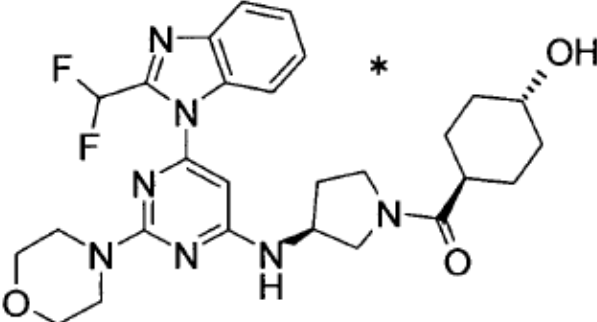
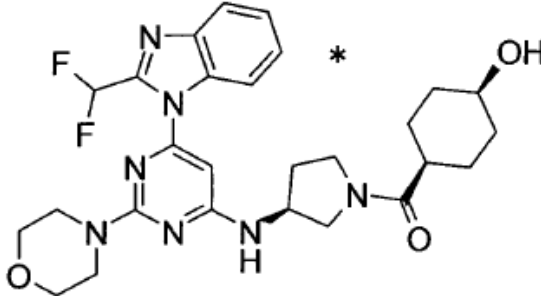
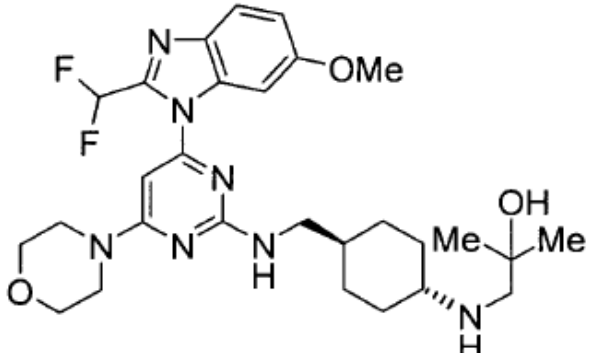
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 133]

Ej	Estr
439#	<p>Chemical structure 439# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-(2-tert-butylaminoethyl)amino group at the 6-position.</p>
440#	<p>Chemical structure 440# is similar to 439# but lacks the tert-butyl group on the secondary amine, instead featuring a primary amine group.</p>
441#	<p>Chemical structure 441# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-(1-methoxy-2-oxo-2-(cyclohexylamino)ethyl)amino group at the 6-position. An asterisk (*) is placed above the structure.</p>
442	<p>Chemical structure 442 features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-(1-hydroxycyclohexyl)oxy group at the 6-position.</p>
443	<p>Chemical structure 443 features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 1-(1-hydroxycyclohexyl)oxy group at the 6-position, with the hydroxyl group on the cyclohexane ring shown with a dashed bond.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 134]

Ej	Estr
444	
445	
446	
447	
448#	

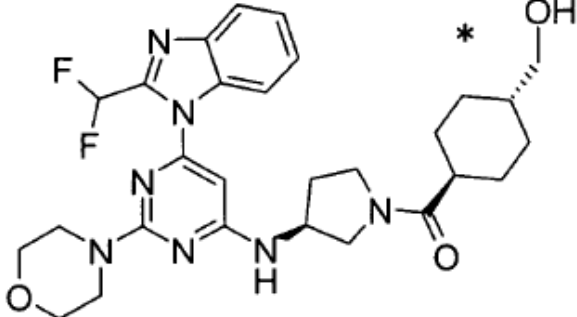
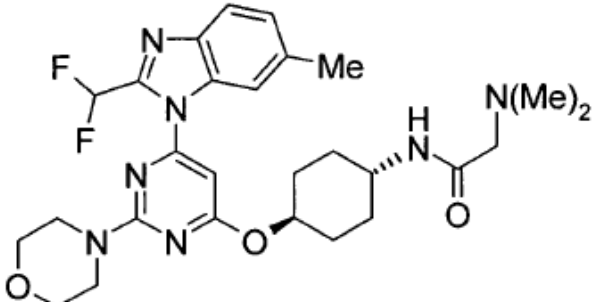
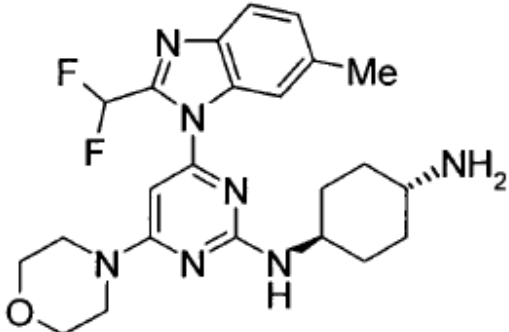
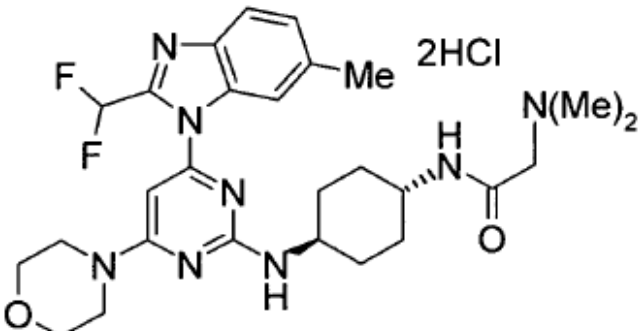
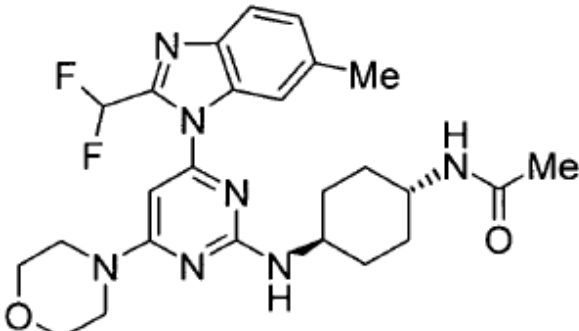
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 135]

Ej	Estr
449#	<p>Chemical structure 449# shows a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 4-methoxyphenyl ring at the 4-position, and a difluoromethyl group at the 5-position. The core is further substituted at the 6-position with a cyclohexane ring, which has an amino group (-NH₂) attached to it.</p>
450#	<p>Chemical structure 450# is similar to 449#, but the amino group on the cyclohexane ring is protected as a tert-butyl carbamate (-NHCO^tBu).</p>
451	<p>Chemical structure 451 features a central pyrimidopyrimidine core with a morpholine ring at the 2-position, a phenyl ring at the 4-position, and a difluoromethyl group at the 5-position. The core is substituted at the 6-position with a cyclohexane ring, which is further substituted with a methoxy group (-OMe) and a pyrrolidine ring connected via a carbonyl group.</p>
452	<p>Chemical structure 452 is similar to 451, but the methoxy group on the cyclohexane ring is shown with a dashed bond, indicating it is on the opposite side of the ring from the other substituents.</p>
453	<p>Chemical structure 453 features a central pyrimidopyrimidine core with a morpholine ring at the 2-position, a phenyl ring at the 4-position, and a difluoromethyl group at the 5-position. The core is substituted at the 6-position with a cyclohexane ring, which is further substituted with a hydroxymethyl group (-CH₂OH) and a pyrrolidine ring connected via a carbonyl group. An asterisk (*) is placed near the hydroxymethyl group.</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 136]

Ej	Estr
454	
455#	
456#	
457#	
458#	

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 137]

Ej	Estr
459#	<p>Chemical structure 459# features a central pyrimidopyrimidine core. The core is substituted with a morpholine ring at the 2-position, a 4-methyl-5-(difluoromethyl)imidazole ring at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with an amino group (-NH₂) at the 1-position.</p>
460#	<p>Chemical structure 460# is similar to 459#, but the amino group on the cyclohexane ring is replaced by a tert-butyl carbamate group (-NHCO^tBu).</p>
461#	<p>Chemical structure 461# is similar to 459#, but the amino group on the cyclohexane ring is replaced by a dimethylacetamide group (-NHCOCH₂NMe₂).</p>
462#	<p>Chemical structure 462# is similar to 461#, but the dimethylacetamide group is replaced by a 1-methyl-2-(dimethylamino)ethanone group (-NHCOCH₂NMe₂).</p>
463#	<p>Chemical structure 463# is similar to 462#, but the 1-methyl-2-(dimethylamino)ethanone group is replaced by a 1,1-dimethyl-2-ethanone group (-NHCOCH₂Me).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 138]

Ej	Estr
464#	<p>Chemical structure 464# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 4-ethoxy-5-(difluoromethyl)-1H-benzotriazol-2-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a tert-butyl carbamate group (-NHCOO^tBu).</p>
465#	<p>Chemical structure 465# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 4-ethoxy-5-(difluoromethyl)-1H-benzotriazol-2-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with an amino group (-NH₂). The structure is shown as a dihydrochloride salt (2HCl).</p>
466#	<p>Chemical structure 466# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 4-ethoxy-5-(difluoromethyl)-1H-benzotriazol-2-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a 1-methyl-2-(2-hydroxyethyl)pyrrolidine-1-carboxamide group. An asterisk (*) is placed above the pyrrolidine ring, indicating it is not claimed.</p>
467#	<p>Chemical structure 467# shows a central pyrimidine ring substituted with a morpholine group at the 2-position, a 4-ethoxy-5-(difluoromethyl)-1H-benzotriazol-2-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a dimethylacetamide group (-NHCOCH₂NMe₂).</p>

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 139]

Ej	Estr
468#	<p>Chemical structure 468# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-phenyl-1H-imidazole-4-yl group at the 6-position. The core is further substituted at the 5-position with a (1-hydroxycyclopentyl)methylamino group.</p>
469#	<p>Chemical structure 469# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-phenyl-1H-imidazole-4-yl group at the 6-position. The core is further substituted at the 5-position with a (1-(tert-butylcarbamoyl)-4-fluorophenyl)methylamino group.</p>
470#	<p>Chemical structure 470# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-phenyl-1H-imidazole-4-yl group at the 6-position. The core is further substituted at the 5-position with a (1-fluorophenyl)methylamino group.</p>
471#	<p>Chemical structure 471# features a central pyrimidopyrimidinone core. The core is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a 2-phenyl-1H-imidazole-4-yl group at the 6-position. The core is further substituted at the 5-position with a (1-(4-morpholinophenyl)-4-fluorophenyl)methylamino group.</p>

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 140]

Ej	Sin	DAT
1#	1	ESI+: 516 RMN1:1,39(9H, s),1,81-1,94(1H, m),2,02-2,16(1H, m),3,11-3,87(11H, m),4,27-4,43(2H, m),6,33-6,46(1H, m),7,29-7,87(6H,m)
2#	1	ESI+: 458 RMN1:1,14-1,27(2H, m),1,46-1,58(1H, m),1,64-1,85(4H, m),2,13(3H, s),2,76(2H, m),3,06-3,34(2H, m),3,40-3,76(8H, m),5,64(1H, s),7,33-7,49(3H, m),7,79-7,86(1H, m),8,32-8,44(1H,m)
3#	1	ESI+: 458 RMN1:0,79-1,84(8H, m),2,12(3H, s),2,67-2,71(2H, m),3,01-3,18(1H, m),3,63-3,68(8H, m),5,21-6,38(1H, m),7,13-7,19(1H, m),7,39-7,86(5H,m)
4#	1	ESI+: 458 RMN1:1,12-1,30(2H, m),1,43-1,60(1H, m),1,63-1,72(2H, m),1,75-1,86(2H, m),2,14(3H, s),2,71-2,80(2H, m),3,21-3,32(2H, m),3,61-3,72(8H, m),6,14(1H, s),7,37-7,89(6H,m)
5#	1	ESI+: 567[M+Na] RMN1:0,98-1,13(2H, m),1,36-1,40(9H, m),1,63-1,83(3H, m),2,57-2,80(2H, m),3,22-3,32(2H, m),3,62-3,84(8H, m),3,87-4,01(2H, m),7,39-8,07(5H, m),8,40-8,58(1H,m)
6#	1	ESI+: 538[M+Na] RMN1:1,39(9H, s),1,60-2,16(2H, m),3,12-3,45(2H, m),3,59-3,76(9H, m),3,98-4,08(1H, m),4,31-4,40(1H, m),6,02-6,09(1H, m),6,34-6,45(1H, m),7,33-7,90(5H,m)
7#	1	ESI+: 552[M+Na] RMN1:1,39(9H, s),1,66-1,98(4H, m),3,57-3,74(10H, m),3,74-3,94(3H, m),6,28-6,41(1H, m),6,99-7,13(1H, m),7,37-7,90(5H,m)
8#	1	ESI+: 524[M+Na] RMN1:1,37(9H, s),3,57-4,17(12H, m),4,48-4,57(1H, m),6,37-6,47(1H, m),7,20-7,97(6H,m)
9#	1	ESI+: 524[M+Na] RMN1:1,37-1,41(9H, m),3,60-3,72(8H, m),3,74-3,84(2H, m),4,13-4,26(2H, m),4,55-4,70(1H, m),6,11(1H, s),7,36-7,66(3H, m),7,70-7,89(2H, m),8,10-8,22(1H,m)
10#	1	ESI+: 528 RMN1:0,79-1,75(9H, m),1,95-2,10(2H, m),2,26-2,45(1H, m),2,78-2,91(2H, m),3,03-3,42(4H, m),3,54-3,71(8H, m),3,79-3,92(2H, m),6,26-6,37(1H, m),7,13-7,18(1H, m),7,39-7,86(5H,m)
11#	1	ESI+: 544 RMN1:0,90-1,12(2H, m),1,32-1,45(9H, m),1,58-1,81(3H, m),2,53-2,80(2H, m),3,06-3,26(2H, m),3,55-3,75(8H, m),3,83-4,00(2H, m),6,23-6,40(1H, m),7,18(1H,s.a.),7,36-7,89(5H,m)

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 141]

Ej	Sin	DAT
12#	1	ESI+: 558 RMN1:0,91-1,12(2H, m),1,23(3H,d,J=6,8 Hz),1,38(9H, s),1,60-1,82(3H, m),2,53-2,78(2H, m),3,06-3,29(3H, m),3,39-3,52(1H, m),3,57-3,66(1H, m),3,68-3,77(1H, m),3,85-4,16(4H, m),4,41(1H,s.a.), 6,20-6,35(1H, m),7,18(1H,s.a.),7,40-7,90(5H,m)
13#	1	ESI+: 558 RMN1:0,91-1,12(2H, m),1,23(3H,d,J=6,8 Hz),1,38(9H, s),1,60-1,82(3H, m),2,53-2,78(2H, m),3,06-3,29(3H, m),3,39-3,52(1H, m),3,57-3,66(1H, m),3,68-3,77(1H, m),3,85-4,16(4H, m),4,41(1H,s.a.), 6,20-6,35(1H, m),7,18(1H,s.a.),7,40-7,90(5H,m)
14#	1	ESI+: 572 RMN1:0,90(3H,t,J=7,5 Hz),0,92-1,11(2H, m),1,38(9H, s),1,60-1,87(5H, m),2,56-2,78(2H, m),3,06-4,44(11H, m),6,18-6,35(1H, m),7,07-7,23(1H, m),7,34-7,89(5H,m)
15#	1	ESI+: 574 RMN1:0,91-1,11(2H, m),1,20-1,31(1H, m),1,32-1,41(9H, m),1,57-1,81(3H, m),2,59-2,80(2H, m),3,02-3,25(3H, m),3,37-3,62(3H, m),3,66-3,77(1H, m),3,81-4,44(5H, m),4,84-4,92(1H, m),6,20-6,36(1H, m),7,15(1H,s.a.),7,35-7,89(5H,m)
16#	1	ESI+: 576 RMN1:0,92-1,11(2H, m),1,20-1,30(1H, m),1,33-1,42(9H, m),1,54-1,80(3H, m),2,54-2,81(2H, m),3,06-4,30(10H, m),4,55-4,83(2H, m),6,29-6,40(1H, m),7,25(1H,s.a.),7,36-7,90(5H,m)
17#	1	ESI+: 548 RMN1:1,40(9H, s),1,56-1,82(2H, m),2,71-3,80(10H, m),3,91-4,31(3H, m),4,66-5,00(1H, m),6,31-6,48(1H, m),7,00-7,94(6H,m)
18#	1	ESI+: 544 RMN1:0,99-1,43(11H, m),1,54-1,80(3H, m),2,69-2,85(1H, m),3,02-4,00(13H, m),6,25-6,42(1H, m),7,12-7,29(1H, m),7,35-7,89(5H,m)
19#	1	ESI+: 544 RMN1:0,99-1,43(11H, m),1,54-1,80(3H, m),2,69-2,85(1H, m),3,02-4,00(13H, m),6,25-6,42(1H, m),7,12-7,29(1H, m),7,35-7,89(5H,m)
20#	1	ESI+: 558 RMN1:1,00-1,42(14H, m),1,53-1,82(3H, m),2,69-2,85(1H, m),2,99-4,16(11H, m),4,32-4,51(1H, m),6,20-6,36(1H, m),7,11-7,28(1H, m),7,35-7,90(5H,m)
21#	1	ESI+: 558 RMN1:1,00-1,41(14H, m),1,54-1,82(3H, m),2,68-2,85(1H, m),3,00-4,17(11H, m),4,42(1H,s.a.), 6,19-6,36(1H, m),7,10-7,27(1H, m),7,35-7,89(5H,m)
22#	22	ESI+: 520 RMN1:2,06-2,27(3H, m),2,79-3,85(14H, m),4,27-4,48(2H, m),5,46-5,70(1H, m),7,35-7,89(11H,m)

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[Tabla 142]

Ej	Sin	DAT
23#	22	ESI+: 506 RMN1:2,98-3,84(14H, m),4,36-4,63(3H, m),6,39-6,52(1H, m),7,21-7,88(11H,m)
24#	22	ESI+: 506 RMN1:1,87-2,54(2H, m),2,96-3,85(12H, m),4,23-4,67(3H, m),6,32-6,53(1H, m),7,28-7,88(11H,m)
25#	22	ESI+: 548 RMN1:1,33-1,96(8H, m),2,76-2,72(16H, m),6,25-6,42(1H, m),6,98-7,21(1H, m),7,38-7,89(9H,m)
26#	26	ESI+: 520 RMN1:1,22-3,08(10H, m),3,57-3,71(8H, m),4,24-4,38(1H, m),6,30-6,42(1H, m),7,11-7,88(11H,m)
27	26	ESI+: 502 RMN1:0,79-0,89(1H, m),1,21-1,38(2H, m),2,62-2,71(2H, m),2,78-2,86(1H, m),3,45-3,61(4H, m),3,61-3,72(8H, m),4,32-4,45(1H, m),6,29-6,44(1H, m),7,36-7,93(6H,m)
28#	26	ESI+: 542 RMN1:0,96-3,38(21H, m),3,56-3,78(8H, m),4,18-4,45(1H, m),6,23-6,37(1H, m),7,08-7,18(1H, m),7,36-7,89(5H,m)
29#	26	ESI+: 556 RMN1:0,74-3,36(23H, m),3,55-3,75(8H, m),4,28-4,37(1H, m),6,24-6,37(1H, m),7,09-7,17(1H, m),7,36-7,90(5H,m)
30#	26	ESI+: 627 RMN1:1,01-3,74(35H, m),3,85-4,01(2H, m),6,24-6,37(1H, m),7,11-7,19(1H, m),7,36-7,89(5H,m)
31#	26+44	ESI+: 541 RMN1:1,44-3,76(31H, m),6,29-6,44(1H, m),7,28-7,89(6H,m)
32#	26+44	ESI+: 567 RMN1:0,70-3,75(33H, m),6,29-6,44(1H, m),7,26-7,89(6H,m)
33#	26+44	ESI+: 569 RMN1:1,35-4,70(31H, m),6,29-6,45(1H, m),7,28-7,89(6H,m)
34#	26+44	ESI+: 605 RMN1:1,45-3,77(31H, m),6,30-6,44(1H, m),7,27-7,89(6H,m)
35#	26+44	ESI+: 522 RMN1:1,49-2,11(5H, m),3,04-3,53(6H, m),3,59-3,75(8H, m),3,83-4,05(1H, m),4,80-5,15(4H, m),6,29-6,44(1H, m),7,25-7,89(6H,m)
36#	26+44	ESI+: 562 RMN1:1,37-2,23(13H, m),2,83-3,49(7H, m),3,57-3,78(8H, m),6,28-6,43(1H, m),7,25-7,35(1H, m),7,37-7,89(5H,m)

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 143]

Ej	Sin	DAT
37#	26+44	ESI+: 542 RMN1:1,00-1,27(5H, m),1,30-1,74(7H, m),1,95-2,10(2H, m),2,30-2,42(1H, m),2,80-2,91(2H, m),3,05-3,34(5H, m),3,39-3,52(1H, m),3,56-3,65(1H, m),3,67-3,97(4H, m),4,00-4,14(1H, m),4,33-4,49(1H, m),6,18-6,32(1H, m),7,13(1H,s.a.),7,35-7,89(5H,m)
38#	26+44	ESI+: 542 RMN1:1,00-1,27(5H, m),1,30-1,74(7H, m),1,95-2,10(2H, m),2,30-2,42(1H, m),2,80-2,91(2H, m),3,05-3,34(5H, m),3,39-3,52(1H, m),3,56-3,65(1H, m),3,67-3,97(4H, m),4,00-4,14(1H, m),4,33-4,49(1H, m),6,18-6,32(1H, m),7,13(1H,s.a.),7,35-7,89(5H,m)
39#	26+44	ESI+: 542 RMN1:1,02-3,36(17H, m),3,42-3,54(2H, m),3,59-3,74(8H, m),3,77-3,89(3H, m),6,39(1H,s.a.),7,25-7,89(6H,m)
40#	26+44	ESI+: 529 RMN1:1,64-2,17(9H, m),2,90-3,03(2H, m),3,23-3,81(13H, m),3,93-4,01(2H, m),4,31(2H,d,J=6,3 Hz),6,43(1H, s),7,39-7,68(3H, m),7,74-7,79(1H, m),7,85-7,90(1H,m)
41#	26+44	ESI+: 528 RMN1:1,43-2,08(9H, m),2,74-2,94(2H, m),3,07-3,38(5H, m),3,40-3,52(2H, m),3,58-3,75(8H, m),3,88-4,01(2H, m),6,28-6,45(1H, m),7,24-7,90(6H,m)
42#	26+44	ESI+: 528 RMN1:1,06-4,30(28H, m),6,30-6,45(1H, m),7,29(1H,s.a.),7,27-7,88(5H,m)
43-1#	43	ESI+: 544 RMN1:1,19-2,25(13H, m),2,79-3,43(7H, m),3,58-3,75(8H, m),4,39-4,62(1H, m),6,30-6,46(1H, m),7,25-7,90(6H,m)
43-2#	43	ESI+: 544 RMN1:1,20-2,18(13H, m),2,82-3,46(7H, m),3,59-3,75(8H, m),4,72-4,91(1H, m),6,26-6,47(1H, m),7,19-7,89(6H,m)
44#	44	ESI+: 520 RMN1:1,68-2,10(5H, m),3,18-3,95(14H, m),6,29-6,45(1H, m),7,31-7,96(11H,m)
45#	45	ESI+: 487 RMN1:1,96-2,57(4H, m),2,75-4,07(20H, m),4,45-4,65(1H, m),6,41-6,59(1H, m),7,37-7,90(6H,m)
46#	45	ESI+: 530 RMN1:1,07-1,30(5H, m),1,43-1,73(3H, m),2,03-2,18(2H, m),2,75-2,86(2H, m),3,07-3,23(4H, m),3,58-3,74(8H, m),4,02-4,11(2H, m),6,23-6,38(1H, m),7,09-7,18(1H, m),7,28-7,87(5H,m)
47#	45+44	ESI+: 501 RMN1:1,36-2,01(5H, m),2,84-4,51(16H, m),6,27-6,45(1H, m),7,20-8,06(8H,m)

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[Tabla 144]

Ej	Sin	DAT
48#	45+44	ESI+: 528 RMN1:1,42-2,03(5H, m),2,49-3,44(7H, m),3,56-4,60(12H, m),6,37(1H,s.a.),7,23-7,88(6H,m)
49#	45+44	ESI+: 515 RMN1:1,37-1,92(5H, m),2,55-2,95(4H, m),3,10-3,48(6H, m),3,60-3,75(8H, m),6,38(1H,s.a.),6,98-7,89(8H,m)
50#	45+44	ESI+: 504 RMN1:1,36-1,93(5H, m),2,01-2,20(2H, m),2,76-2,94(2H, m),3,03-3,54(6H, m),3,60-3,74(8H, m),4,42-4,63(2H, m),6,29-6,45(1H, m),7,24-7,90(6H,m)
51#	45+44	ESI+: 518 RMN1:1,35-1,92(9H, m),2,74-3,53(8H, m),3,57-3,73(8H, m),4,36-4,57(2H, m),6,29-6,44(1H, m),7,23-7,34(1H, m),7,27-7,88(5H,m)
52#	52	ESI+: 520 RMN1:1,09-1,31(2H, m),1,46-1,72(2H, m),1,87-1,98(2H, m),2,20-2,34(2H, m),2,77-2,91(2H, m),3,09-3,21(2H, m),3,60-3,73(8H, m),3,73-3,83(2H, m),4,17-4,47(2H, m),4,81-4,87(1H, m),6,26-6,37(1H, m),7,12-7,20(1H, m),7,38-7,90(5H,m)
53	53	ESI+: 416 RMN1:1,93-2,02(1H, m),2,11-2,23(1H, m),3,07-3,92(12H, m),4,42-4,53(1H, m),3,46(1H,s.a.),7,39-7,87(7H, m),9,35(2H,s.a.)
54	54	ESI+: 430 RMN1:1,27-1,38(2H, m),1,70-1,88(2H, m),2,86-2,98(2H, m),3,57-3,78(11H, m),6,28-6,38(1H, m),6,94-7,06(1H, m),7,36-7,87(6H,m)
55#	54	ESI+: 445 RMN1 :0,97-1,13(2H, m),1,57-1,73(3H, m),2,31-2,48(2H, m),2,86-2,96(2H, m),3,16-3,32(2H, m),3,62-3,86(8H, m),7,38-7,52(2H, m),7,63-8,08(3H, m),8,42-8,59(1H,m)
56	54	ESI+: 416 RMN1:1,57-1,65(1H, m),1,86-2,04(1H, m),2,59-2,78(2H, m),2,83-3,07(2H, m),3,58-3,72(8H, m),4,17-4,27(1H, m),6,28-6,43(1H, m),7,00-7,18(1H, m),7,37-7,87(5H,m)
57	54	ESI+: 402 RMN1:3,44-3,60(4H, m),3,62-3,75(8H, m),4,56-4,69(1H, m),6,30-6,42(1H, m),6,83(1H, s),7,37-7,93(5H, m),8,31(1H,s)
58	54	ESI+: 402 RMN1:3,41-3,49(2H, m),3,59-3,71(10H, m),4,70-4,81(1H, m),6,10(1H, s),7,36-7,65(3H, m),7,69-7,88(2H, m),7,98-8,06(1H,m)
59	54	ESI+: 499 RMN1:1,52-1,66(4H, m),2,62-2,69(1H, m),2,85-2,94(1H, m),3,39-3,53(4H, m),3,62-3,72(8H, m),4,52-4,63(2H, m),6,37-6,49(1H, m),7,37-7,97(6H,m)

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 145]

Ej	Sin	DAT
60#	54	ESI+: 444 RMN1:0,91-3,28(11H, m),3,55-3,76(8H, m),6,23-6,39(1H, m),7,07-7,19(1H, m),7,36-7,89(5H,m)
61#	54	ESI+: 458 RMN1:0,91-1,11(2H, m),1,23(3H,d,J=6,7 Hz),1,54-1,70(3H, m),2,31-2,44(2H, m),2,84-2,95(2H, m),3,03-3,52(5H, m),3,56-3,77(2H, m),3,88-3,98(1H, m),4,00-4,16(1H, m),4,33-4,50(1H, m),6,18-6,32(1H, m),7,05-7,19(1H, m),7,58-7,88(5H,m)
62#	54	ESI+: 458 RMN1:0,91-1,11(2H, m),1,23(3H,d,J=6,7 Hz),1,54-1,70(3H, m),2,31-2,45(2H, m),2,84-2,97(2H, m),3,03-3,53(5H, m),3,57-3,77(2H, m),3,88-3,98(1H, m),4,00-4,16(1H, m),4,33-4,50(1H, m),6,18-6,32(1H, m),7,05-7,19(1H, m),7,58-7,88(5H,m)
63#	54	ESI+: 445 RMN1:1,09-1,23(2H, m),1,62-1,72(2H, m),1,78-1,91(1H, m),2,40-2,50(2H, m),2,91-2,98(2H, m),3,64-3,79(8H, m),4,22(2H,d,J=6,4 Hz),6,42(1H, s),7,39-7,50(2H, m),7,54(1H,t,J=52,5 Hz),7,74-7,89(2H,m)
64#	54	ESI+: 444 RMN1:0,93-1,13(1H, m),1,19-1,37(2H, m),1,44-1,80(3H, m),2,07-2,45(2H, m),2,72-2,99(2H, m),3,02-3,20(2H, m),3,56-3,74(8H, m),6,22-6,39(1H, m),7,13(1H,s.a.),7,36-7,89(5H,m)
65#	54	ESI+: 444 RMN1:0,93-1,13(1H, m),1,19-1,37(2H, m),1,44-1,80(3H, m),2,07-2,45(2H, m),2,72-2,99(2H, m),3,02-3,20(2H, m),3,56-3,74(8H, m),6,22-6,39(1H, m),7,13(1H,s.a.),7,36-7,89(5H,m)
66#	66	ESI+: 515 RMN1:1,22-1,51(2H, m),1,77-2,00(2H, m),2,11-2,23(6H, s),2,63-2,83(1H, m),2,96-3,18(3H, m),3,56-3,75(8H, m),3,90-4,05(2H, m),4,18-4,31(1H, m),6,28-6,43(1H, m),7,04-7,17(1H, m),7,37-7,89(5H,m)
67#	66	ESI+: 530 RMN1:0,95-1,31(2H, m),1,67-1,91(3H, m),2,11-2,21(6H, m),2,86-3,15(3H, m),3,22-3,33(2H, m),3,63-3,85(8H, m),3,99-4,09(1H, m),4,30-4,39(1H, m),7,39-7,53(2H, m),7,64-8,09(3H, m),8,41-8,59(1H,m)
68#	66	ESI+: 501 RMN1:1,80-2,25(10H, m),2,92-3,01(2H, m),3,45-3,75(10H, m),4,32-4,45(1H, m),6,33-6,47(1H, m),7,31-7,88(6H,m)
69#	66	ESI+: 487 RMN1:2,17(6H, s),2,83-2,96(2H, m),3,85-3,74(8H, m),3,79-3,85(1H, m),4,01-4,19(2H, m),4,39-4,61(2H, m),6,37-6,48(1H, m),7,37-7,89(6H,m)
70	66	ESI+: 599

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[Tabla 146]

Ej	Sin	DAT
71#	71	ESI+: 509[M+Na] RMN1:0,96-1,21(4H, m),1,66-1,90(3H, m),1,95-1,99(3H, m),2,91-3,04(1H, m),3,23-3,32(2H, m),3,63-3,87(8H, m),4,32-4,41(1H, m),7,39-7,54(2H, m),7,63-8,09(3H, m),8,41-8,59(1H,m)
72#	66+44	ESI+: 529 RMN1:0,92-1,28(2H, m),1,67-1,93(3H, m),2,59-2,86(7H, m),2,91-3,30(3H, m),3,54-4,41(12H, m),6,26-6,44(1H, m),7,27(1H,s.a.),7,37-7,90(5H,m)
73#	66+44	ESI+: 543 RMN1:0,89-1,28(2H, m),1,64-1,91(3H, m),2,45-3,28(15H, m),3,76-3,97(8H, m),4,31-4,41(1H, m),6,38(1H,s.a.),7,25-7,99(6H,m)
74#	74	ESI+: 520
75#	74+44	ESI+: 538 RMN1:1,60-2,07(5H, m),3,17-3,95(14H, m),6,29-6,45(1H, m),7,29-7,97(10H,m)
76#	74+44	ESI+: 538 RMN1:1,41-1,72(2H, m),1,79-1,95(3H, m),2,95-3,35(4H, m),3,59-3,76(10H, m),6,38(1H,s.a.), 6,80-7,91(10H,m)
77#	74+44	ESI+: 538 RMN1:1,33-1,53(2H, m),1,68-1,88(3H, m),2,68-2,83(2H, m),3,18-3,32(2H, m),3,34-3,44(2H, m),3,61-3,73(8H, m),6,36(1H,s.a.),6,97-7,90(10H,m)
78#	74+44	ESI+: 550 RMN1:1,74-2,08(5H, m),3,18-3,78(17H, m),6,36(1H,s.a.),7,02-7,13(2H, m),7,26-7,90(8H,m)
79#	74+44	ESI+: 534 RMN1:1,67-2,08(5H, m),2,33(3H, s),3,16-3,77(14H, m),6,36(1H,s.a.),7,25-7,89(10H,m)
80#	80	ESI+: 545 RMN1:1,11-1,26(2H, m),1,40(9H, s),1,70-1,79(2H, m),1,89-2,03(1H, m),2,64-2,85(2H, m),3,63-3,80(8H, m),3,91-4,05(2H, m),4,27(2H,d,J=6,4 Hz),6,43(1H, s),7,38-7,50(2H, m),7,54(1H,t,J=52,5 Hz),7,73-7,89(2H,m)
81#	80	ESI+: 559 RMN1:1,10-1,27(5H, m),1,40(9H, s),1,70-1,79(2H, m),1,91-2,03(1H, m),2,68-2,84(2H, m),3,17-3,29(1H, m),3,40-3,49(1H, m),3,55-3,62(1H, m),3,68-3,75(1H, m),3,89-4,04(3H, m),4,19-4,33(3H, m),4,56-4,64(1H, m),6,43(1H, s),7,39-7,50(2H, m),7,54(1H,t,J=52,5 Hz),7,74-7,90(2H,m)
82#	82	ESI+: 422[M+Na]
83#	83	ESI+: 487
84#	84	ESI+: 628

[Tabla 147]

Ej	Sin	DAT
85#	52	ESI+: 556 RMN1:1,03(6H, s),1,43(12H,s.a.),2,28(2H,s.a.),3,01-3,14(2H, m),3,57-3,72(8H, m),4,01(1H,s.a.),6,21-6,37(1H, m),6,76-7,02(1H, m),7,34-7,96(5H,m)
86#	86	ESI+: 584
87#	87	ESI+: 586 RMN1:1,50-1,81(7H, m),2,23(3H, a.),3,16-3,25(1H, m),3,28-3,36(2H, m),3,54(3H, s),3,70(4H, a.),3,74(4H, a.),3,81(1H, a.),4,08-4,18(1H, m),4,99-5,08(1H, m), 6,40(1H, s),7,38-7,50(3H, m),7,53(1H,t,J=52,5 Hz),7,75(1H,d,J=7,8 Hz),7,86(1H,d,J=7,8 Hz)
88#	88	ESI+: 606
89#	89	ESI+: 556 RMN1:1,36-1,73(8H, m),1,81-1,91(2H, m),1,97-2,21(4H, m),2,97(2H, s),3,05-3,16(1H, m),3,60-3,80(9H, m),5,00-5,10(1H, m),6,40(1H, s),7,38-7,68(4H, m),7,72-7,78(1H, m),7,83-7,89(1H,m)
90#	54	ESI+: 472
91#	91	ESI+: 514[M+Na] RMN1:1,44-1,67(5H, m),1,76-2,03(3H, m),2,76-2,87(1H, m),2,95-3,09(1H, m),3,12-3,23(1H, m),3,62-3,94(10H, m),7,39-7,52(2H, m),7,70-8,28(3H, m),8,43-8,58(1H,m)
92#	92	ESI+: 502
93#	93	ESI+: 458
94#	94	ESI+: 530[M+Na] RMN1:1,47-1,73(4H, m),1,80-2,00(4H, m),3,29-3,92(13H, m),7,38-8,24(5H, m),8,43-8,56(1H,m)
95#	92	ESI+: 531
96#	92	ESI+: 516 RMN1:1,39(9H, s),2,15-2,34(4H, m),3,61-3,72(8H, m),3,99-4,13(1H, m),4,38-4,50(1H, m),6,09(1H, s),7,25-7,94(7H,m)
97#	92	ESI+: 544
98#	92	ESI+: 531 RMN1:1,38(9H, s),1,42-2,36(6H, m),3,54-4,12(9H, m),5,48(1H, m),6,97(1H,d,J=8 Hz),7,18-7,93(5H,m)
99#	71	ESI+: 570 RMN1:1,51-1,79(7H, m),1,84(3H, s),2,17-2,34(3H, m),3,17-3,26(1H, m),3,27-3,38(2H, m),3,70(4H, a.),3,74(4H, a.),3,82(1H, a.),4,98-5,10(1H, m),6,40(1H, s),7,38-7,49(2H, m),7,54(1H,t,J=52,4 Hz),7,74(1H,d,J=7,8 Hz),7,86(1H,d,J=7,4 Hz),8,15(1H,d,J=8,2 Hz)
100#	66+44	ESI+: 529 RMN1:1,20-1,90(8H, m),2,72-2,85(6H, m),3,58-4,38(13H, m),6,26(1H, s),7,39-7,69(4H, m),7,72-7,68(1H, m),7,84-7,89(1H, m),8,54-8,63(1H,m)
101#	66	ESI+: 676

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 148]

Ej	Sin	DAT
102#	66	ESI+: 676
103#	66	ESI+: 516
104#	66	ESI+: 516
105#	66	ESI+: 544
106#	66	ESI+: 552
107	66	ESI+: 541
108	66	ESI+: 541
109	66	ESI+: 541
110#	66	ESI+: 542
111#	66	ESI+: 515
112#	66	ESI+: 463 RMN1:1,23(4H, s),3,57(8H, s),6,21-8,09(12H,m)
113#	66	ESI+: 529
114#	66	ESI+: 529
115#	66	ESI+: 556
116#	66	ESI+: 583 RMN1:0,2-0,6(4H, m),0,65-2(12H, m),2,17(6H, s),2,80(2H, s),3,0-4,0(9H, m),6,30(1H,s.a.),7,0-8,0(5H,m)
117#	66	ESI+: 585
118#	66+44	ESI+: 529
119#	66+44	ESI+: 501
120#	45+44	ESI+: 554 RMN1:1,54(6H,s.a.),1,82(6H,s.a.),2,87-3,02(2H, m),3,07-3,20(2H, m),3,29-3,39(2H, m),3,57-3,76(8H, m),3,81-4,01(4H, m),6,27-6,46(1H, m),7,14(1H,s.a.),7,35-7,92(5H,m)
121#	45+44	ESI+: 570 RMN1:1,25(6H,s.a.),1,44-2,97(15H, m),3,13(3H,s.a.),3,39-3,49(1H, m),3,58-3,76(8H, m),6,29-6,46(1H, m),7,08-7,91(6H,m)
122#	45+44	ESI+: 514
123#	45+44	ESI+: 514
124#	45+44	ESI+: 542
125#	45	ESI+: 542 RMN1:0,75-2,16(10H, m),2,22(3H, s),2,43(4H,s.a.),2,95-3,18(2H, m),3,42-3,72(12H, m),6,36(1H,s.a.),7,02-7,39(4H, m),7,61-7,71(1H,m)
126#	45	ESI+: 570
127#	45	ESI+: 574 RMN1:0,80-2,18(15H, m),3,02(2H, s),3,14(2H,d,J=5,2 Hz),3,61-3,77(9H, m),4,48(1H,t,J=5,2 Hz),5,01-5,10(1H, m),6,39(1H, s),7,39-7,66(4H, m),7,70-7,77(1H, m),7,84-7,88(1H,m)

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 149]

Ej	Sin	DAT
128#	45	ESI+: 600 RMN1:1,34-2,40(19H, m),3,05(2H, s),3,58-3,78(9H, m),4,29(1H,d,J=4,0 Hz),5,0-5,15(1H, m),6,39(1H, s),7,39-7,66(4H, m),7,72-7,76(1H, m),7,84-7,88(1H,m)
129#	45	ESI+: 600 RMN1:0,81-2,28(19H, m),3,05(2H, s),3,61-3,77(9H, m),4,45(1H,d,J=4,4 Hz),5,0-5,15(1H, m),6,39(1H, s),7,39-7,66(4H, m),7,72-7,76(1H, m),7,84-7,88(1H,m)
130#	45	ESI+: 598 RMN1:0,17-0,68(4H, m),0,76-2,13(22H, m),3,01-3,60(6H, m),6,31(1H,s.a.),6,73(1H,s.a.),7,25-8,03(5H,m)
131#	45+44	ESI+: 542
132#	45+44	ESI+: 542
133#	89	ESI+: 556 RMN1:0,05-0,11(2H, m),0,36-0,44(2H, m),0,80-0,90(2H, m),1,37-1,63(4H, m),1,81-1,92(2H, m),2,09-2,19(2H, m),2,27-2,37(2H, m),3,06(2H, s),3,60-3,78(9H, m),5,00-5,10(1H, m),6,40(1H, s),7,38-7,68(4H, m),7,72-7,78(1H, m),7,83-7,88(1H,m)
134#	89	ESI+: 570 RMN1:1,20-1,72(12H, m),1,82-1,92(2H, m),2,05-2,18(3H, m),2,89-2,98(1H, m),3,03(2H, s),3,60-3,80(9H, m),5,01-5,11(1H, m),6,40(1H, s),7,38-7,68(4H, m),7,72-7,77(1H, m),7,84-7,89(1H,m)
135#	89	ESI+: 584 RMN1:0,79-2,35(20H, m),3,06(2H, m),3,60-3,77(9H, m),5,01-5,11(1H, m),6,40(1H, s),7,39-7,68(4H, m),7,72-7,78(1H, m),7,84-7,89(1H,m)
136#	89	ESI+: 586 RMN1:1,18-1,31(2H, m),1,36-1,63(4H, m),1,65-1,75(2H, m),1,81-1,91(2H, m),2,08-2,18(2H, m),3,08(2H, s),3,21-3,34(4H, m),3,60-3,86(11H, m),5,01-5,11(1H, m),6,40(1H, s),7,38-7,68(4H, m),7,72-7,77(1H, m),7,84-7,89(1H,m)
137#	89	ESI+: 556 RMN1:0,26-0,31(2H, m),0,46-0,52(2H, m),1,15(3H, s),1,37-1,62(4H, m),1,80-1,90(2H, m),2,07-2,18(2H, m),2,33-2,44(1H, m),3,06-3,11(2H, m),3,59-3,78(9H, m),5,00-5,11(1H, m),6,40(1H, s),7,38-7,68(4H, m),7,72-7,78(1H, m),7,83-7,89(1H,m)
138#	89	ESI+: 572 RMN1:1,35-3,80(27H, m),5,00-5,11(1H, m),6,40(1H, s),7,38-7,69(4H, m),7,71-7,78(1H, m),7,83-7,90(1H,m)
139#	89	ESI+: 572 RMN1:1,35-3,80(27H, m),5,00-5,11(1H, m),6,40(1H, s),7,37-7,69(4H, m),7,71-7,78(1H, m),7,82-7,89(1H,m)

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[Tabla 150]

Ej	Sin	DAT
140#	89	ESI+: 596 RMN1:0,58-2,21(19H, m),2,81-3,06(3H, m),3,59-3,80(9H, m),5,00-5,12(1H, m),6,40(1H, s),7,39-7,69(4H, m),7,72-7,79(1H, m),7,84-7,89(1H,m)
141#	89	ESI+: 636 RMN1:1,37-1,65(16H, m),1,80-1,90(2H, m),1,94-2,04(4H, m),2,08-2,18(2H, m),3,03(2H, s),3,59-3,79(9H, m),5,02-5,13(1H, m),6,40(1H, s),7,39-7,71(4H, m),7,72-7,78(1H, m),7,83-7,89(1H,m)
142#	89	ESI+: 652 RMN1:1,35-1,62(16H, m),1,81-1,90(2H, m),2,05-2,19(5H, m),3,02(2H, s),3,59-3,79(9H, m),4,40(1H, s),5,02-5,12(1H, m),6,40(1H, s),7,38-7,70(4H, m),7,72-7,78(1H, m),7,83-7,89(1H,m)
143#	89	ESI+: 614 RMN1:1,07(3H, s),1,15-2,22(18H, m),3,06(2H, s),3,59-3,80(9H, m),3,93(1H, s),5,01-5,12(1H, m),6,40(1H, s),7,38-7,69(4H, m),7,72-7,78(1H, m),7,83-7,89(1H,m)
144#	89	ESI+: 614 RMN1:1,11-2,46(21H, m),3,10(2H, s),3,65-3,87(9H, m),4,17(1H, s),5,05-5,17(1H, m),6,46(1H, s),7,43-7,75(4H, m),7,77-7,84(1H, m),7,88-7,95(1H,m)
145#	52	ESI+: 558
146#	1	ESI+: 572
147#	1	ESI+: 572
148#	1	ESI+: 558
149#	1	ESI+: 530
150#	1	ESI+: 474[M+Na] RMN1:3,63-3,93(8H, m),7,41-8,76(10H,m)
151#	1	ESI+: 530
152#	1	ESI+: 584
153#	1	ESI+: 574 RMN1:0,85-1,13(2H, m),1,38(9H, s),1,56-1,80(3H, m),2,57-2,76(2H, m),3,06-3,24(2H, m),3,51-3,75(8H, m),3,83-4,03(5H, m),6,20-6,35(1H, m),6,91(1H,d,J=8,0 Hz),7,09-7,80(4H,m)
154#	1	ESI+: 612
155#	1	ESI+: 453 RMN1:2,45(3H, s),3,37-3,75(8H, m),4,53-4,61(2H, m),6,25-6,49(1H, m),7,10-7,91(6H, m),8,38-8,56(2H,m)
156#	1	ESI+: 523
157#	1	ESI+: 536
158#	1	ESI+: 593 RMN1:1,19(3H,t,J=8,0 Hz),3,01-3,13(4H, m),3,44-3,54(4H, m),3,56-3,94(8H, m),4,06(2H,q,J=8,0 Hz),4,31-4,45(2H, m),6,25-6,40(1H, m),6,92(2H,d,J=12 Hz),7,10-7,94(8H,m)

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 151]

Ej	Sin	DAT
159#	1	ESI+: 494 RMN1:1,41(3H,d,J=8,0 Hz),3,40-3,78(8H, m),4,33-4,47(1H, m),6,29-6,47(1H, m),6,92-7,96(11H, m),9,84-10,17(1H,m)
160#	1	ESI+: 511 RMN1:0,62-0,84(2H, m),0,86-1,03(2H, m),3,47-3,88(10H, m),6,18-6,42(1H, m),6,91-7,93(10H,m)
161#	1	ESI+: 508
162#	1	ESI+: 522 RMN1:2,73-2,92(4H, m),3,47-3,82(12H, m),4,48-4,65(2H, m),6,21-6,44(1H, m),6,86-7,98(10H,m)
163#	1	ESI+: 430
164#	1	ESI+: 446 RMN1:1,28-1,43(2H, m),1,50-1,69(4H, m),1,70-1,79(1H, m),1,92-2,03(1H, m),3,69(4H,d,J=4,7 Hz), 3,72(4H,d,J=4,7 Hz),3,90(1H, a.),4,70(1H,d,J=4,7 Hz),5,15-5,22(1H, m),6,39(1H, s),7,39-7,52(2H, m),7,55(1H,t,J=52,5 Hz),7,77(1H,d,J=7,9 Hz),7,87(1H,d,J=7,9 Hz)
165#	1	ESI+: 446 RMN1:1,20-1,43(4H, m),1,67(2H, a.),1,90(1H, a.),2,12(1H, a.),3,53-3,64(1H, m),3,69(4H,d,J=4,2 Hz),3,73(4H,d,J=3,7 Hz),4,86-4,95(1H, m),4,94(1H,d,J=4,7 Hz),6,39(1H, s),7,40-7,50(2H, m),7,55(1H,t,J=52,5 Hz),7,77(1H,d,J=7,9 Hz),7,87(1H,d,J=7,9 Hz)
166#	1	ESI+: 486 RMN1:0,94-1,31(14H, m),1,72(1H, a.),1,82(1H, a.),3,64(4H, a.),3,68(4H, a.),4,19(1H, a.),6,32(1H, a.),6,96(1H, a.),7,33-7,88(5H,m)
167#	1	ESI+: 446
168#	1	ESI+: 482[M+Na] RMN1:1,02-1,16(3H, m),1,331,45(2H, m),1,55-1,79(6H, m),3,64-4,09(10H, m),7,37-8,10(5H, m),8,39-8,63(1H,m)
169#	1	ESI+: 482[M+Na] RMN1:1,00-1,06(3H, m),1,35-1,92(8H, m),3,61-3,94(9H, m),4,26-4,33(1H, m),7,38-8,09(5H, m),8,40-8,63(1H,m)
170#	1	ESI+: 498 RMN1:1,30-1,42(2H, m),1,60-1,71(4H, m),1,72-1,84(2H, m),1,94-2,08(3H, m),2,09-2,20(2H, m),3,63-3,88(8H, m),3,97-4,12(1H, m),4,40-4,50(1H, m),7,38-7,52(2H, m),7,62-8,20(3H, m),8,41-8,66(1H,m)
171#	1	ESI+: 454[M+Na]
172#	1	ESI+: 430
173#	1	ESI+: 476 RMN1:1,34-1,74(6H, m),1,86-2,03(2H, m),2,69-2,77(2H, m),3,13-3,27(1H, m),3,48-3,88(10H, m),7,33-7,53(2H, m),7,62-8,18(3H, m),8,40-8,58(1H,m)
174#	1	ESI+: 540

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 152]

Ej	Sin	DAT
175#	1	ESI+: 444 RMN1:0,99-1,38(4H, m),1,38-1,76(4H, m),1,76-2,10(2H, m),3,25-3,54(2H, m),3,54-3,75(8H, m),6,22-6,39(1H, m),6,87-7,02(1H, m),7,35-7,91(5H,m)
176#	1	ESI+: 444 RMN1:1,13-1,85(10H, m),2,94-3,11(1H, m),3,51-3,76(8H, m),3,76-3,90(1H, m),6,24-6,44(1H, m),6,44-6,73(1H, m),7,35-7,91(5H,m)
177#	1	ESI+: 503
178#	1	ESI+: 498 RMN1:1,42-1,65(6H, m),1,92-2,07(6H, m),2,16-2,24(2H, m),3,64-3,83(8H, m),4,55-4,60(1H, m),7,38-8,15(5H, m),8,44-8,63(1H,m)
179#	1	ESI+: 487
180#	1	ESI+: 522[M+Na]
181#	1+44	ESI+: 556
182#	1	ESI+: 523
183#	1	ESI+: 654[M+Na] RMN1:1,01-1,82(12H, m),3,31-3,45(4H, m),3,59-3,74(9H, m),5,06(2H, s),6,25-6,38(1H, m),6,89-7,04(1H, m),7,27-7,88(10H,m)
184#	1	ESI+: 501
185#	1	ESI+: 572
186#	1	ESI+: 559
187#	1	ESI+: 572
188#	22	ESI+: 495
189#	93	ESI+: 469
190#	83	ESI+: 473 RMN1:1,18-1,35(2H, m),1,39-1,55(2H, m),1,85-2,10(4H, m),2,16-2,27(1H, m),3,60-3,87(9H, m),6,09(1H, s),7,35-7,66(4H, m),7,68-7,74(1H, m),7,82-7,87(1H, m),12,08(1H,s.a.)
191#	26	ESI+: 556
192#	26	ESI+: 558
193#	26	ESI+: 526 RMN1:0,98-1,13(2H, m),1,19(6H, a.),1,57(2H,d,J=11,2 Hz),1,72(6H, a.),2,13(2H, a.),2,79(1H, a.),3,16(2H, a.),3,30(1H, a.),3,64(4H, a.),3,68(4H, a.),6,31(1H, a.),7,15(1H, a.),7,37-7,47(2H, m),7,53(1H, a.),7,76(1H,d,J=7,9 Hz),7,85(1H,d,J=7,7 Hz)
194#	26	ESI+: 556 RMN1:0,92-1,02(2H, m),1,08(6H,d,J=6,1 Hz),1,12(2H, a.),1,50(1H, a.),1,66(2H,b r),1,68(2H, a.),2,05(2H, a.),2,45(1H, a.),2,82(2H, a.),3,14(1H, s),3,18(1H, s),3,28-3,38(2H, m),3,63(4H, a.),3,68(4H, a.),6,31(1H, a.),7,13(1H, a.),7,36-7,47(2H, m),7,50-7,72(1H, m),7,77(1H,d,J=7,6 Hz),7,85(1H,d,J=7,6 Hz)
195#	26	ESI+: 540

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 153]

Ej	Sin	DAT
196#	26	ESI+: 570 RMN1:1,41-1,65(6H, m),1,72-2,00(6H, m),2,07(3H, s),2,10-2,19(2H, m),2,76(2H, s),2,87-2,97(1H, m),3,60-3,79(9H, m),5,00-5,10(1H, m),6,40(1H, s),7,38-7,68(4H, m),7,72-7,78(1H, m),7,83-7,89(1H,m)
197#	26	ESI+: 500
198#	26	ESI+: 584 RMN1:1,49-2,30(16H, m),2,66-2,71(6H, m),3,64-3,84(9H, m),4,98-5,11(1H, m),6,40(1H, s),7,39-7,69(3H, m),7,72-7,77(1H, m),7,84-7,89(1H, m),8,19-8,29(1H, m),10,75-1,88(1H,m)
199#	26	ESI+: 598 RMN1:0,80-2,30(22H, m),3,08-3,17(1H, m),3,56-3,79(9H, m),5,01-5,11(1H, m),6,40(1H, s),7,38-7,70(4H, m),7,72-7,78(1H, m),7,84-7,89(1H,m)
200#	26+44	ESI+: 542
201#	26+44	ESI+: 562
202#	26+44	ESI+: 596
203#	26+44	ESI+: 542
204#	26+44	ESI+: 514
205#	53	ESI+: 472
206#	53	ESI+: 458
207#	53	ESI+: 430
208#	53	ESI+: 474
209#	53	ESI+: 498 RMN1:0,16-0,73(4H, m),1,02-2,20(10H, m),2,80-3,99(11H, m),6,33(1H,s.a.),7,24-8,01(5H, m),8,21(2H,s.a.)
210#	53	ESI+: 472
211#	54	ESI+: 472
212#	54	ESI+: 484
213#	54	ESI+: 478
214#	54	ESI+: 512
215#	54	ESI+: 542 RMN1:1,38-2,42(14H, m),3,55-3,78(9H, m),5,00-5,10(1H, m),6,40(1H, s),7,38-7,89(6H,m)
216#	54	ESI+: 556 RMN1:1,35-2,18(16H, m),3,54-3,78(9H, m),5,02-5,11(1H, m),6,40(1H, s),7,39-7,88(6H,m)
217#	54	ESI+: 444
218#	54	ESI+: 444
219#	54	ESI+: 472
220#	54	ESI+: 486
221#	54	ESI+: 431
222#	54	ESI+: 431

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 154]

Ej	Sin	DAT
223#	53	ESI+: 500
224#	26	ESI+: 556 RMN1:1,07(6H,d,J=6,2 Hz),1,14(2H, a.),1,16(2H, a.),1,52(1H, a.),1,70(2H, a.),1,72-1,79(2H, m),1,86(2H, a.),2,28(1H, a.),3,02(2H, a.),3,13(1H, a.),3,20(1H, a.),3,63(4H, a.), 3,68(4H, a.),3,73(2H, a.),6,31(1H, a.),7,14(1H,t,J=5,7 Hz),7,36-7,48(2H, m),7,49-7,73(1H, m),7,76(1H,d,J=7,7 Hz)17,85(1H,d,J=7,7 Hz)
225#	92	ESI+: 544
226#	92	ESI+: 555
227#	66	ESI+: 642
228#	66	ESI+: 656
229#	1	ESI+: 586
230#	1	ESI+: 572
231#	1	ESI+: 516
232#	1	ESI+: 516
233#	54	ESI+: 416
234#	54	ESI+: 416
235#	54	ESI+: 458
236#	1	ESI+: 558
237#	237	ESI+: 527
238#	238	ESI+: 586
239#	239	ESI+: 472
240#	240	ESI+: 514
241#	241	ESI+: 520
242-1#	242+44	ESI+: 472
242-2#	242+44	ESI+: 486
243#	243	ESI+: 526
244#	244	ESI+: 419
245#	245	ESI+: 616
246#	246	ESI+: 570
247#	247	ESI+: 531
248#	248	ESI+: 585 RMN1:1,27-2,31(10H, m),3,06-3,38(2H, m),3,53(3H, s),3,56-3,92(10H, m),4,06-4,20(1H, m),6,22-6,43(1H, m),6,88-7,13(1H, m),7,34-7,96(6H,m)
249-1	249	ESI+: 542 RMN1:1,33-1,88(8H, m),2,21-2,30(1H, m),3,20(3H, s),3,60-3,71(8H, m),3,75-3,81(1H, m),4,01-4,06(1H, m),4,15-4,19(1H, m),4,48-4,50(1H, m),4,59-4,71(1H, m),6,12(1H, s),7,37-7,64(3H, m),7,12-7,74(1H, m),7,73(1H,d,J=8 Hz),7,86(1H,d,J=7,6 Hz),8,12-8,20(1H,m)

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 155]

Ej	Sin	DAT
249-2	249	ESI+: 542 RMN1:1,07-2,21(8H, m),3,22(3H, s),3,62-3,71(8H, m),3,75-3,81(1H, m),4,02-4,06(1H, m),4,15-4,19(1H, m),4,49-4,53(1H, m),4,59-4,70(1H, m),6,12(1H, s),3,78-3,62(5H, m),7,73(1H,d,J=8,0 Hz),7,86(1H,d,J=7,5 Hz),8,13-8,19(1H,m)
250#	1	ESI+: 438
251#	1	ESI+: 439
252#	1	ESI+: 439
253#	1	ESI+: 439
254#	1	ESI+: 452
255#	1	ESI+: 498
256#	1	ESI+: 432
257#	1	ESI+: 424
258#	1	ESI+: 454
259#	1	ESI+: 426
260#	1	ESI+: 425
261#	1	ESI+: 433
262#	1	ESI+: 504[M+Na]
263#	1	ESI+: 504[M+Na]
264#	1	ESI+: 468[M+Na]
265#	1	ESI+: 496
266#	1	ESI+: 445
267#	1	ESI+: 445
268#	1	ESI+: 445
269#	1	ESI+: 497
270#	1	ESI+: 508
271#	1	ESI+: 497
272#	1	ESI+: 459
273#	1	ESI+: 481[M+Na]
274#	1	ESI+: 429
275#	1	ESI+: 530[M+Na]
276#	1	ESI+: 497
277#	1	ESI+: 547[M+Na]
278#	1	ESI+: 553[M+Na]
279#	1	ESI+: 567[M+Na]
280#	94	ESI+: 454
281#	1	ESI+: 440
282#	1	ESI+: 442
283#	1	ESI+: 463
284#	1	ESI+: 464
285#	1	ESI+: 464
286#	1	ESI+: 481

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 156]

287#	1	ESI+: 496
288#	1	ESI-:479
289#	74	ESI+: 520
290#	1	ESI+: 478
291#	1	ESI+: 520
292#	26+44	ESI+: 520
293#	74	ESI+: 570
294#	92	ESI+: 504[M+Na]
295#	SinP.8	ESI+: 452
296#	240+44	ESI+: 522
297#	22	ESI+: 556
298#	22	ESI+: 542
299#	22	ESI+: 542
300#	74	ESI+: 522
301#	74	ESI+: 480
302#	1	ESI+: 520
303#	1	ESI+: 544
304#	54	ESI+: 444
305#	1	ESI+: 573
306#	1	ESI+: 587
307#	66+44	ESI+: 529
308#	SinP.81	ESI+: 489
309#	SinP.81	ESI+: 503
310#	1	ESI+: 497
311#	74	ESI+: 453
312#	74	ESI+: 454
313#	74	ESI+: 453
314#	74	ESI+: 521
315#	74	ESI+: 520
316#	1	ESI+: 575[M+Na]
317#	54	ESI+: 453
318#	240+44	ESI+: 523
319#	1	ESI+: 485
320#	54	ESI+: 458
321#	54	ESI+: 458
322#	26	ESI+: 542
323#	26	ESI+: 542
324#	26	ESI+: 528
325#	1	ESI+: 532
326#	66	ESI+: 529
327#	1	ESI+: 520

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 157]

Ej	Sin	DAT
328#	1	ESI+: 520
329#	66	ESI+: 501
330#	SinP.148	ESI+: 488
331#	66	ESI+: 534
332#	66	ESI+: 534
333#	66	ESI+: 534
334#	74	ESI+: 506
335#	74	ESI+: 538
336#	74	ESI+: 538
337#	74	ESI+: 550
338#	74	ESI+: 566
339#	74	ESI+: 524
340#	92	ESI+: 515
341#	84	ESI+: 628
342	26	ESI+: 500
343#	66	ESI+: 550
344#	66	ESI+: 554
345#	66	ESI+: 538
346#	66	ESI+: 538
347#	66	ESI+: 538
348#	74	ESI+: 580
349#	74	ESI+: 566
350#	66	ESI+: 569
351#	66	ESI+: 521
352#	66	ESI+: 521
353#	66	ESI+: 521
354#	53	ESI+: 430
355#	26	ESI+: 520
356#	26	ESI+: 520
357#	66	ESI+: 552
358#	89+44	ESI+: 584
359#	92	ESI+: 556
360#	92	ESI+: 555
361#	93	ESI+: 469
362#	26+44	ESI+: 540
363#	92	ESI+: 488
364#	26	ESI+: 514
365#	26	ESI+: 528
366#	241	ESI+: 534
367#	22	ESI+: 437
368#	84	ESI+: 664[M+Na]

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 158]

Ej	Sin	DAT
369#	1	ESI+: 536
370#	92	ESI+: 585 RMN1:1,33(3H, a.),1,52-1,81(5H, m),2,10(2H, a.),2,24(1H, a.),3,15-3,25(1H, m),3,54(3H, s),3,67(8H, a.),3,75(1H, a.),4,06-4,18(1H, m),6,10(1H, s),7,35-7,50(5H, m),7,51(1H,t,J=52,7 Hz),7,71(1H,d,J=7,9 Hz),7,85(1H,d,J=7,9 Hz)
371#	92	ESI+: 585 RMN1:1,20-1,33(3H, m),1,50-1,83(5H, m),2,01-2,18(2H, m),2,17-2,31(1H, m),3,13-3,25(1H, m),3,54(3H, s),3,59-3,91(10H, m),4,05-4,19(1H, m),6,10(1H, s),7,34-7,54(5H, m),7,72(1H,d,J=8,2 Hz),7,85(1H,d,J=7,7 Hz)
372#	1	ESI+: 588
373#	1	ESI+: 446
374#	53	ESI+: 488
375#	26	ESI+: 572
376#	1	ESI+: 536
377#	1	ESI+: 544
378	54	ESI+: 444
379#	92	ESI+: 544
380#	54	ESI+: 444
381#	26	ESI+: 528
382#	66	ESI+: 529
383	26	ESI+: 528
384#	26	ESI+: 562
385#	43	ESI+: 556
386#	43	ESI+: 556
387#	88	ESI+: 632
388#	85	ESI+: 600
389#	87	ESI+: 586 RMN1:1,52-1,82(7H, m),2,23(3H, a.),3,17-3,24(1H, m),3,28-3,36(1H, m),3,54(3H, s),3,70(4H, a.),3,75(4H, a.),3,81(1H, a.),4,13(1H,q,J=9,3 Hz),5,00-5,08 (1H, m),6,40(1H, s),7,38-7,50(3H, m),7,53(1H,t,J=52,2 Hz),7,75(1H,d,J=7,7 Hz),7,86(1H,d,J=7,7H)
390#	1	ESI+: 550
391#	1	ESI+: 536
392	26	ESI+: 555
393#	26	ESI+: 556
394#	26	ESI+: 570
395#	26	ESI+: 500
396#	26	ESI+: 628
397#	1	ESI+: 475

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 159]

Ej	Sin	DAT
398#	1	ESI+: 522
399#	66	ESI+: 537
400#	43	ESI+: 558
401#	43	ESI+: 558
402#	26	ESI+: 546
403#	26	ESI+: 576
404#	89	ESI+: 544
405#	89	ESI+: 544
406	54	ESI+: 444
407#	44	ESI+: 569
408	26	ESI+: 528
409#	1	ESI+: 558
410#	1	ESI+: 584
411#	54	ESI+: 484
412#	52	ESI+: 556
413#	89	ESI+: 570
414#	89	ESI+: 584
415#	1	ESI+: 545
416	54	ESI+: 445
417	26	ESI+: 529
418#	240+44	ESI+: 538
419#	89	ESI+: 574
420#	240	ESI+: 538
421#	26	ESI+: 570
422#	422	ESI+: 542
423#	87	ESI+: 600 RMN1:1,16(3H,t,J=7,1 Hz),1,50-1,83(7H, m),2,23(3H, a.),3,15-3,25(1H, m),3,27-3,36(1H, m),3,70(4H,d,J=4,7 Hz),3,74(4H,d,J=4,6 Hz),3,77-3,86(1H, m),3,99(2H,q,J=7,1 Hz),4,12(1H,q,J=9,1 Hz),4,98-5,09(1H, m),6,40(1H, s),7,34-7,50(3H, m),7,53(1 H,t,J=52,5 Hz),7,75(1H,d,J=7,6 Hz),7,86(1H,d,J=7,6 Hz)
424#	87	ESI+: 600
425#	83	ESI-:474
426#	92	ESI+: 531
427#	1	ESI+: 503
428#	1	ESI+: 517
429#	54	ESI+: 417
430#	54	ESI+: 431
431	54	ESI+: 403
432-1	432	ESI+: 528
432-2	432	ESI+: 528
433	54	ESI+: 417

los compuestos marcados no están englobados en las reivindicaciones

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[Tabla 160]

Ej	Sin	DAT
434#	92	ESI+: 446
435#	92	ESI+: 516
436	54	ESI+: 416
437#	92	ESI+: 530
438#	54	ESI+: 430
439#	92	ESI+: 516
440#	54	ESI+: 416
441#	248	ESI+: 585 RMN1:1,27-2,29(10H, m),3,07-3,21(2H, m),3,53(3H, s),3,57-3,83(10H, m),4,06-4,18(1H, m),6,22-6,41(1H, m),6,87-7,08(1H, m),7,31-7,92 (6H,m)
442	66	ESI+: 529
443	66	ESI+: 529
444	66	ESI+: 528
445	66	ESI+: 528
446	66	ESI+: 542
447	66	ESI+: 542
448#	52	ESI+: 560
449#	54	ESI+: 488
450#	1	ESI+: 588
451	249	ESI+: 543 RMN1:1,34-1,45(4H, m),1,53-1,65(2H, m),1,78-1,88(2H, m),2,25-2,35(1H, m),3,19(3H, s),3,66-3,76(8H, m),3,86-3,91(1H, m),4,19-4,34(2H, m),4,60-4,66(1H, m),5,44-5,50(1H, m),6,52(1H, s), 7,41-7,67(4H, m),7,77-7,79(1H, m),7,86-7,88(1H,m)
452	249	ESI+: 543 RMN1:1,03-1,40(4H, m),1,67-1,75(2H, m),1,96-2,25(3H, m),3,00-3,12(1H, m),3,22(3H, s),3,66-3,76(8H, m),3,85-3,92(1H, m),4,18-4,33(2H, m),4,60-4,67(1H, m),5,43-5,51(1H, m),6,52(1H, s),7,42-7,67(3H, m),7,78(1H,d,J=7,4 Hz),7,87(1H,d,J=7,4 Hz)
453	66	ESI+: 556 RMN1:1,38-1,66(10H, m),1,81-2,02(1H, m),2,05-2,30(1H, m),3,31-3,40(2H, m),3,40-3,52(1H, m),3,56-3,63(2H, m),3,84-3,94(1H, m),3,66(4H, a.),3,70(4H, a.),4,37(1H,dt,J=1,4,5,2 Hz), 4,43-4,60(1H, m),6,14(1H, a.),7,36-7,50(2H, m),7,52(1H,t,J=52,7 Hz),7,73(1H,d,J=7,6 Hz),7,75-7,88(1H, m),7,86(1H,d,J=7,8 Hz)
454	66	ESI+: 556 RMN1:0,85-1,01(2H, m),1,33(4H, a.),1,67-1,80(4H, m),1,82-2,03(1H, m),2,09-2,40(1H, m),3,17-3,23(2H, m),3,34-3,50(1H, m),3,57-3,63(2H, m),3,66(4H, a.),3,70(4H, a.),3,91(1H, a.),4,36(1H,t,J=5,3 Hz),4,44-4,60(1H, a.),6,14(1 H,d,J=4,8 Hz),7,37-7,49(2H, m),7,52(1H,t,J=52,7 Hz),7,72(1H,d,J=8,3 Hz),7,75-7,88(1H, a.),7,85(1H,d,J=7,9 Hz)

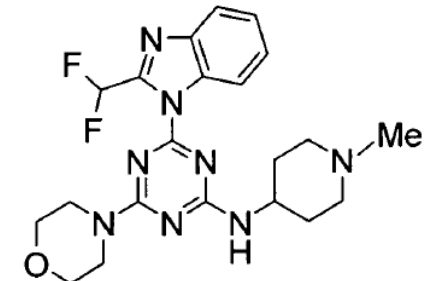
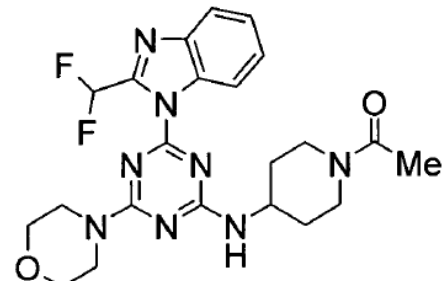
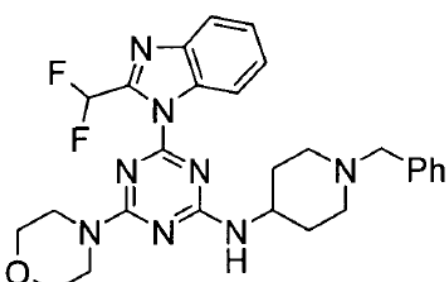
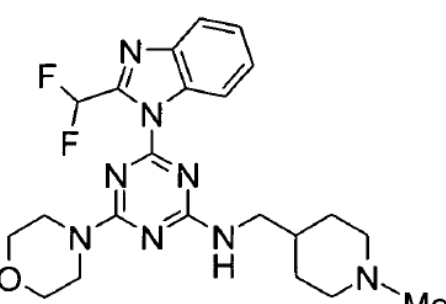
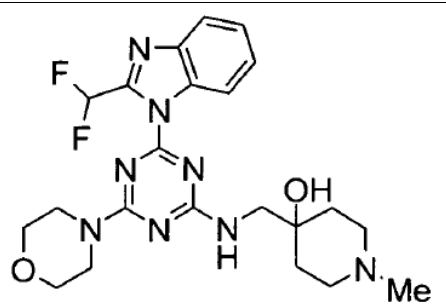
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 161]

Ej	Sin	DAT
455#	66	ESI+: 544
456#	1	ESI+: 458
457#	66+44	ESI+: 543
458#	71	ESI+: 500
459#	54	ESI+: 458
460#	92	ESI+: 558
461#	66	ESI+: 543
462#	66	ESI+: 557
463#	71	ESI+: 514
464#	1	ESI+: 589
465#	53	ESI+: 489
466#	85	ESI+: 586
467#	66	ESI+: 574
468#	422	ESI+: 593
469#	1	ESI+: 562
470#	54	ESI+: 462
471#	26	ESI+: 546

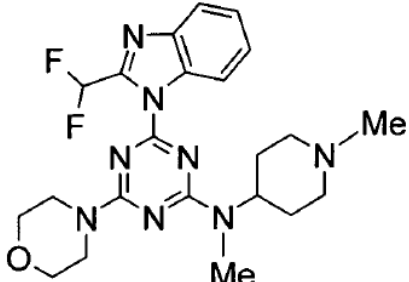
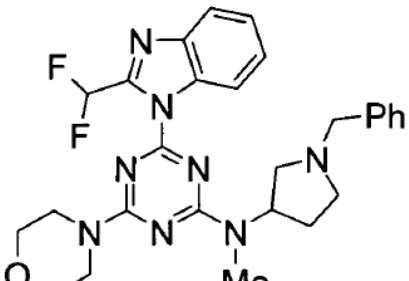
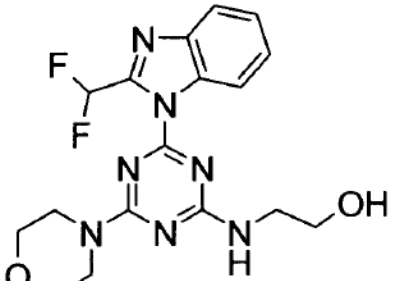
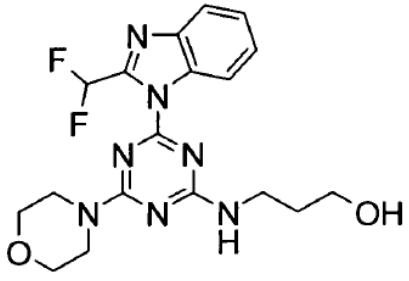
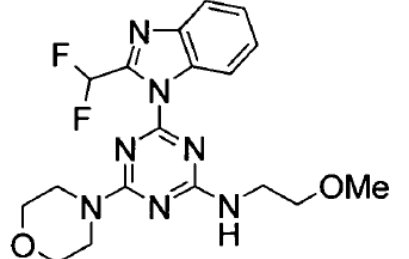
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 162]

Ej	Estr	ESI+	TR
A1#		445	2,19
A2#		473	2,81
A3#		521	2,56
A4#		459	2,28
A5#		475	2,19

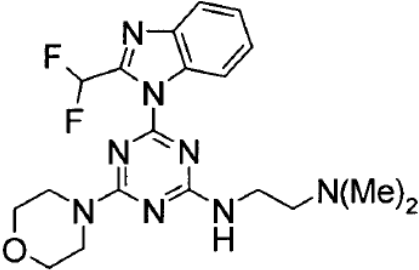
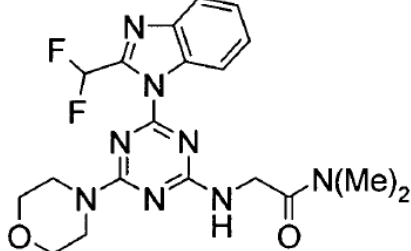
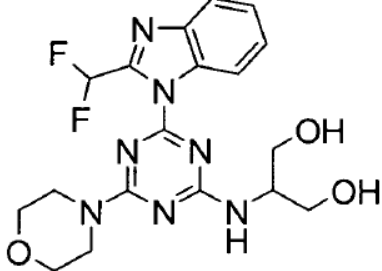
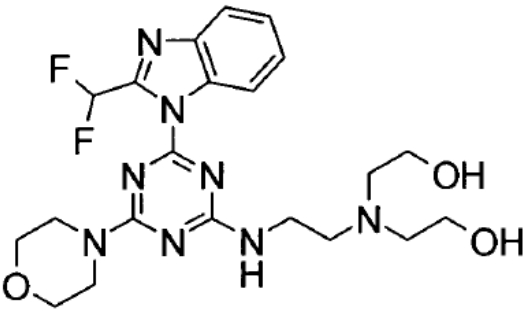
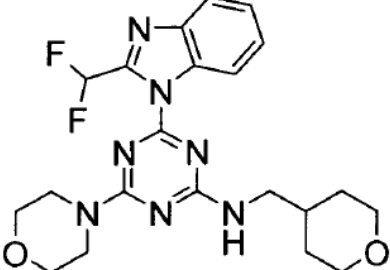
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 163]

Ej	Estr	ESI+	TR
A6#		459	2,33
A7#		521	2,61
A8#		392	2,58
A9#		406	2,67
A10#		406	2,87

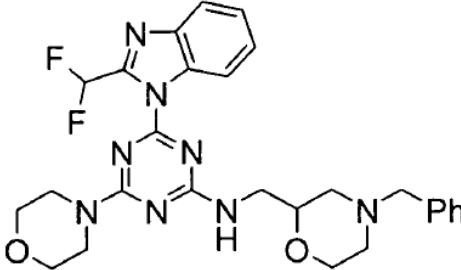
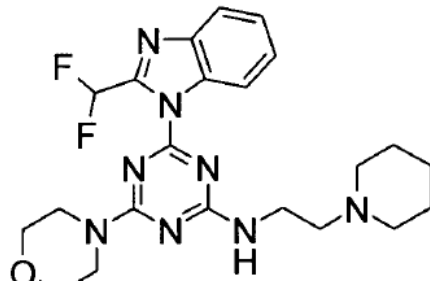
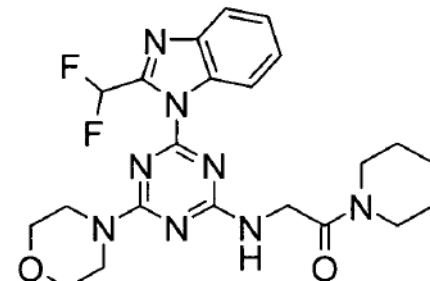
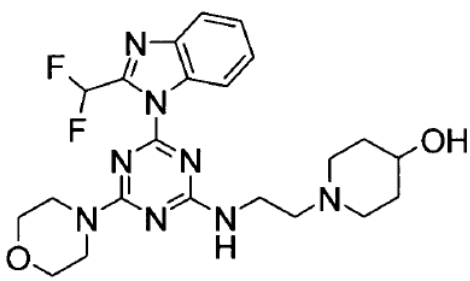
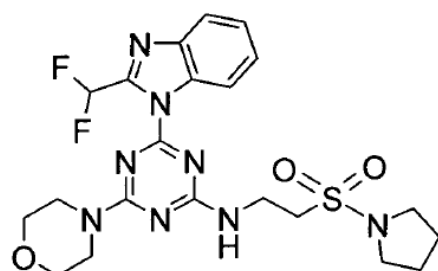
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 164]

Ej	Estr	ESI+	TR
A11#		419	2,1
A12#		433	2,59
A13#		422	2,37
A14#		479	2,06
A15#		446	3,03

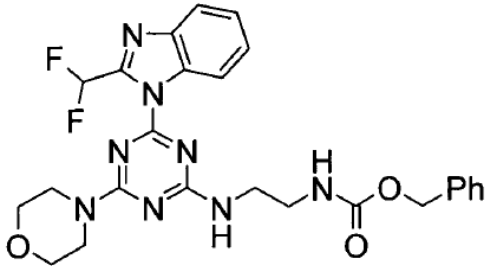
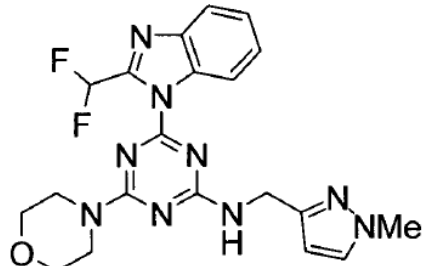
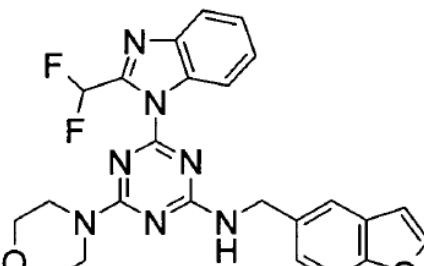
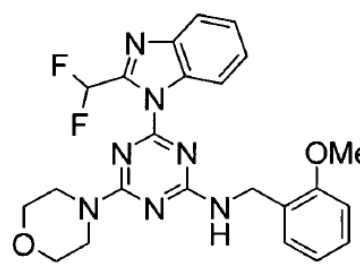
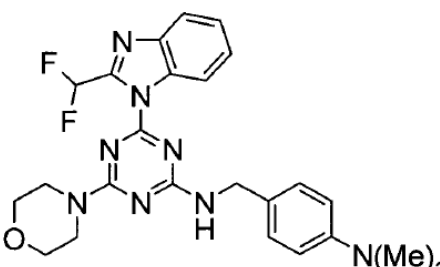
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 165]

Ej	Estr	ESI+	TR
A16#		537	2,46
A17#		459	2,16
A18#		473	2,95
A19#		475	2,09
A20#		509	2,89

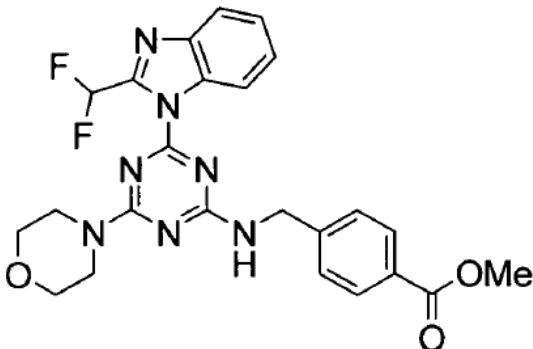
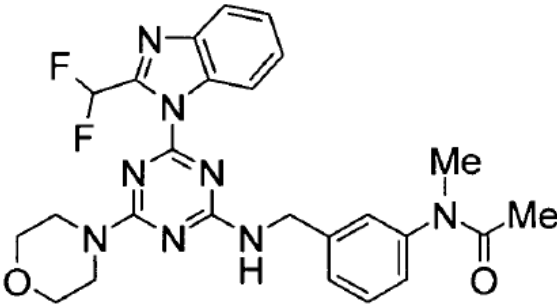
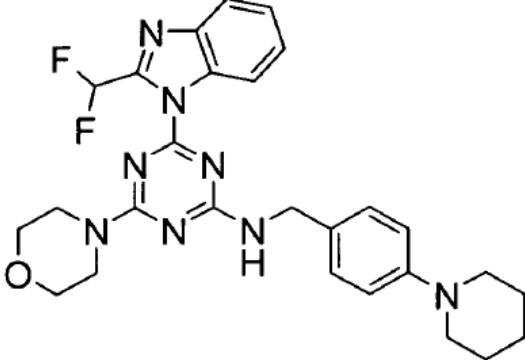
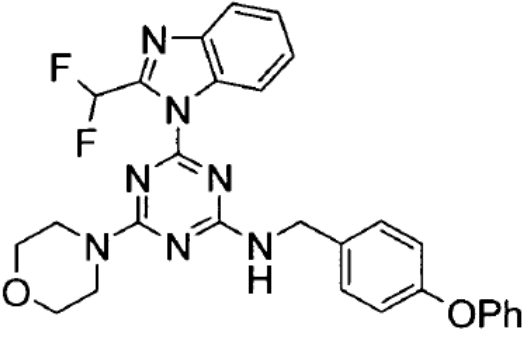
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 166]

Ej	Estr	ESI+	TR
A21#		525	3,18
A22#		442	2,8
A23#		478	3,41
A24#		468	3,39
A25#		481	2,51

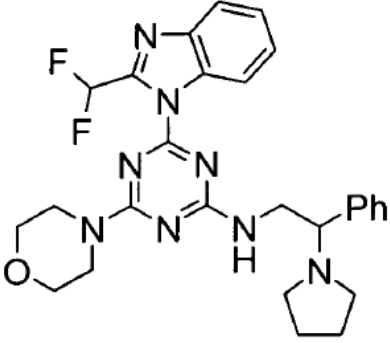
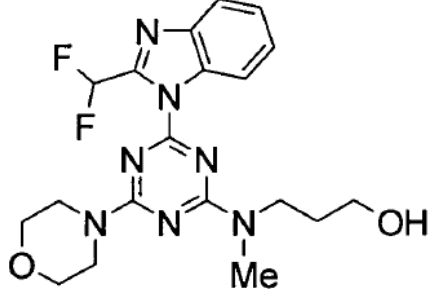
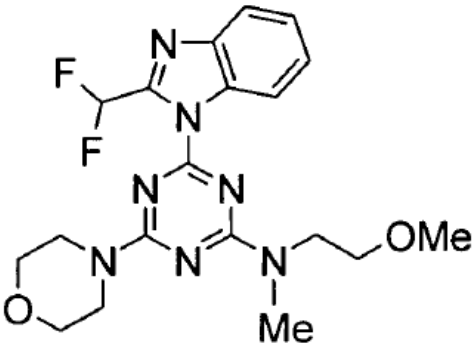
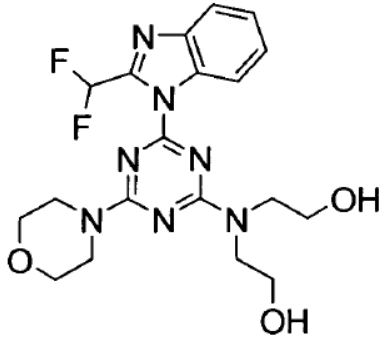
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 167]

Ej	Estr	ESI+	TR
A26#		496	3,24
A27#		509	3,01
A28#		521	2,51
A29#		530	3,74

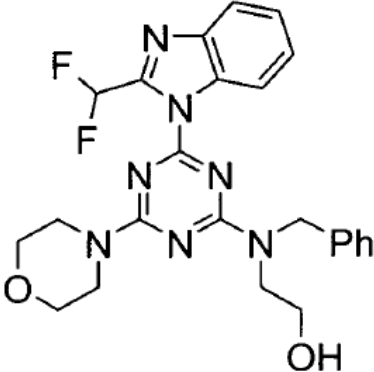
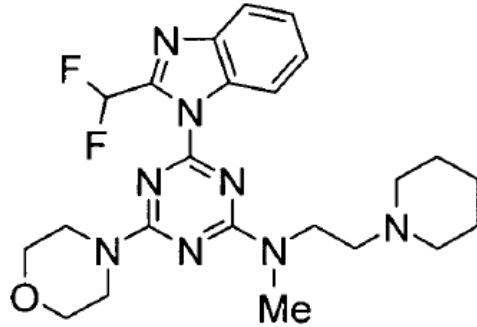
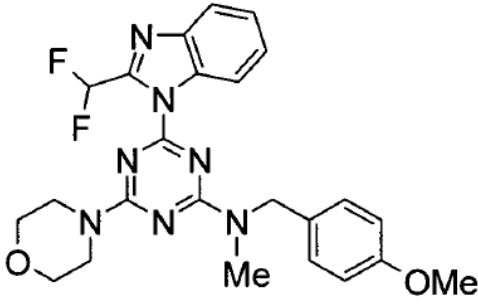
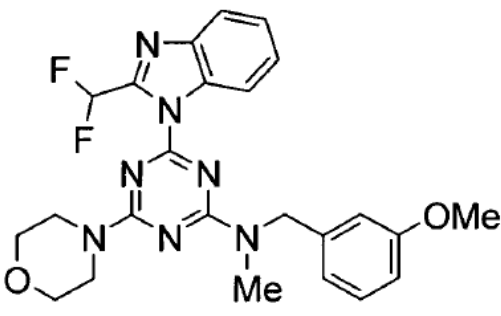
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 168]

Ej	Estr	ESI+	TR
A30#		521	2,51
A31#		420	2,92
A32#		420	3,17
A33#		436	2,58

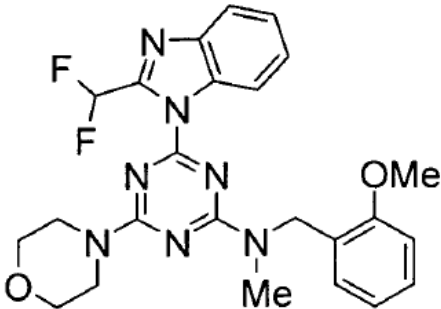
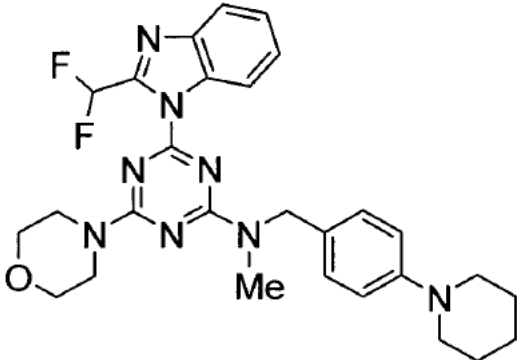
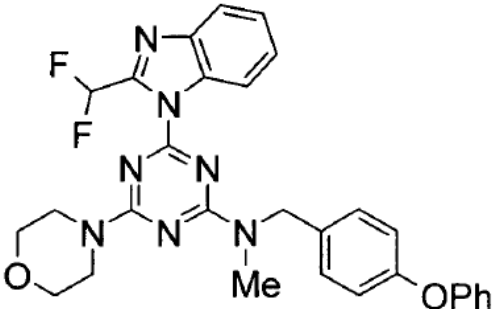
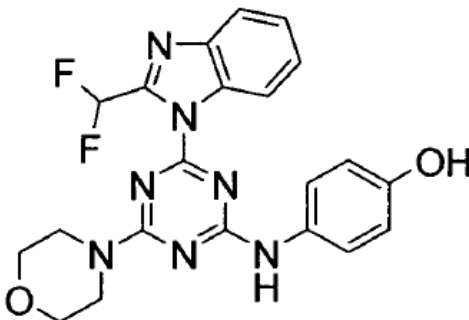
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 169]

Ej	Estr	ESI+	TR
A34#		482	3,31
A35#		473	2,29
A36#		482	3,6
A37#		482	3,59

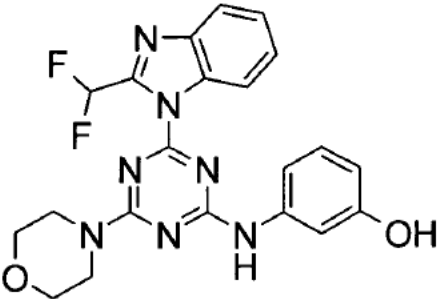
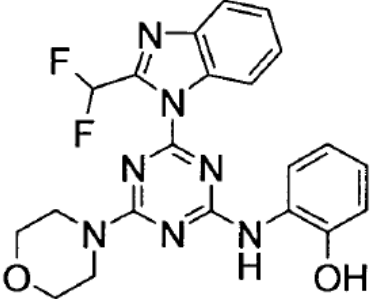
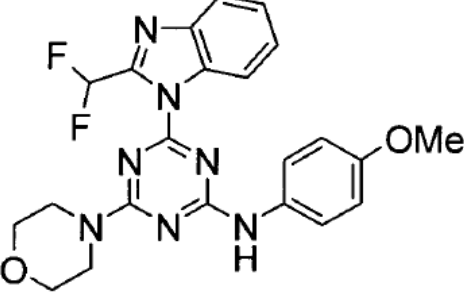
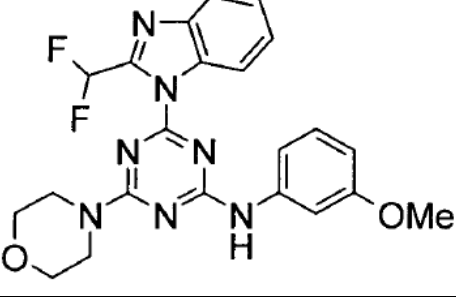
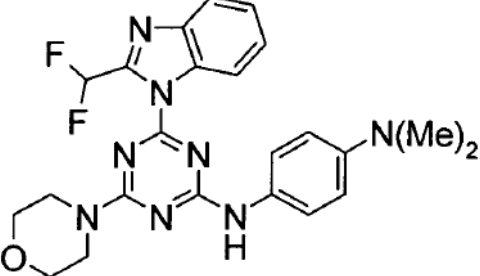
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 170]

Ej	Estr	ESI+	TR
A38#		482	3,68
A39#		535	2,76
A40#		544	3,95
A41#		440	2,94

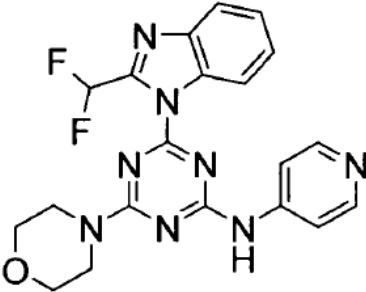
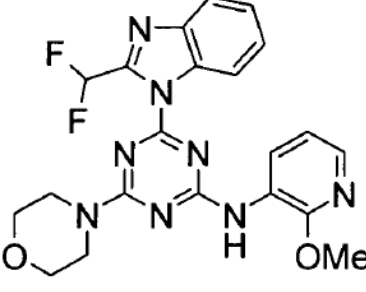
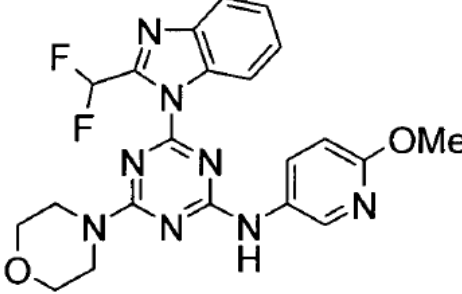
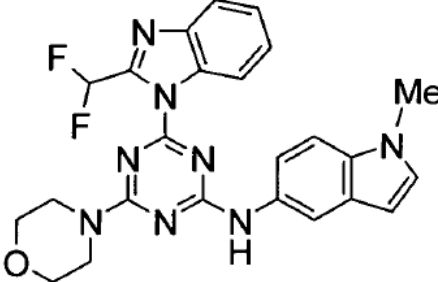
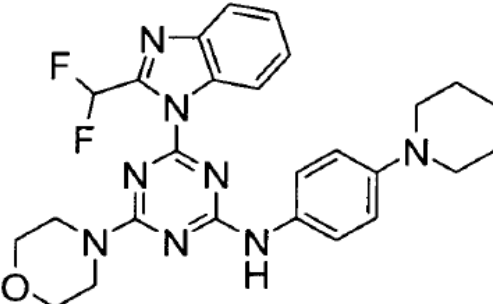
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 171]

Ej	Estr	ESI+	TR
A42#		440	3,01
A43#		440	3,16
A44#		454	3,3
A45#		454	3,36
A46#		467	2,54

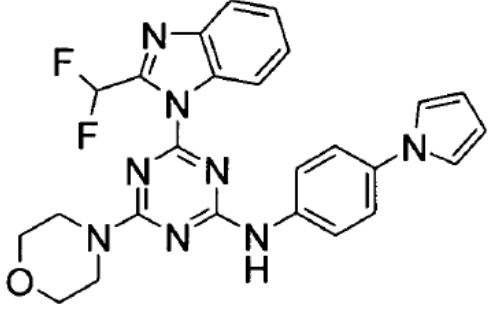
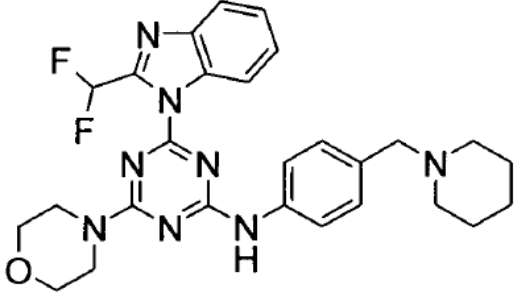
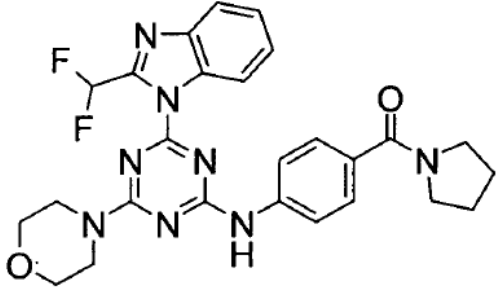
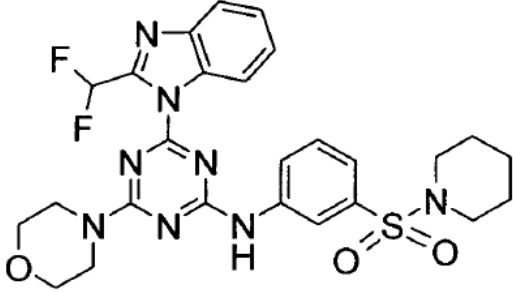
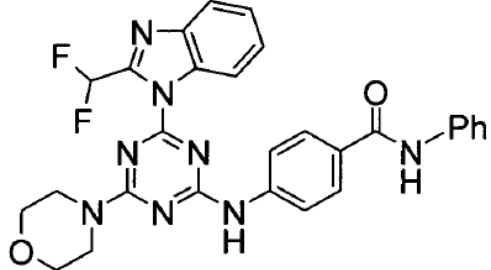
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 172]

Ej	Estr	ESI+	TR
A47#		425	2,29
A48#		455	3,24
A49#		455	3,15
A50#		477	3,37
A51#		507	2,54

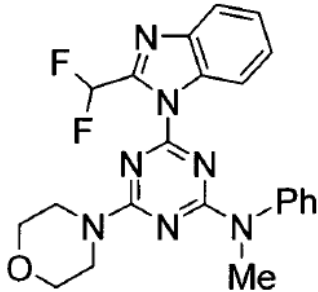
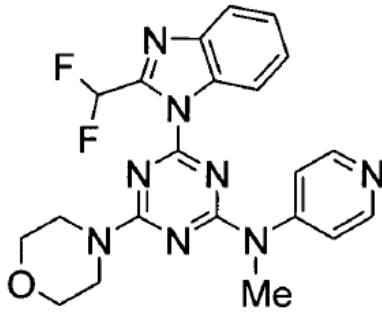
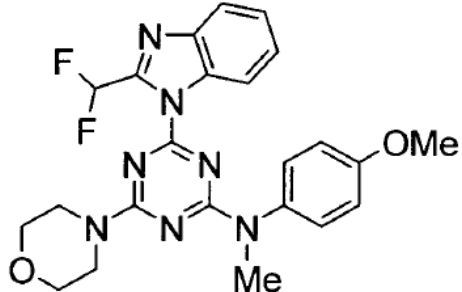
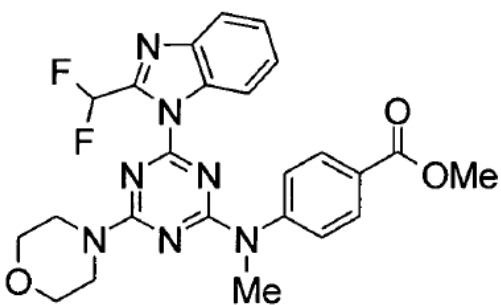
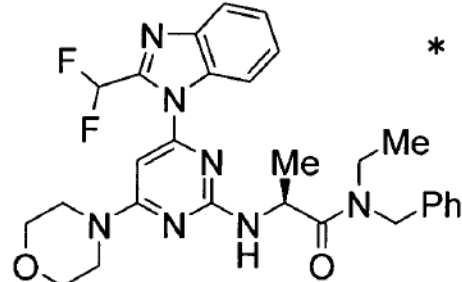
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 173]

Ej	Estr	ESI+	TR
A52#		489	3,63
A53#		521	2,57
A54#		521	3,16
A55#		571	3,46
A56#		543	3,31

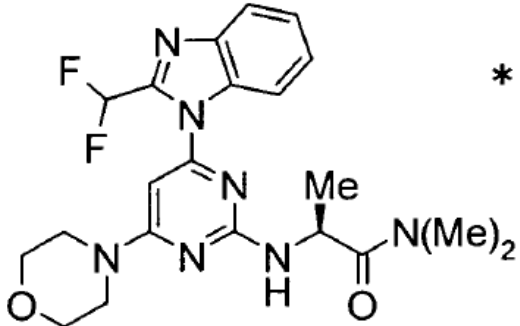
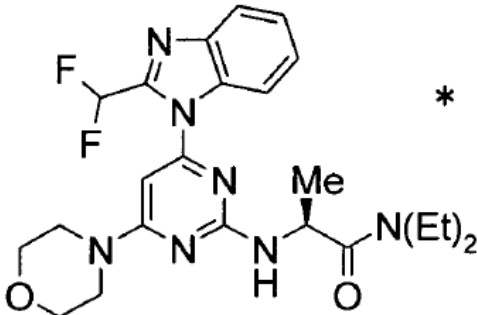
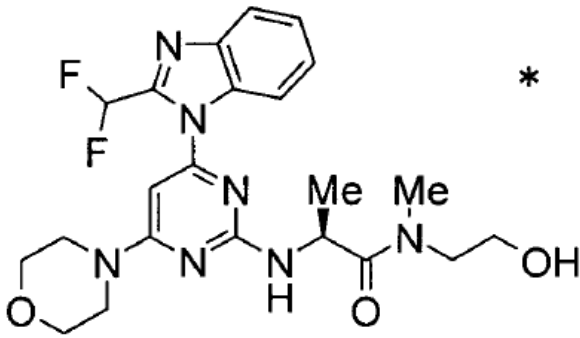
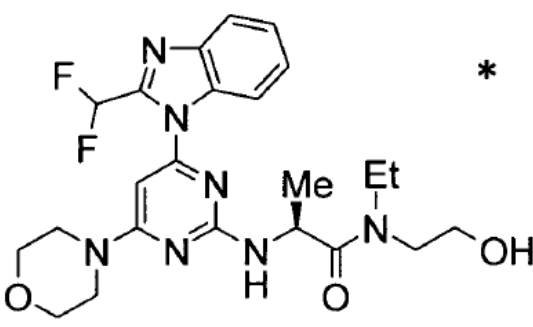
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 174]

Ej	Estr	ESI+	TR
A57#		438	3,55
A58#		439	2,25
A59#		468	3,53
A60#		496	3,47
A61#		536	2,9

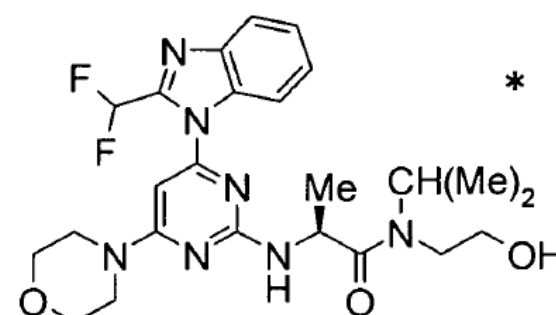
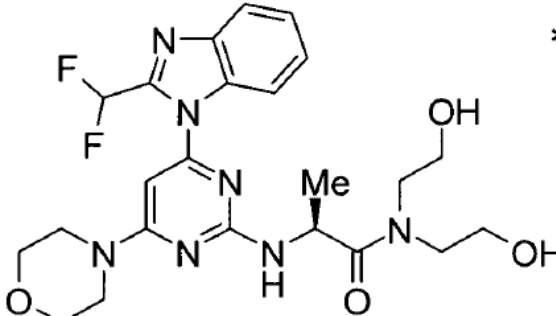
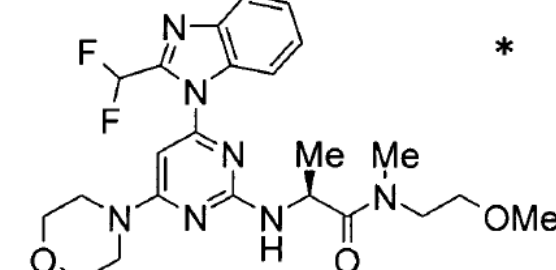
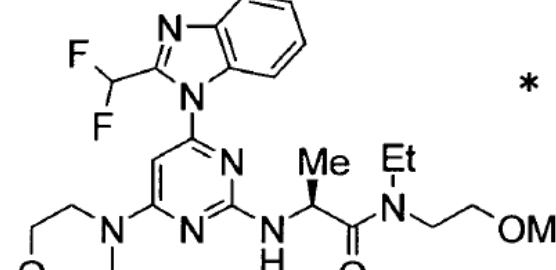
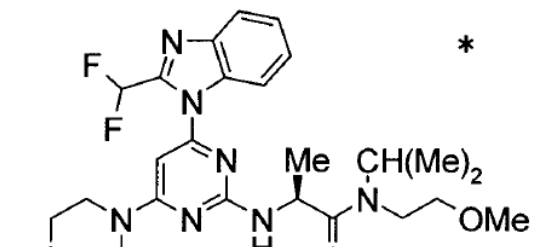
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 175]

Ej	Estr	ESI+	TR
A62#		446	2,42
A63#		474	2,67
A64#		476	2,3
A65#		490	2,41

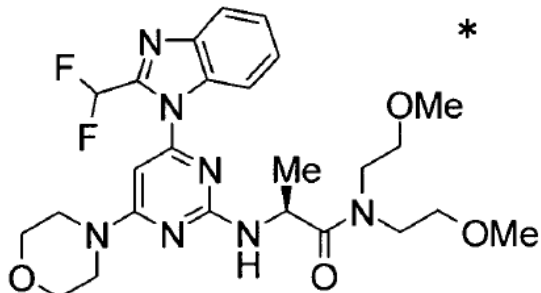
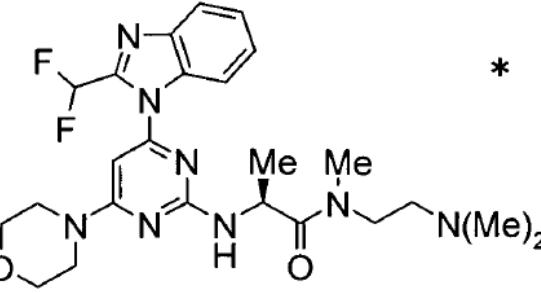
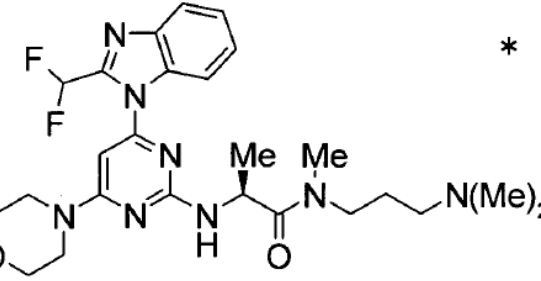
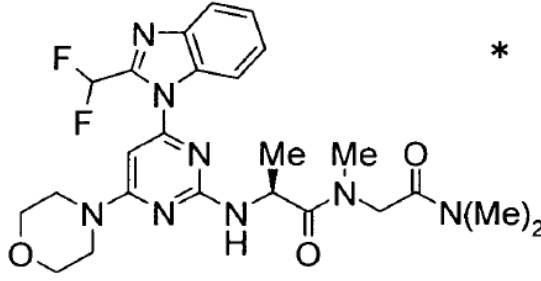
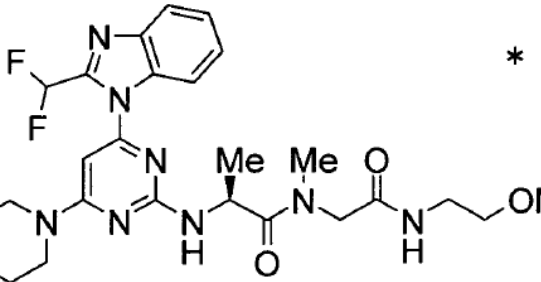
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 176]

Ej	Estr	ESI+	TR
A66#		504	2,51
A67#		506	2,18
A68#		490	2,52
A69#		504	2,64
A70#		518	2,74

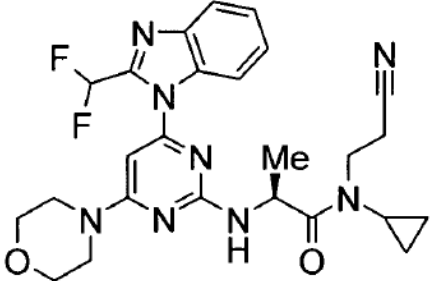
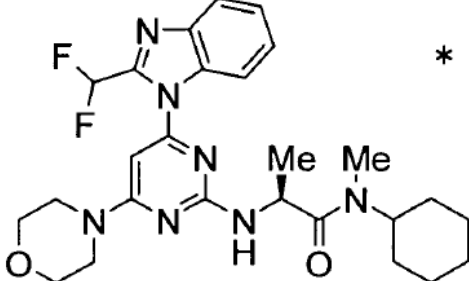
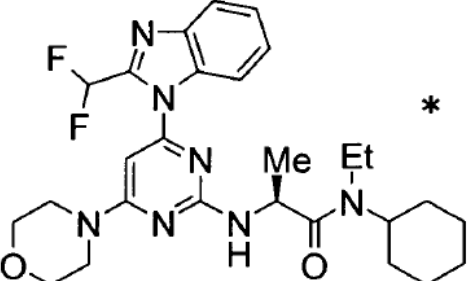
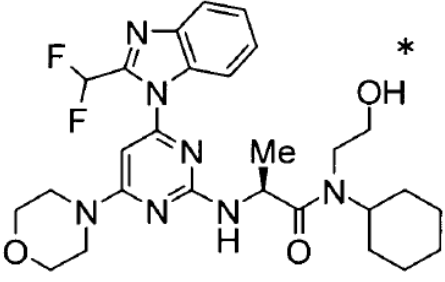
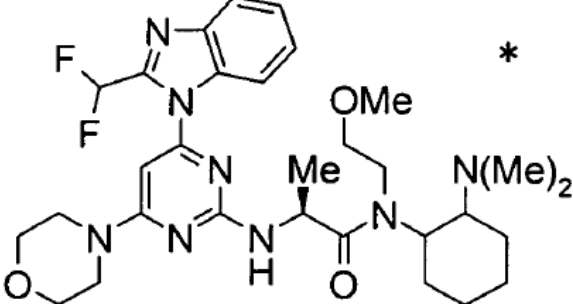
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 177]

Ej	Estr	ESI+	TR
A71#		534	2,62
A72#		503	1,87
A73#		517	1,88
A74#		517	2,35
A75#		547	2,36

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 178]

Ej	Estr	ESI+	TR
A76#		511	2,53
A77#		514	2,94
A78#		528	3,06
A79#		544	2,79
A80#		601	2,07

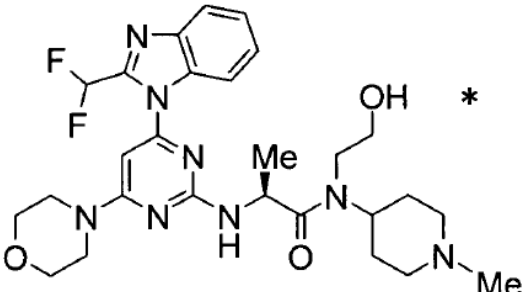
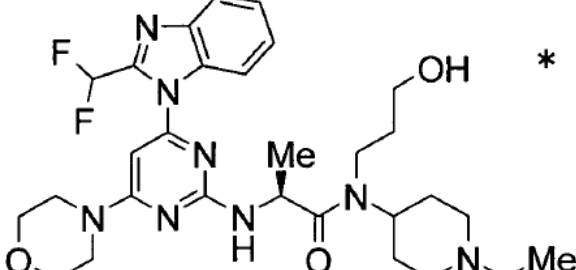
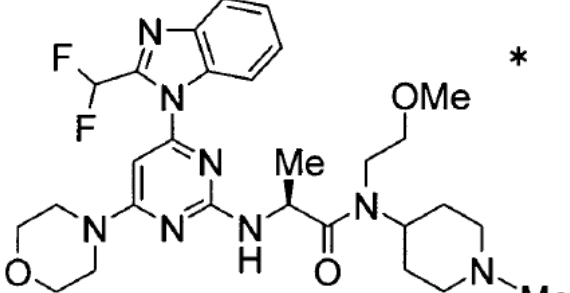
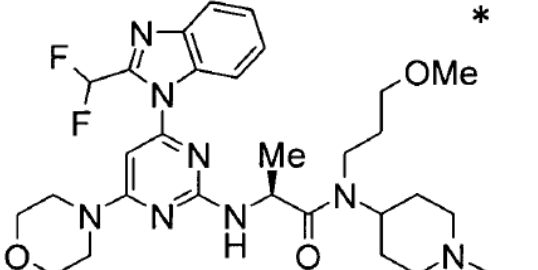
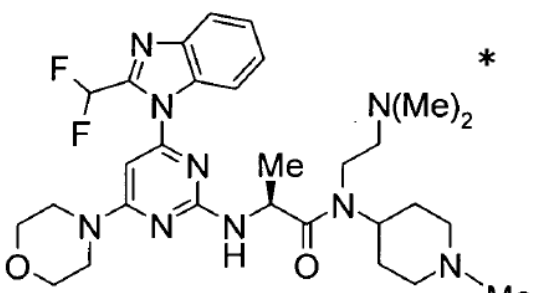
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 179]

Ej	Estr	ESI+	TR
A81#	<p>The structure of A81# features a central pyrimidopyrimidinone ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a methylamino group at the 6-position. The methylamino group is further substituted with a methyl group and a dimethylaminoethyl group attached to a cyclohexane ring.</p>	571	2,31
A82#	<p>The structure of A82# is similar to A81# but the dimethylaminoethyl group is replaced by a 1-(2-(pyrimidin-2-yl)ethyl)pyrrolidine group.</p>	593	2,73
A83#	<p>The structure of A83# is similar to A81# but the dimethylaminoethyl group is replaced by a cyclopropyl group attached to a morpholine ring.</p>	542	2,69
A84#	<p>The structure of A84# is similar to A82# but the pyrrolidine ring is substituted with a methyl group.</p>	529	1,88

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 180]

Ej	Estr	ESI+	TR
A85#		559	1,84
A86#		587	1,88
A87#		573	2,02
A88#		587	2,05
A89#		586	1,41

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 181]

Ej	Estr	ESI+	TR
A90#	<p>Chemical structure of compound A90#: A pyridine ring substituted with a morpholine group at the 4-position, a 1H-imidazole ring at the 2-position, and a 2,2-difluoroethyl group at the 3-position. The imidazole ring is further substituted with a methyl group and a (1-methylpiperidin-4-yl)acetamide group. The structure is marked with an asterisk (*).</p>	600	1,41
A91#	<p>Chemical structure of compound A91#: A pyridine ring substituted with a morpholine group at the 4-position, a 1H-imidazole ring at the 2-position, and a 2,2-difluoroethyl group at the 3-position. The imidazole ring is further substituted with a methyl group and a (1-methylpiperidin-4-yl)acetamide group. The piperidine ring is also substituted with a cyclopropyl group and a methyl group. The structure is marked with an asterisk (*).</p>	583	2,58
A92#	<p>Chemical structure of compound A92#: A pyridine ring substituted with a morpholine group at the 4-position, a 1H-imidazole ring at the 2-position, and a 2,2-difluoroethyl group at the 3-position. The imidazole ring is further substituted with a methyl group and a (1-methylpiperidin-4-yl)acetamide group. The piperidine ring is substituted with a methoxy group and a methyl group. The structure is marked with an asterisk (*).</p>	601	2,46
A93#	<p>Chemical structure of compound A93#: A pyridine ring substituted with a morpholine group at the 4-position, a 1H-imidazole ring at the 2-position, and a 2,2-difluoroethyl group at the 3-position. The imidazole ring is further substituted with a methyl group and a (1-methylpiperidin-4-yl)acetamide group. The piperidine ring is substituted with two methyl groups and an ethyl ester group. The structure is marked with an asterisk (*).</p>	587	2,69

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 182]

Ej	Estr	ESI+	TR
A94#	<p>Chemical structure of compound A94#: A pyridine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[4,5-b]pyridin-2-ylidene group at the 4-position, and a (S)-1-(2-(dimethylamino)ethyl)propan-2-ylideneamino group at the 6-position. The imidazo[4,5-b]pyridine ring has a difluoromethyl group at the 5-position. An asterisk (*) is present in the top right corner of the structure area.</p>	530	2,78
A95#	<p>Chemical structure of compound A95#: A pyridine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[4,5-b]pyridin-2-ylidene group at the 4-position, and a (S)-1-(2-(dimethylamino)ethyl)propan-2-ylideneamino group at the 6-position. The imidazo[4,5-b]pyridine ring has a difluoromethyl group at the 5-position. An asterisk (*) is present in the top right corner of the structure area.</p>	530	2,52
A96#	<p>Chemical structure of compound A96#: A pyridine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[4,5-b]pyridin-2-ylidene group at the 4-position, and a (S)-1-(2-(N-methyl)pyrrolidin-1-yl)propan-2-ylideneamino group at the 6-position. The imidazo[4,5-b]pyridine ring has a difluoromethyl group at the 5-position. An asterisk (*) is present in the top right corner of the structure area.</p>	543	1,93
A97#	<p>Chemical structure of compound A97#: A pyridine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[4,5-b]pyridin-2-ylidene group at the 4-position, and a (S)-1-(2-(N-methyl)pyrrolidin-1-yl)propan-2-ylideneamino group at the 6-position. The imidazo[4,5-b]pyridine ring has a difluoromethyl group at the 5-position. An asterisk (*) is present in the top right corner of the structure area.</p>	543	1,93
A98#	<p>Chemical structure of compound A98#: A pyridine ring substituted with a morpholine group at the 2-position, a 1H-imidazo[4,5-b]pyridin-2-ylidene group at the 4-position, and a (S)-1-(2-(N-methyl)pyrrolidin-1-yl)propan-2-ylideneamino group at the 6-position. The imidazo[4,5-b]pyridine ring has a difluoromethyl group at the 5-position. An asterisk (*) is present in the top right corner of the structure area.</p>	543	1,91

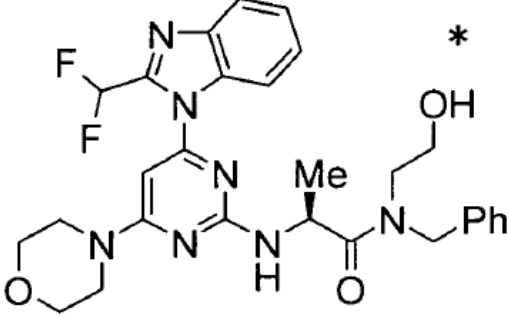
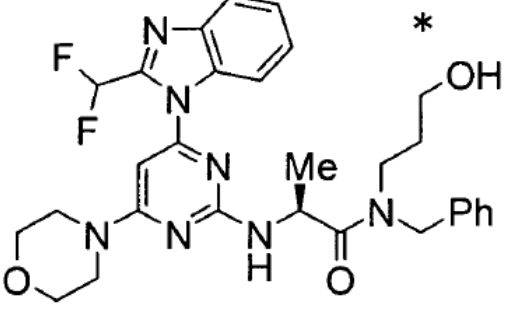
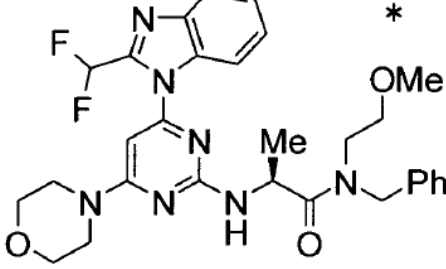
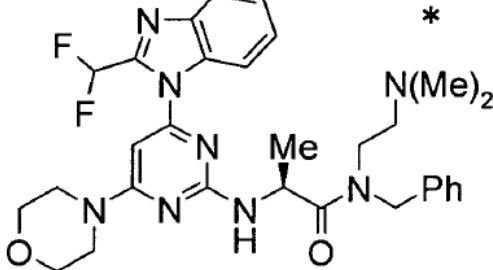
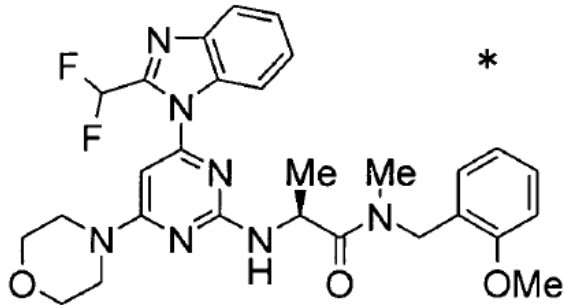
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 183]

Ej	Estr	ESI+	TR
A99#	<p>Chemical structure of compound A99#: A benzimidazole ring with a difluoromethyl group at the 2-position is attached to the 4-position of a pyrimidine ring. The pyrimidine ring is substituted at the 2-position with a morpholine group and at the 6-position with a secondary amide group. The secondary amide nitrogen is bonded to a chiral center with a methyl group and another methyl group, which is further bonded to a tertiary amide nitrogen. This tertiary amide nitrogen is bonded to a propyl chain that ends in a morpholine ring.</p>	543	1,91
A100#	<p>Chemical structure of compound A100#: Similar to A99#, but the propyl chain is replaced by a pentyl chain ending in a morpholine ring.</p>	573	1,93
A101#	<p>Chemical structure of compound A101#: Similar to A99#, but the tertiary amide nitrogen is bonded to a 2-hydroxypropyl chain ending in a morpholine ring.</p>	575	1,92
A102#	<p>Chemical structure of compound A102#: Similar to A99#, but the tertiary amide nitrogen is bonded to a propyl chain that ends in a morpholine ring via a carbonyl group (forming a secondary amide).</p>	559	2,35
A103#	<p>Chemical structure of compound A103#: Similar to A99#, but the tertiary amide nitrogen is bonded to a 2-hydroxypropyl chain that ends in a morpholine ring via an ether linkage.</p>	588	2,91

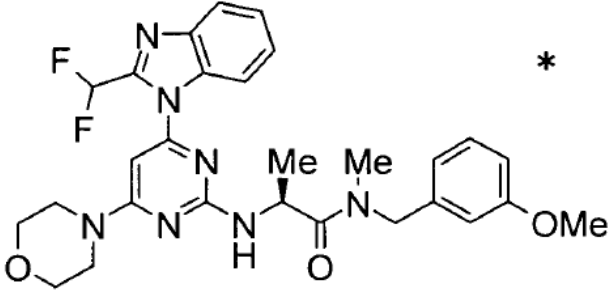
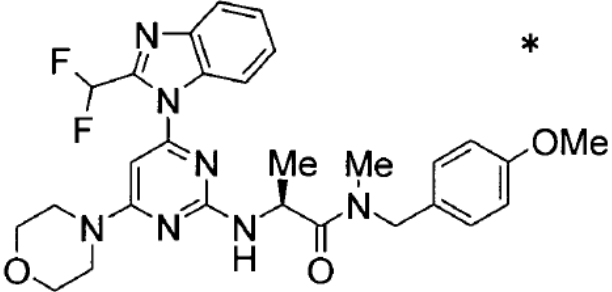
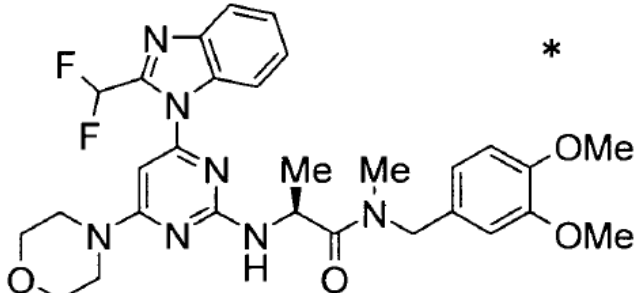
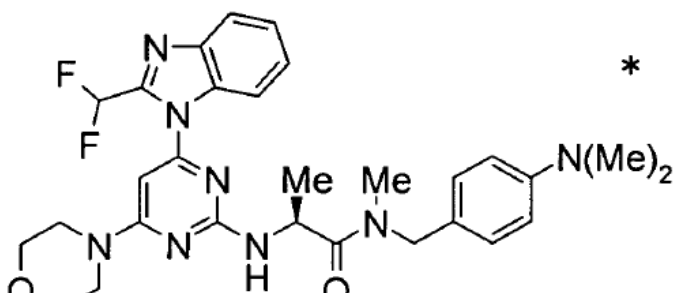
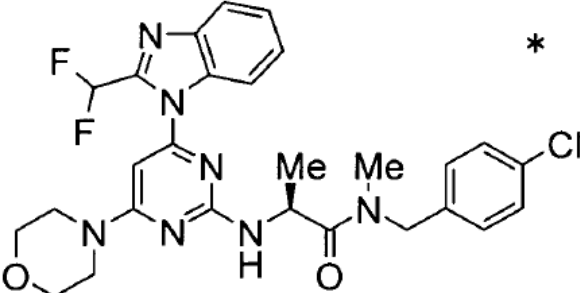
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 184]

Ej	Estr	ESI+	TR
A104#		552	2,66
A105#		566	2,69
A106#		566	2,88
A107#		579	2,21
A108#		552	2,86

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 185]

Ej	Estr	ESI+	TR
A109#		552	2,79
A110#		552	2,78
A111#		582	2,65
A112#		565	2,62
A113#		556	2,89

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 186]

Ej	Estr	ESI+	TR
A114#	<p>Chemical structure of compound A114#: A central pyrimidopyrimidinone ring system substituted with a morpholine group, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a methylamino group. The methylamino group is further substituted with a methyl group and a piperazine ring, which is in turn substituted with a 4-methoxybenzyl group. An asterisk (*) is present in the top right corner of the structure area.</p>	635	2,25
A115#	<p>Chemical structure of compound A115#: Similar to A114#, but the piperazine ring is substituted with a methyl group and a 2-pyridylmethyl group. An asterisk (*) is present in the top right corner of the structure area.</p>	523	2,39
A116#	<p>Chemical structure of compound A116#: Similar to A115#, but the 2-pyridylmethyl group is replaced by a 3-pyridylmethyl group. An asterisk (*) is present in the top right corner of the structure area.</p>	523	2,16
A117#	<p>Chemical structure of compound A117#: Similar to A116#, but the 3-pyridylmethyl group is replaced by a 4-pyridylmethyl group. An asterisk (*) is present in the top right corner of the structure area.</p>	523	2,02
A118#	<p>Chemical structure of compound A118#: Similar to A117#, but the 4-pyridylmethyl group is replaced by a 1-methyl-1H-tetrazol-5-ylmethyl group. An asterisk (*) is present in the top right corner of the structure area.</p>	528	2,31

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 187]

Ej	Estr	ESI+	TR
A119#	<p>Chemical structure of compound A119#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-((methyl(morpholin-2-ylmethyl)amino)acetyl)amino group.</p>	580	2,74
A120#	<p>Chemical structure of compound A120#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-((methyl(2-hydroxyethyl)pyridin-4-ylmethyl)amino)acetyl)amino group.</p>	553	1,93
A121#	<p>Chemical structure of compound A121#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-((methyl(2-hydroxyethyl)pyridin-3-ylmethyl)amino)acetyl)amino group.</p>	567	1,96
A122#	<p>Chemical structure of compound A122#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-((methyl(2-methoxyethyl)pyridin-4-ylmethyl)amino)acetyl)amino group.</p>	581	2,34
A123#	<p>Chemical structure of compound A123#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-((methyl(2-(dimethylamino)ethyl)pyridin-4-ylmethyl)amino)acetyl)amino group.</p>	580	1,66

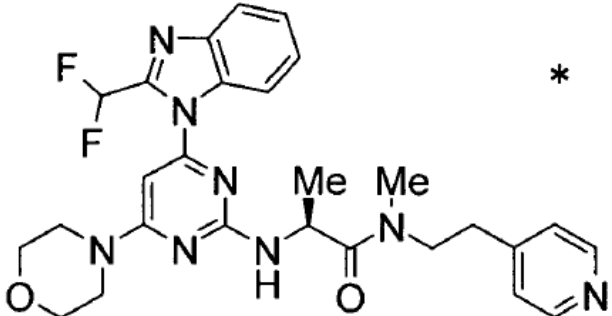
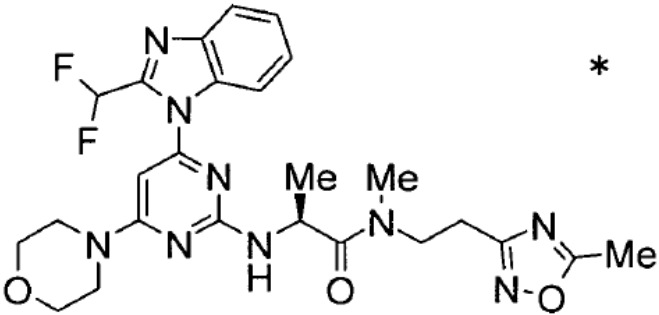
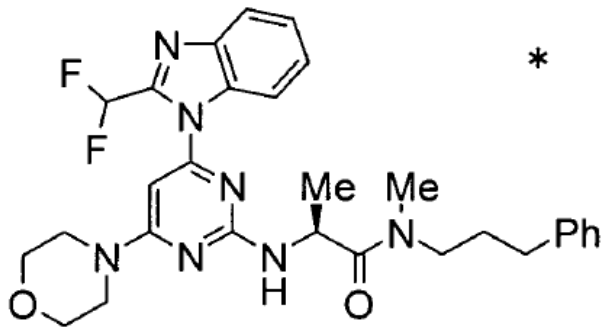
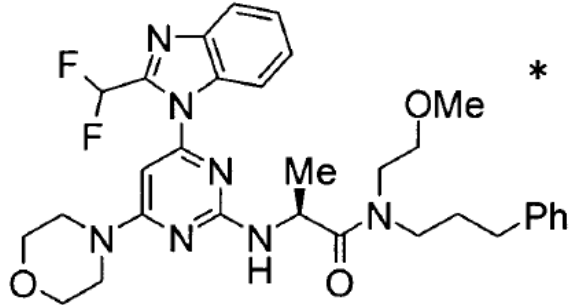
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 188]

Ej	Estr	ESI+	TR
A124#	<p>Chemical structure of compound A124#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a methyl group. The methyl group is attached to a chiral center, which is also bonded to a hydrogen atom and a carbonyl group. The carbonyl group is further substituted with a 2-(dimethylamino)ethyl group and a 2-pyridylmethyl group.</p>	594	1,62
A125#	<p>Chemical structure of compound A125#: Similar to A124#, but the 2-(dimethylamino)ethyl group is replaced by a morpholine ring.</p>	622	1,69
A126#	<p>Chemical structure of compound A126#: Similar to A124#, but the methyl group is attached to a nitrogen atom that is also bonded to another methyl group and a 2-phenylethyl group.</p>	536	2,88
A127#	<p>Chemical structure of compound A127#: Similar to A124#, but the methyl group is attached to a nitrogen atom that is also bonded to another methyl group and a 2-(3,4-dimethoxyphenyl)ethyl group.</p>	596	2,72
A128#	<p>Chemical structure of compound A128#: Similar to A124#, but the methyl group is attached to a nitrogen atom that is also bonded to another methyl group and a 2-(1-hydroxyethyl)ethyl group.</p>	566	2,75

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 189]

Ej	Estr	ESI+	TR
A129#		537	1,99
A130#		542	2,5
A131#		550	2,95
A132#		594	3,01

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 190]

Ej	Estr	ESI+	TR
A133#	<p>Chemical structure of compound A133#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a methyl group. The methyl group is attached to a chiral center that is also bonded to a hydrogen atom and a carbonyl group. The carbonyl group is further substituted with a dimethylamino group and a 3-phenylpropyl group.</p>	607	2,37
A134#	<p>Chemical structure of compound A134#: Similar to A133#, but the dimethylamino group is replaced by a dimethylamino group and a 1-phenylethanol group.</p>	582	2,73
A135#	<p>Chemical structure of compound A135#: Similar to A133#, but the dimethylamino group is replaced by a dimethylamino group and a 1-(1-methyl-1H-imidazol-2-yl)propyl group.</p>	554	1,88
A136#	<p>Chemical structure of compound A136#: Similar to A133#, but the dimethylamino group is replaced by a dimethylamino group and a 4-(morpholin-2-yl)benzyl group.</p>	607	2,72
A137#	<p>Chemical structure of compound A137#: Similar to A133#, but the dimethylamino group is replaced by a piperidine ring.</p>	486	2,72

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 191]

Ej	Estr	ESI+	TR
A138#	<p>Chemical structure of compound A138#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(morpholin-2-yl)propanamide group. An asterisk (*) is present in the upper right of the structure.</p>	488	2,38
A139#	<p>Chemical structure of compound A139#: Similar to A138#, but the morpholine ring is substituted with a methyl group (Me) on the nitrogen atom. An asterisk (*) is present in the upper right of the structure.</p>	501	1,77
A140#	<p>Chemical structure of compound A140#: Similar to A138#, but the morpholine ring is substituted with a hydroxyl group (OH) on the carbon atom adjacent to the nitrogen. An asterisk (*) is present in the upper right of the structure.</p>	502	2,41
A141#	<p>Chemical structure of compound A141#: Similar to A138#, but the morpholine ring is substituted with a hydroxyl group (OH) on the carbon atom adjacent to the nitrogen. An asterisk (*) is present in the upper right of the structure.</p>	502	2,34
A142#	<p>Chemical structure of compound A142#: Similar to A138#, but the morpholine ring is substituted with a methoxy group (OMe) on the carbon atom adjacent to the nitrogen. An asterisk (*) is present in the upper right of the structure.</p>	516	2,56

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 192]

Ej	Estr	ESI+	TR
A143#	<p>Chemical structure of compound A143#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(2-hydroxyethyl)piperidin-1-yl group.</p>	518	2,26
A144#	<p>Chemical structure of compound A144#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(3-methoxypropyl)piperidin-1-yl group.</p>	559	1,85
A145#	<p>Chemical structure of compound A145#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(N,N-dimethylpiperidin-1-yl)propan-1-yl group.</p>	529	1,83
A146#	<p>Chemical structure of compound A146#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(N-methylpiperidin-1-yl)propan-1-yl group.</p>	529	2,25
A147#	<p>Chemical structure of compound A147#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(2-hydroxyethyl)piperidin-1-yl group.</p>	573	2,28

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 193]

Ej	Estr	ESI+	TR
A148#	<p>The structure of A148# features a central pyrimidopyrimidine ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a methylamino group at the 6-position. The methyl group is attached to the nitrogen of the methylamino group. This methylamino group is further substituted with a piperidine ring, which is in turn connected to a morpholine ring. An asterisk (*) is placed above the morpholine ring.</p>	571	1,83
A149#	<p>The structure of A149# is similar to A148#, but the piperidine ring is substituted with a hydroxyl group (-OH) and a phenyl group (-Ph) at the 4-position. An asterisk (*) is placed above the phenyl group.</p>	578	2,71
A150#	<p>The structure of A150# is similar to A148#, but the piperidine ring is connected to a morpholine ring via a methylene bridge (-CH₂-). An asterisk (*) is placed above the morpholine ring.</p>	585	1,87
A151#	<p>The structure of A151# is similar to A148#, but the piperidine ring is substituted with a pyrrolidine ring at the 4-position. An asterisk (*) is placed above the pyrrolidine ring.</p>	472	2,55
A152#	<p>The structure of A152# is similar to A148#, but the piperidine ring is substituted with two fluorine atoms (-F₂) at the 4-position. An asterisk (*) is placed above the piperidine ring.</p>	522	2,62

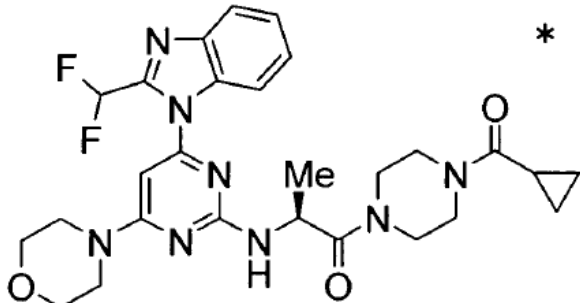
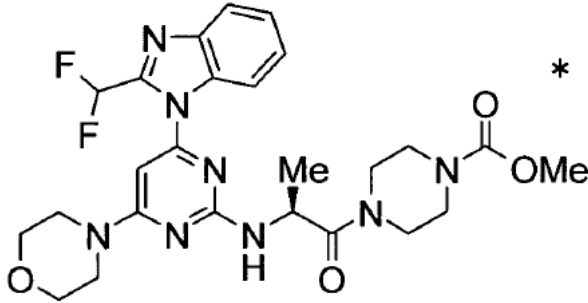
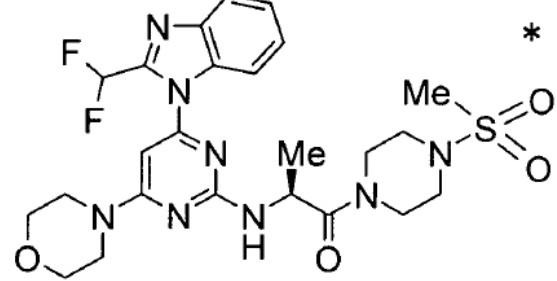
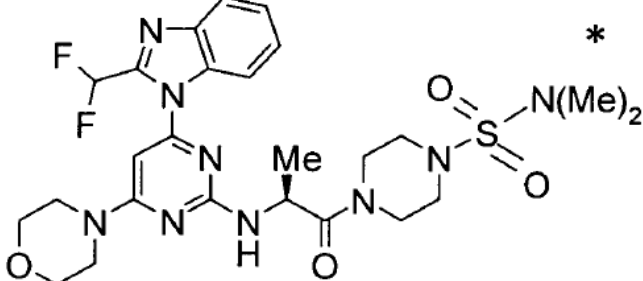
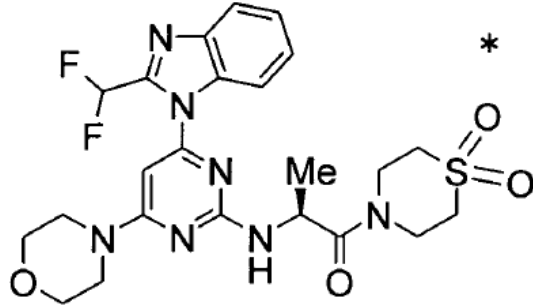
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 194]

Ej	Estr	ESI+	TR
A153#	<p>Chemical structure of compound A153#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-1-methyl-2-((S)-2-methylmorpholine-1-carbonyl)ethan-1-amine group. An asterisk (*) is present near the morpholine ring.</p>	516	2,61
A154#	<p>Chemical structure of compound A154#: Similar to A153#, but the morpholine ring is replaced by a piperazine ring substituted with an ethyl group (Et). An asterisk (*) is present near the piperazine ring.</p>	515	1,76
A155#	<p>Chemical structure of compound A155#: Similar to A153#, but the morpholine ring is replaced by a piperazine ring substituted with a methyl group (Me). An asterisk (*) is present near the piperazine ring.</p>	515	1,8
A156#	<p>Chemical structure of compound A156#: Similar to A153#, but the morpholine ring is replaced by a piperazine ring with a secondary amide group (NH) and a carbonyl group (C=O). An asterisk (*) is present near the piperazine ring.</p>	501	2,13
A157#	<p>Chemical structure of compound A157#: Similar to A153#, but the morpholine ring is replaced by a piperazine ring substituted with a methyl group (Me) and a carbonyl group (C=O). An asterisk (*) is present near the piperazine ring.</p>	515	2,19

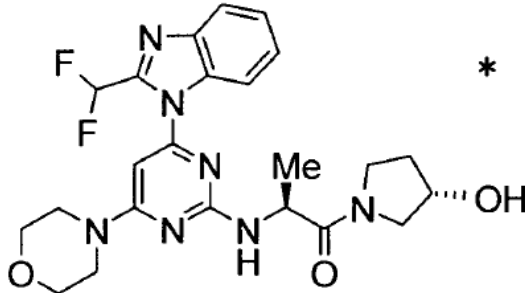
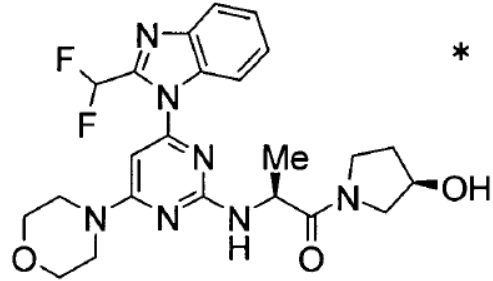
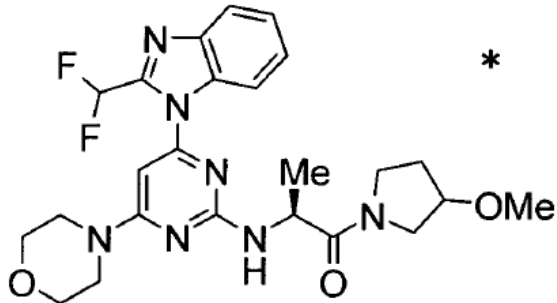
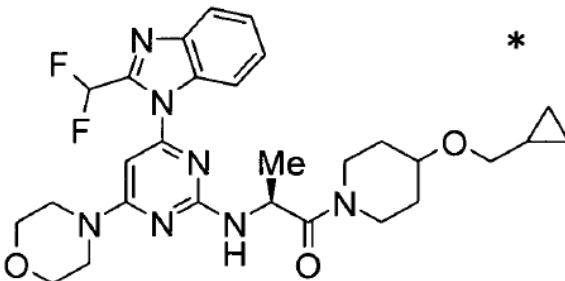
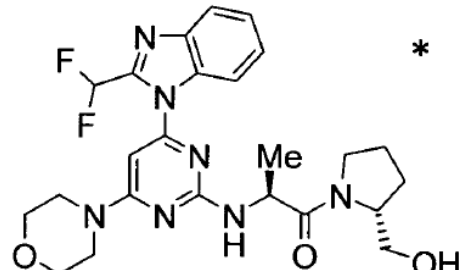
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 195]

Ej	Estr	ESI+	TR
A158#		555	2,42
A159#		545	2,45
A160#		565	2,3
A161#		594	2,45
A162#		536	2,21

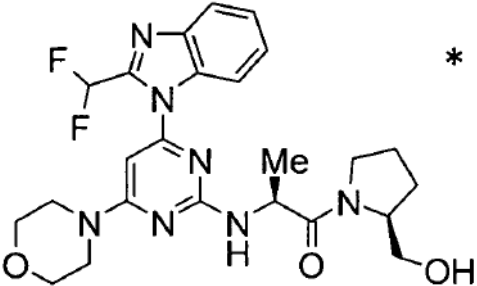
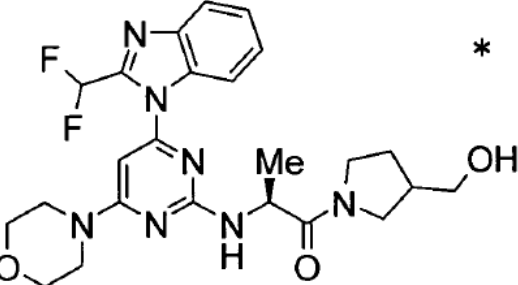
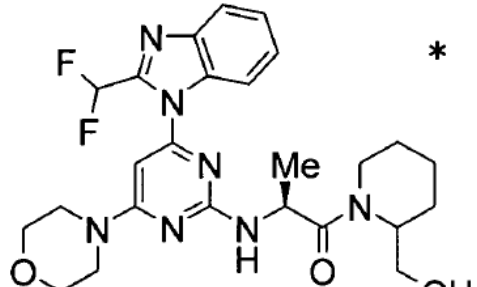
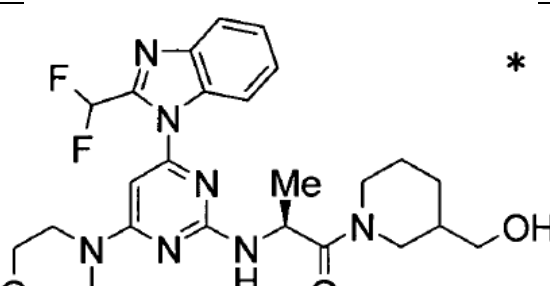
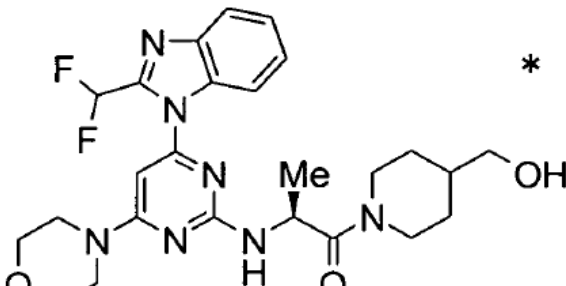
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 196]

Ej	Estr	ESI+	TR
A163#		488	2,3
A164#		488	2,29
A165#		502	2,49
A166#		556	2,84
A167#		502	2,44

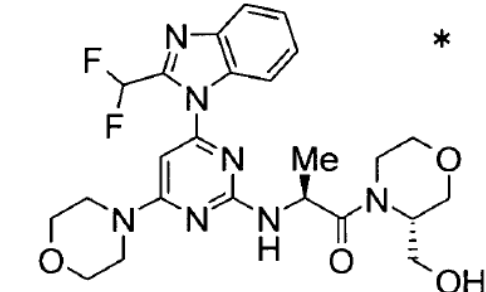
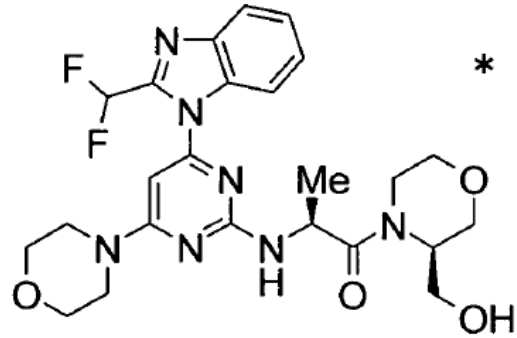
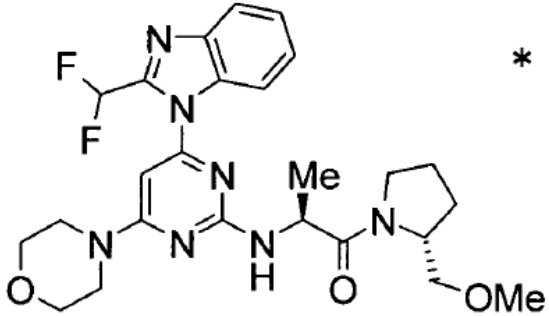
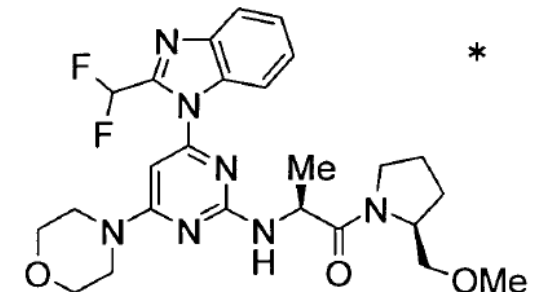
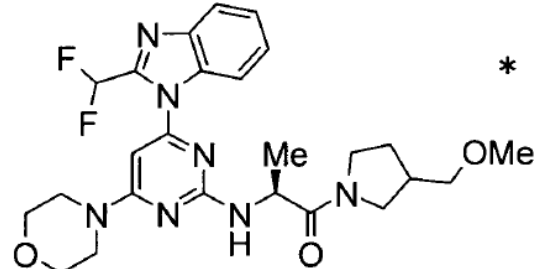
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 197]

Ej	Estr	ESI+	TR
A168#		502	2,44
A169#		502	2,33
A170#		516	2,54
A171#		516	2,46
A172#		516	2,41

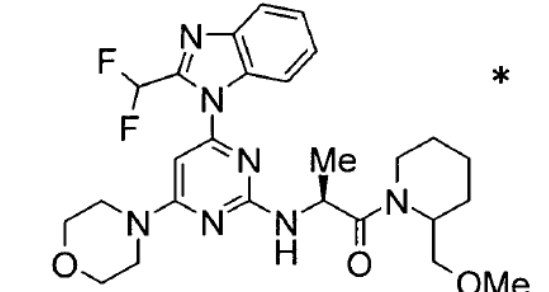
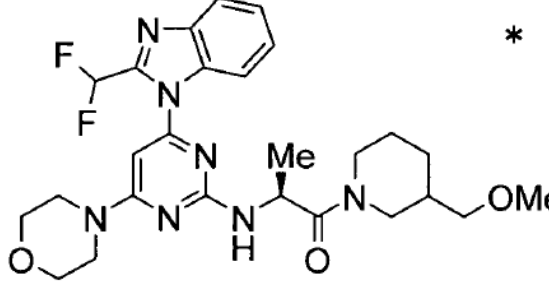
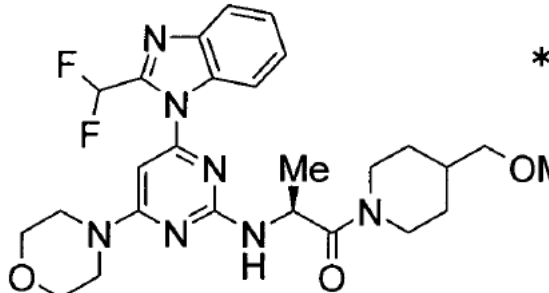
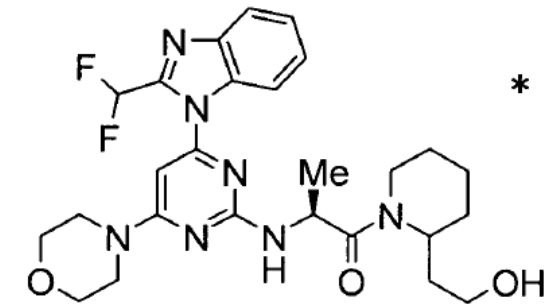
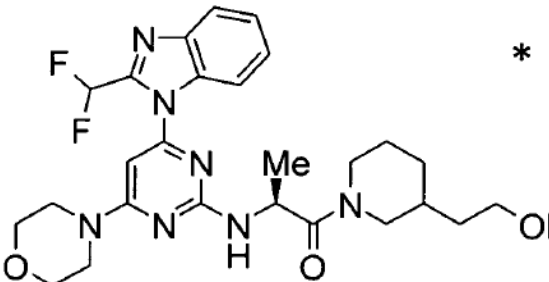
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 198]

Ej	Estr	ESI+	TR
A173#		518	2,29
A174#		518	2,3
A175#		516	2,64
A176#		516	2,66
A177#		516	2,57

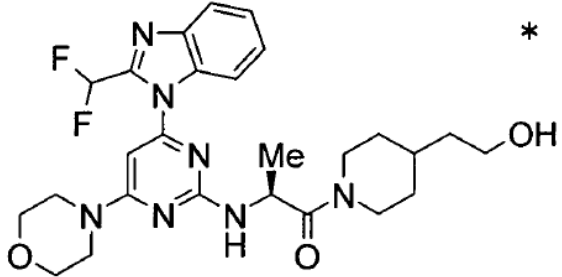
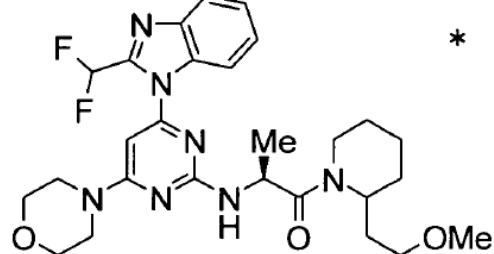
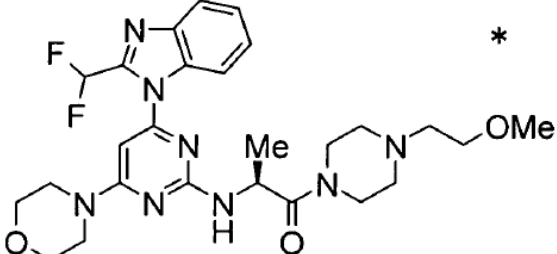
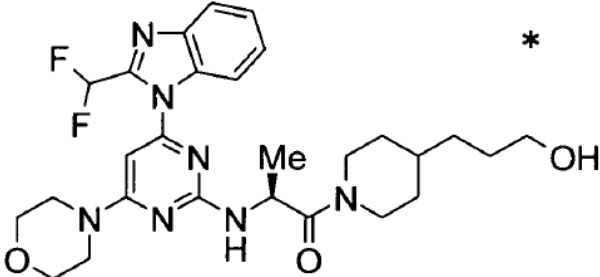
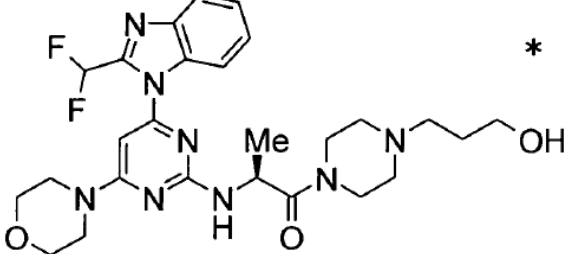
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 199]

Ej	Estr	ESI+	TR
A178#		530	2,76
A179#		530	2,72
A180#		530	2,66
A181#		530	2,6
A182#		530	2,54

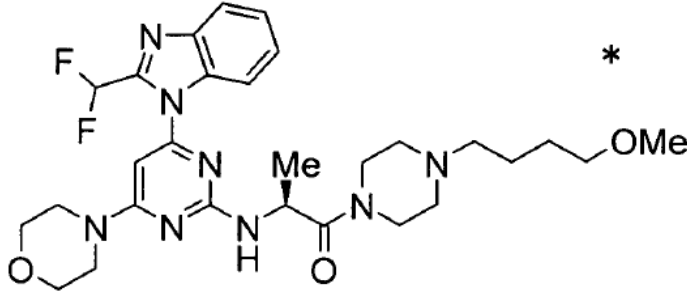
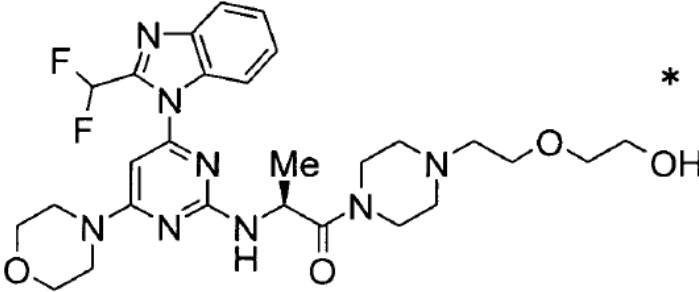
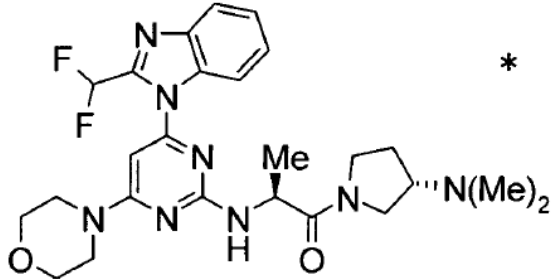
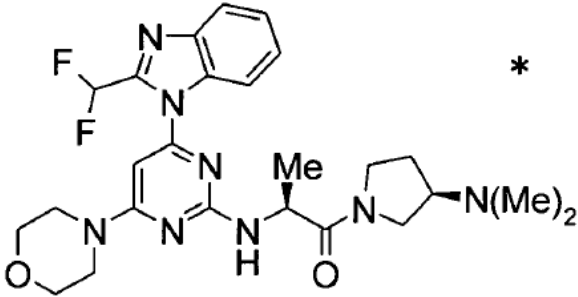
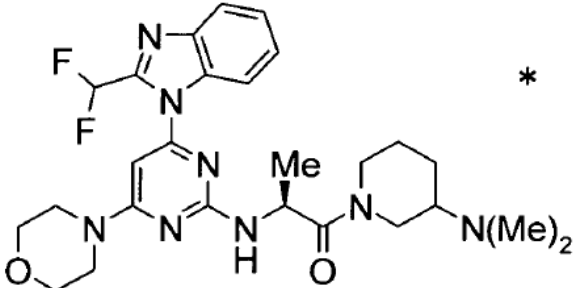
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 200]

Ej	Estr	ESI+	TR
A183#		530	2,48
A184#		544	2,78
A185#		545	1,81
A186#		544	2,58
A187#		545	1,74

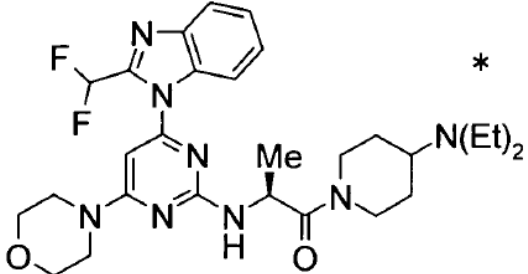
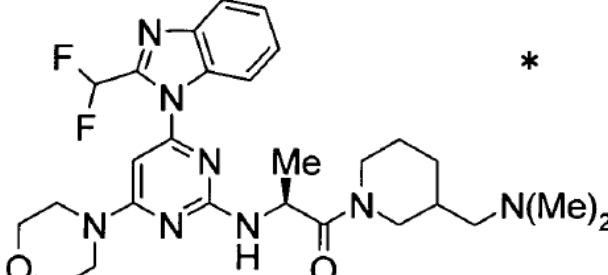
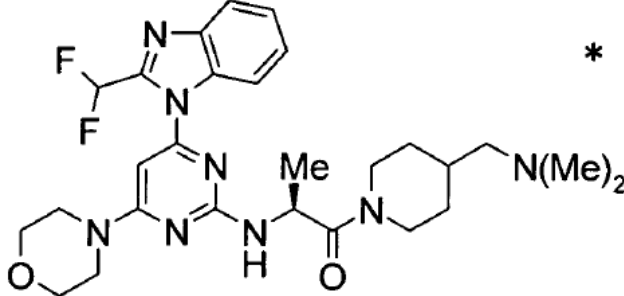
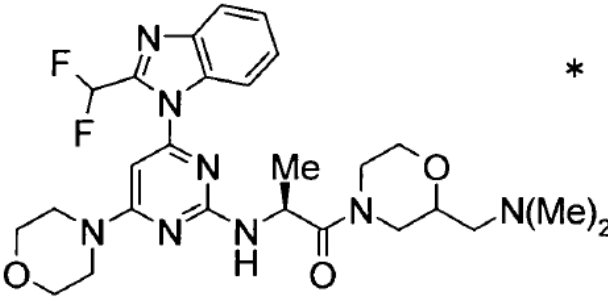
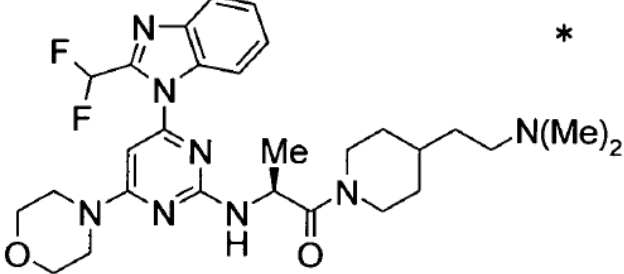
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 201]

Ej	Estr	ESI+	TR
A188#		573	1,85
A189#		575	1,76
A190#		515	1,77
A191#		515	1,76
A192#		529	1,87

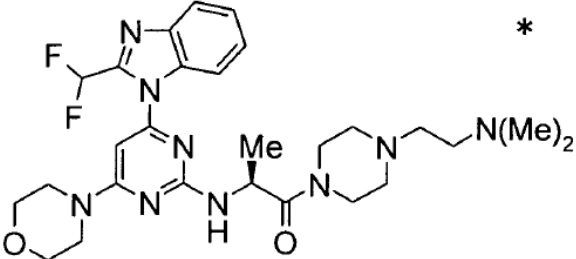
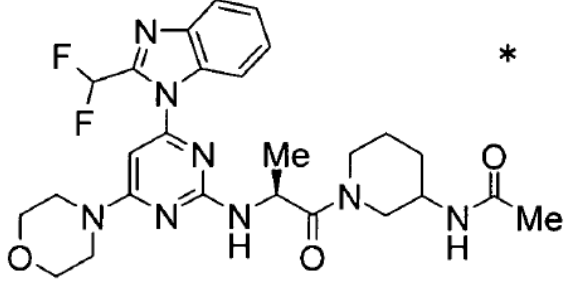
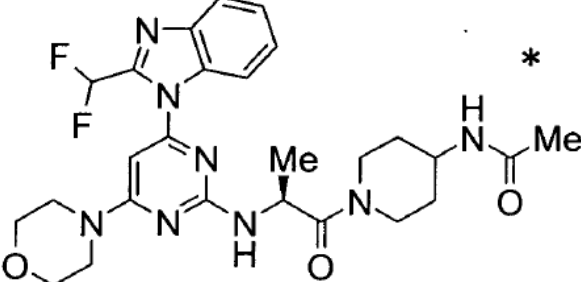
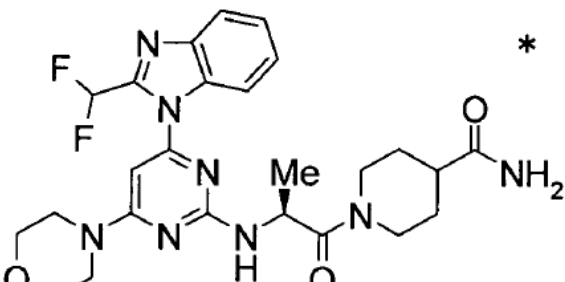
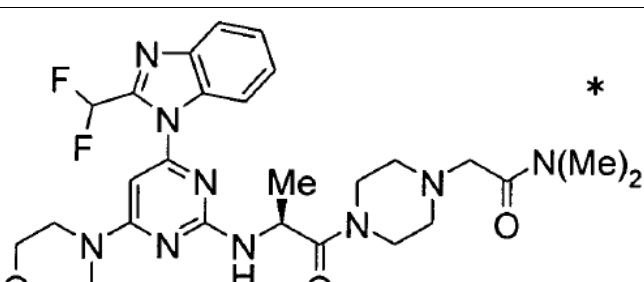
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 202]

Ej	Estr	ESI+	TR
A193#		557	1,85
A194#		543	1,95
A195#		543	1,85
A196#		545	1,81
A197#		557	1,91

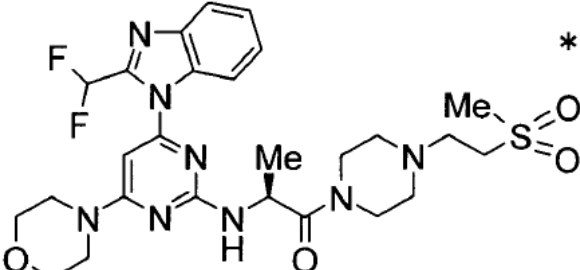
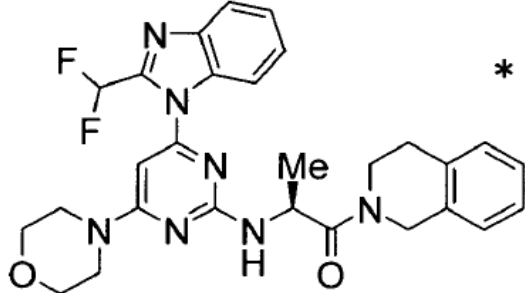
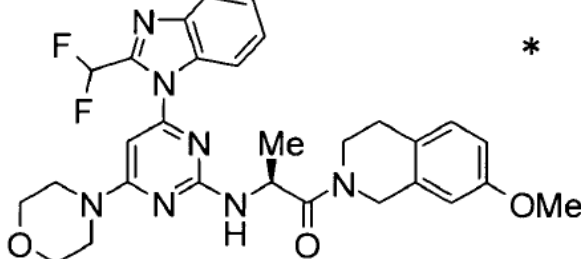
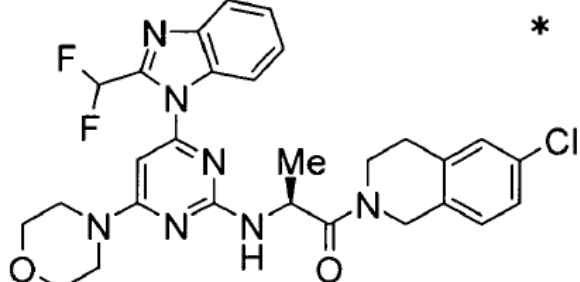
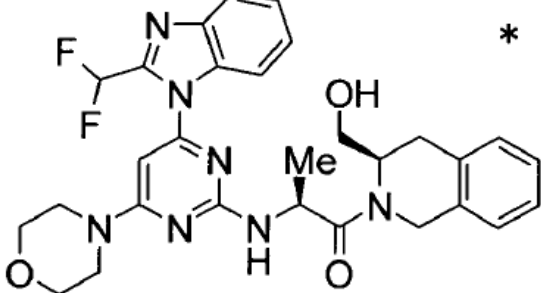
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 203]

Ej	Estr	ESI+	TR
A198#		558	1,82
A199#		543	2,37
A200#		543	2,35
A201#		529	2,26
A202#		572	1,83

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 204]

Ej	Estr	ESI+	TR
A203#		593	2,08
A204#		534	2,84
A205#		564	2,83
A206#		568	2,95
A207#		564	2,71

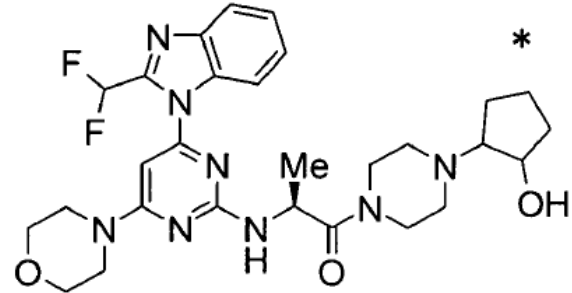
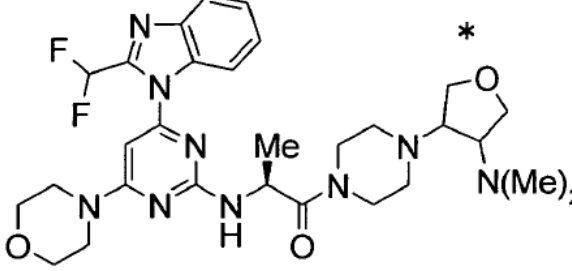
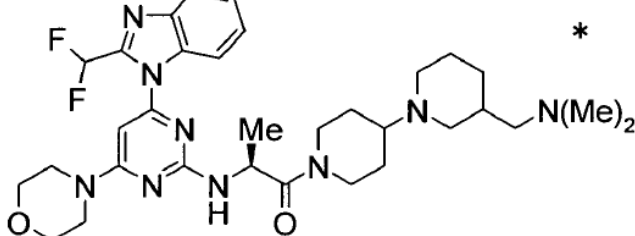
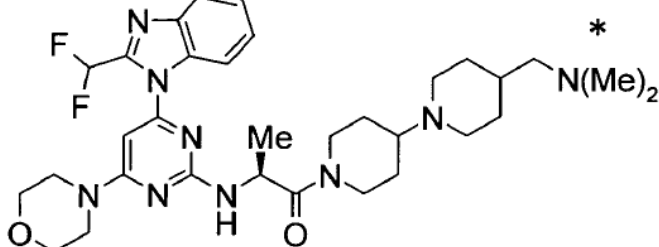
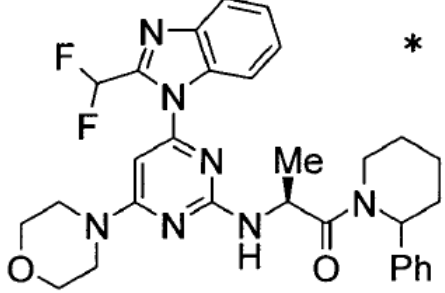
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 205]

Ej	Estr	ESI+	TR
A208#	<p>Chemical structure of compound A208#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a (1S)-1-hydroxy-2-methyl-2-(1,2,3,4-tetrahydroquinolin-2-yl)ethanone group. An asterisk (*) is present in the upper right of the structure.</p>	564	2,71
A209#	<p>Chemical structure of compound A209#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a (1S)-1-methyl-2-(1,2,3,4,5,6-hexahydroindolo[1,2-b]pyridin-2-yl)ethanone group. An asterisk (*) is present in the upper right of the structure.</p>	569	1,89
A210#	<p>Chemical structure of compound A210#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a (1S)-1-methyl-2-(1,2,3,4,5,6-hexahydroindolo[1,2-b]pyridin-2-yl)ethanone group. An asterisk (*) is present in the upper right of the structure.</p>	555	1,84
A211#	<p>Chemical structure of compound A211#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a (1S)-1-methyl-2-(1,2,3,4,5,6-hexahydroindolo[1,2-b]pyridin-2-yl)ethanone group. An asterisk (*) is present in the upper right of the structure.</p>	585	1,81
A212#	<p>Chemical structure of compound A212#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a (1S)-1-methyl-2-(1,2,3,4,5,6-hexahydroindolo[1,2-b]pyridin-2-yl)ethanone group. An asterisk (*) is present in the upper right of the structure.</p>	584	1,56

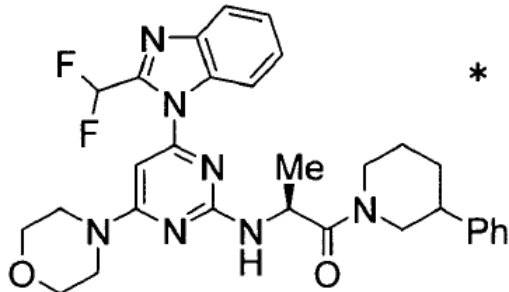
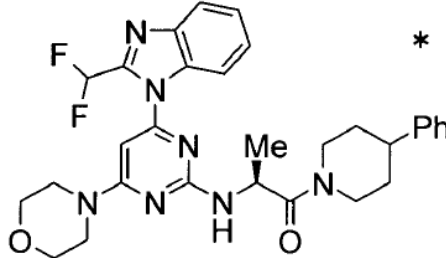
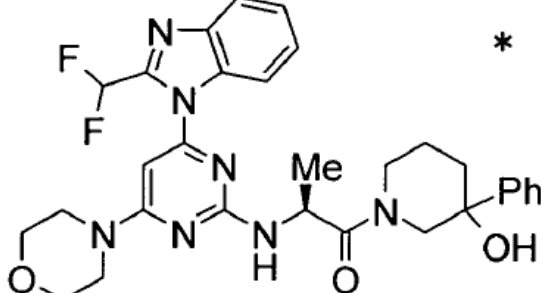
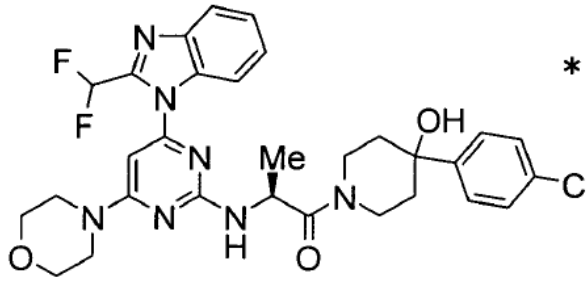
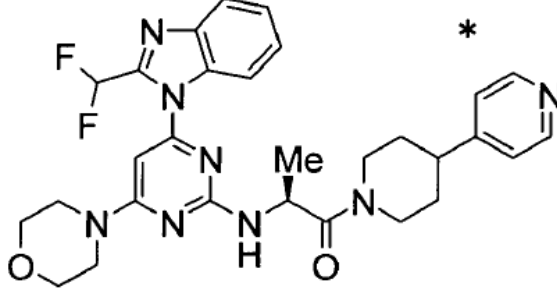
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 206]

Ej	Estr	ESI+	TR
A213#		571	1,81
A214#		600	1,86
A215#		626	1,49
A216#		626	1,48
A217#		562	3,02

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 207]

Ej	Estr	ESI+	TR
A218#		562	3
A219#		562	2,98
A220#		578	2,83
A221#		612	2,86
A222#		563	2,02

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 208]

Ej	Estr	ESI+	TR
A223#	<p>Chemical structure of compound A223#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a methylamino group. The methylamino group is linked to a piperidine ring, which is further substituted with a benzoxazole ring. An asterisk (*) is placed above the benzoxazole ring.</p>	603	2,87
A224#	<p>Chemical structure of compound A224#: Similar to A223#, but the benzoxazole ring is replaced by a benzimidazole ring. An asterisk (*) is placed above the benzimidazole ring.</p>	603	2,34
A225#	<p>Chemical structure of compound A225#: Similar to A223#, but the piperidine ring is substituted with a morpholine ring. An asterisk (*) is placed above the morpholine ring.</p>	583	2,08
A226#	<p>Chemical structure of compound A226#: Similar to A223#, but the piperidine ring is substituted with a morpholine ring. An asterisk (*) is placed above the morpholine ring.</p>	583	1,91
A227#	<p>Chemical structure of compound A227#: Similar to A223#, but the piperidine ring is substituted with a morpholine ring. An asterisk (*) is placed above the morpholine ring.</p>	585	2,08

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 209]

Ej	Estr	ESI+	TR
A228#	<p>Chemical structure of A228#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(piperidin-1-yl)ethanone group. A piperidine ring is attached to the morpholine ring via its nitrogen atom, marked with an asterisk (*).</p>	585	1,98
A229#	<p>Chemical structure of A229#: Similar to A228#, but the piperidine ring is attached to the morpholine ring via its nitrogen atom, which is also substituted with a methyl group. Marked with an asterisk (*).</p>	598	1,46
A230#	<p>Chemical structure of A230#: Similar to A228#, but the piperidine ring is attached to the morpholine ring via its nitrogen atom, which is also substituted with a hydroxyl group. Marked with an asterisk (*).</p>	599	1,92
A231#	<p>Chemical structure of A231#: Similar to A228#, but the piperidine ring is attached to the morpholine ring via its nitrogen atom, which is also substituted with a 1,2,3,4-tetrahydro-1H-indol-5-yl group. Marked with an asterisk (*).</p>	617	3,14
A232#	<p>Chemical structure of A232#: Similar to A228#, but the piperidine ring is attached to the morpholine ring via its nitrogen atom, which is also substituted with a benzyl group (Ph). Marked with an asterisk (*).</p>	576	3,08

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 210]

Ej	Estr	ESI+	TR
A233#	<p>The structure of A233# features a central pyrimidopyrimidine core. At the 2-position, there is a morpholine ring. At the 4-position, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At the 6-position, there is a methylamino group (-NHMe). At the 7-position, there is a piperidine ring substituted with a benzyl group (-CH2Ph). An asterisk (*) is located in the upper right corner of the structure area.</p>	576	3,09
A234#	<p>The structure of A234# is similar to A233#, but the piperidine ring at the 7-position is substituted with a 1-phenylethanol group (-CH(OH)Ph). An asterisk (*) is located in the upper right corner of the structure area.</p>	592	2,79
A235#	<p>The structure of A235# is similar to A233#, but the piperidine ring at the 7-position is substituted with a phenoxymethyl group (-CH2OPh). An asterisk (*) is located in the upper right corner of the structure area.</p>	578	2,97
A236#	<p>The structure of A236# is similar to A233#, but the piperidine ring at the 7-position is substituted with a 3-pyridylmethyl group (-CH2C5H4N). An asterisk (*) is located in the upper right corner of the structure area.</p>	577	2,09
A237#	<p>The structure of A237# is similar to A233#, but the piperidine ring at the 7-position is substituted with a (2S)-pyrrolidin-2-ylmethyl group (-CH2N(C2H4)C(=O)Me). An asterisk (*) is located in the upper right corner of the structure area.</p>	598	1,94

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 211]

Ej	Estr	ESI+	TR
A238#	<p>Chemical structure of compound A238#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(2-phenylethyl)piperidin-1-ylamino group.</p>	590	3,17
A239#	<p>Chemical structure of compound A239#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(2-phenylethanol-1-yl)piperidin-1-ylamino group.</p>	607	2,03
A240#	<p>Chemical structure of compound A240#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(N-ethyl-2-phenylethyl)piperidin-1-ylamino group.</p>	619	2,24
A241#	<p>Chemical structure of compound A241#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(2-phenoxyethyl)piperidin-1-ylamino group.</p>	607	2,2
A242#	<p>Chemical structure of compound A242#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a (S)-1-methyl-2-(N-methyl-2-phenylethyl)piperidin-1-ylamino group.</p>	634	2,23

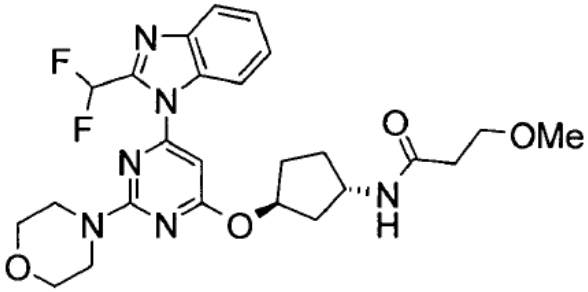
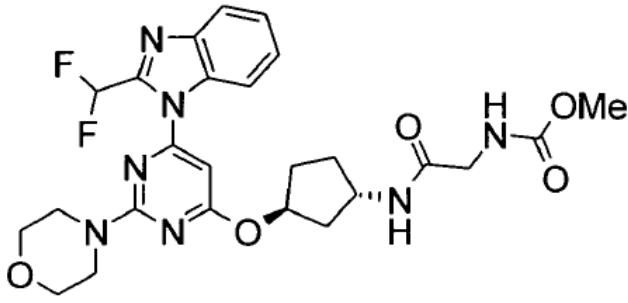
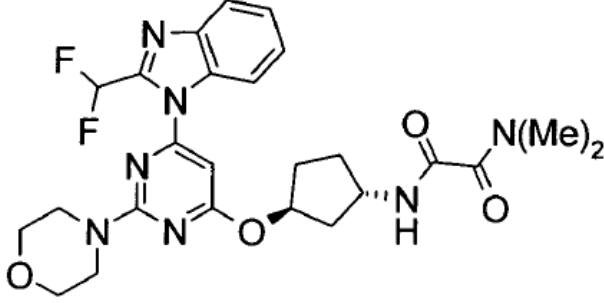
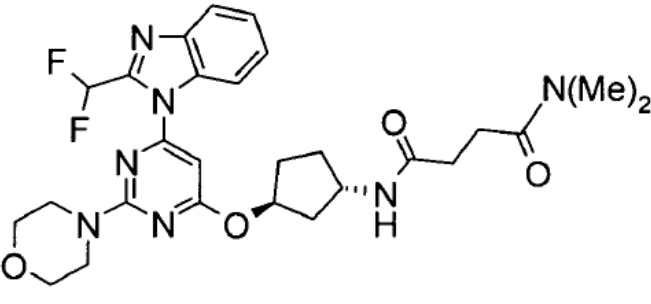
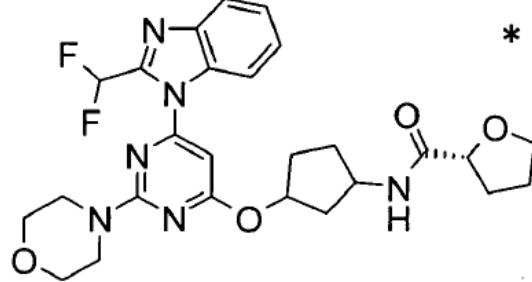
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 212]

Ej	Estr	ESI+	TR
A243#	<p>Chemical structure of compound A243#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, a methyl group, and a piperazine ring. The piperazine ring is further substituted with a propyl chain ending in a benzenesulfonyl group (SO₂Ph). An asterisk (*) is present in the upper right of the structure.</p>	655	2,46
A244#	<p>Chemical structure of compound A244#: Similar to A243#, but the piperazine ring is substituted with a propyl chain ending in a phenyl ether group (OPh). An asterisk (*) is present in the upper right of the structure.</p>	621	2,19
A245#	<p>Chemical structure of compound A245#: Similar to A243#, but the piperazine ring is substituted with a cyclopentane ring. The cyclopentane ring is further substituted with a hydroxyacetyl group (-NHCOCH₂OH). An asterisk (*) is present in the upper right of the structure.</p>	489	2,66
A246#	<p>Chemical structure of compound A246#: Similar to A245#, but the cyclopentane ring is substituted with a hydroxypropyl group (-NHCOCH₂CH₂OH).</p>	503	2,66
A247#	<p>Chemical structure of compound A247#: Similar to A245#, but the cyclopentane ring is substituted with a methoxyacetyl group (-NHCOCH₂OMe).</p>	503	2,8

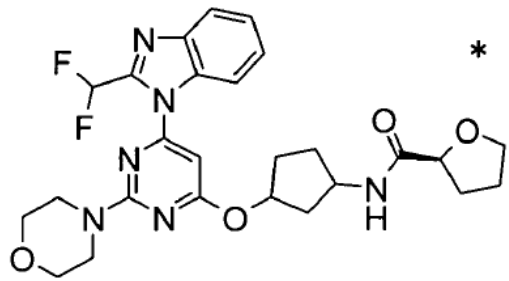
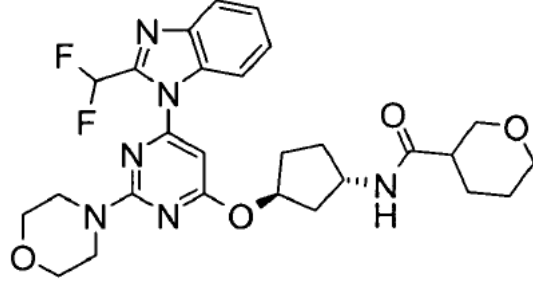
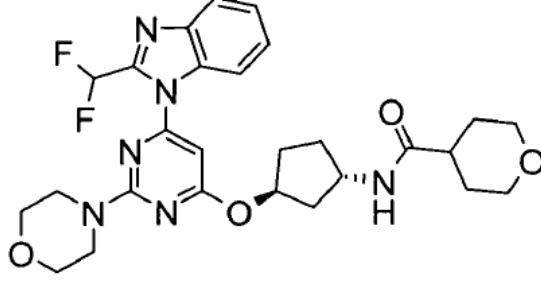
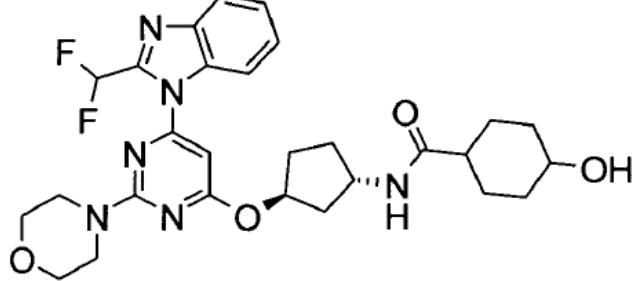
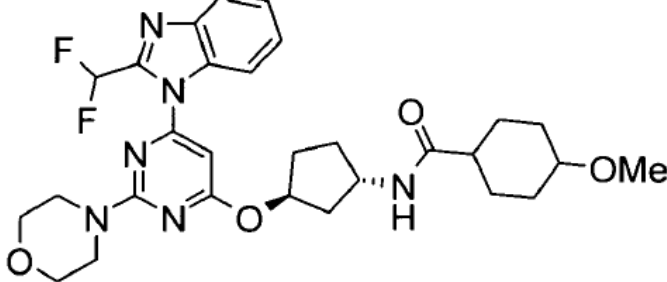
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 213]

Ej	Estr	ESI+	TR
A248#		517	2,78
A249#		546	2,69
A250#		530	2,72
A251#		558	2,75
A252#		529	2,88

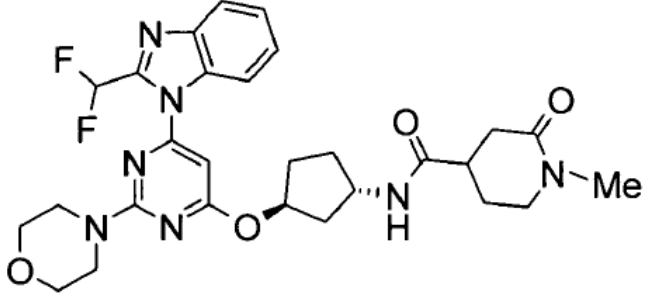
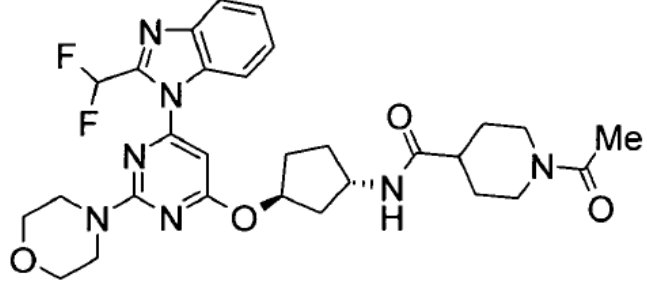
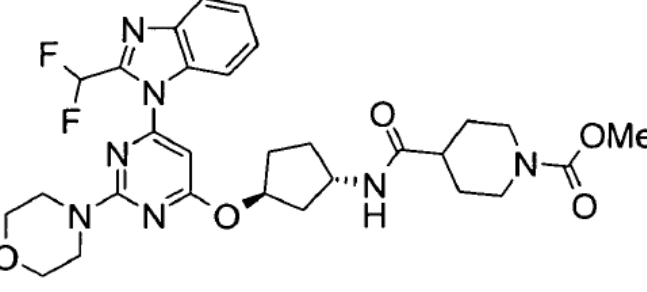
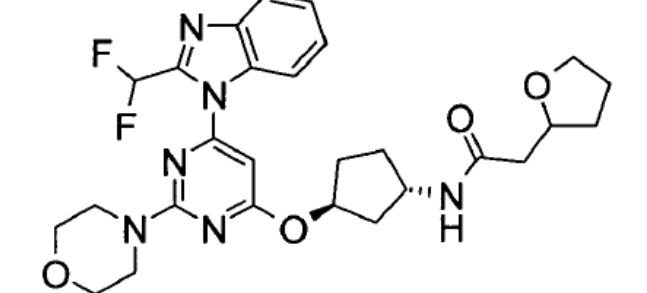
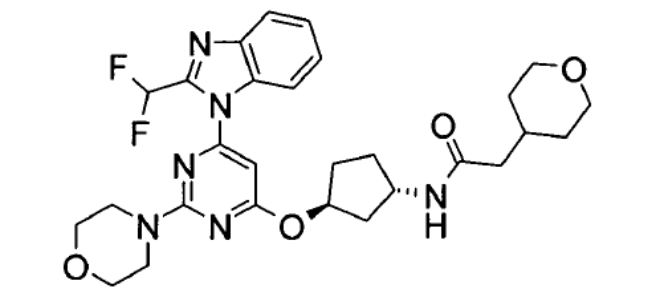
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 214]

Ej	Estr	ESI+	TR
A253#		529	2,88
A254#		543	2,88
A255#		543	2,81
A256#		557	2,79
A257#		571	2,97

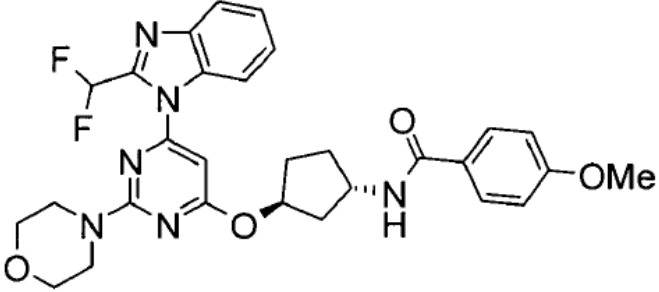
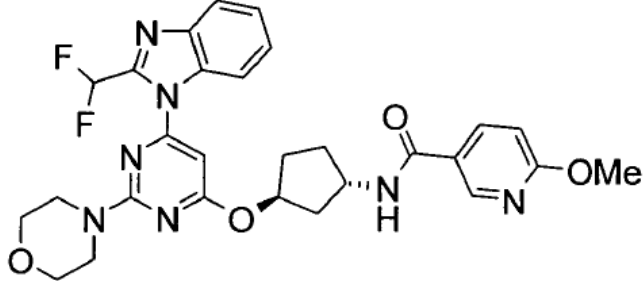
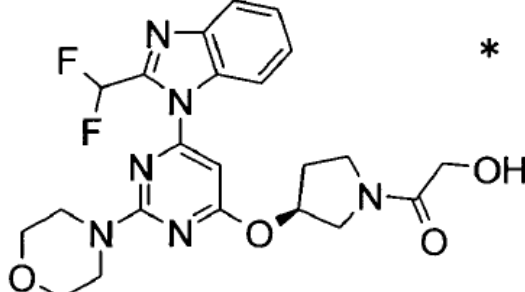
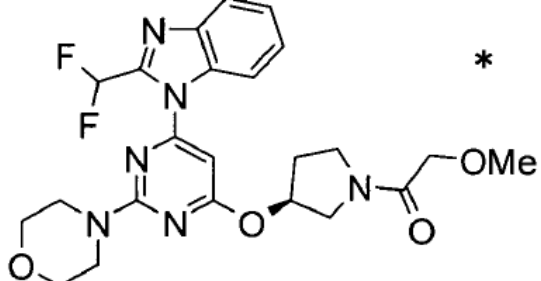
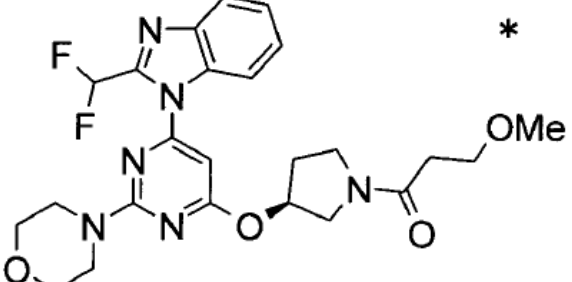
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 215]

Ej	Estr	ESI+	TR
A258#		570	2,7
A259#		584	2,74
A260#		600	2,88
A261#		543	2,87
A262#		557	2,86

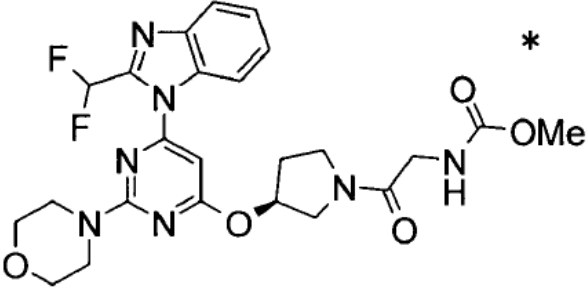
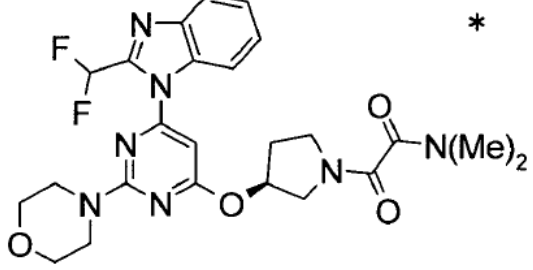
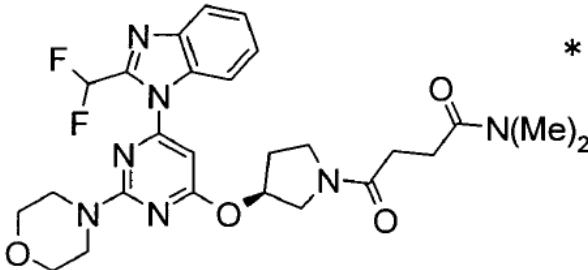
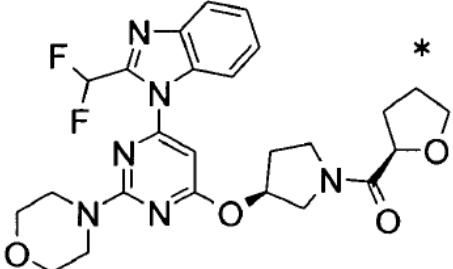
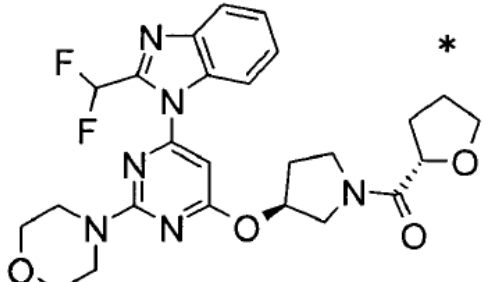
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 216]

Ej	Estr	ESI+	TR
A263#		565	3,02
A264#		566	3
A265#		475	2,46
A266#		489	2,57
A267#		503	2,65

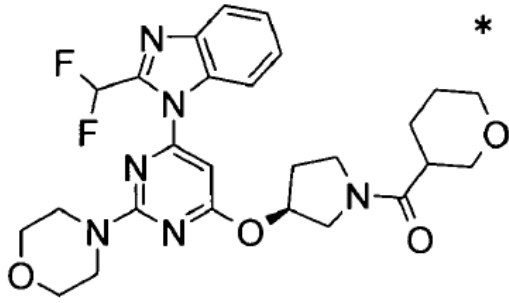
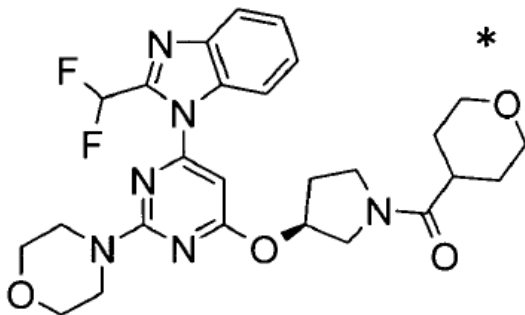
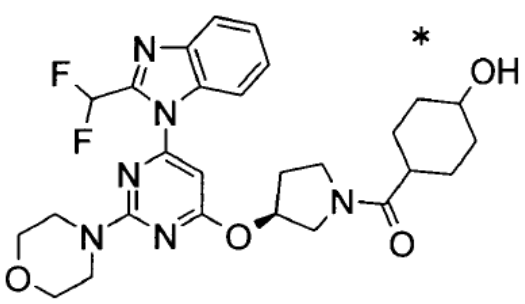
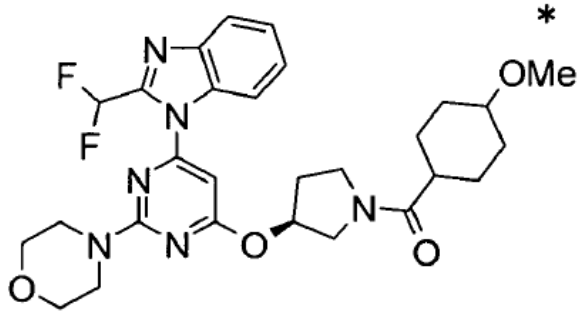
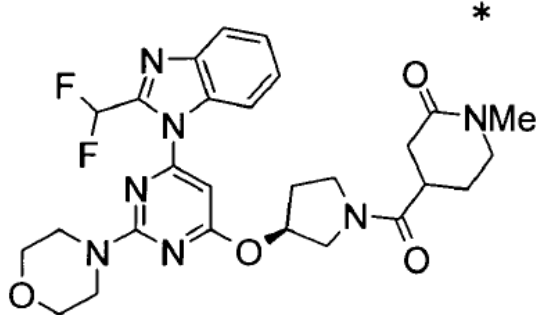
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 217

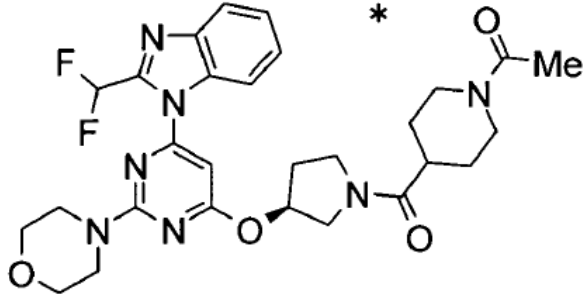
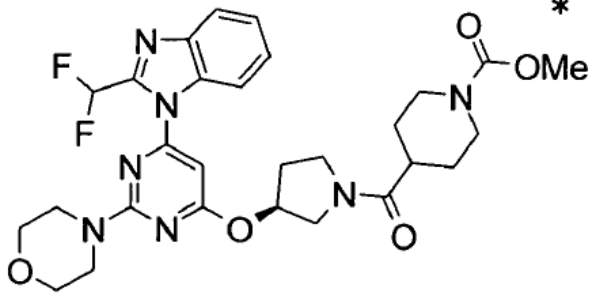
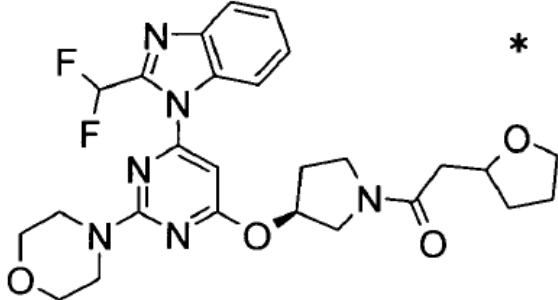
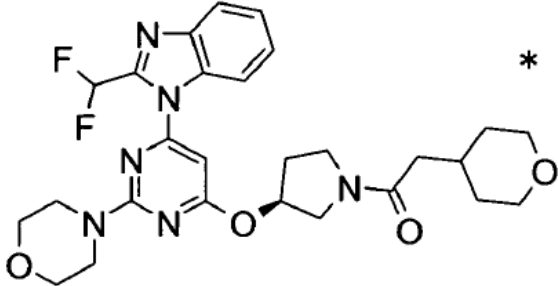
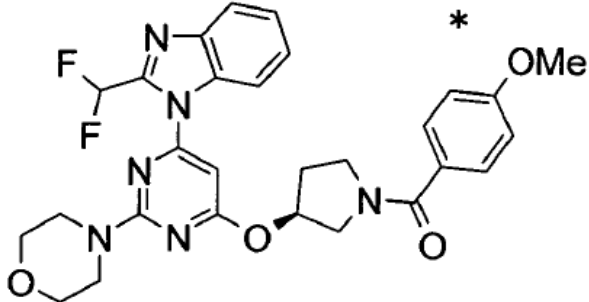
Ej	Estr	ESI+	TR
A268#		532	2,54
A269#		516	2,49
A270#		544	2,6
A271		515	2,68
A272		515	2,69

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 218]

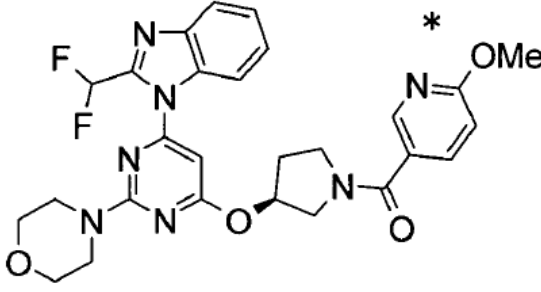
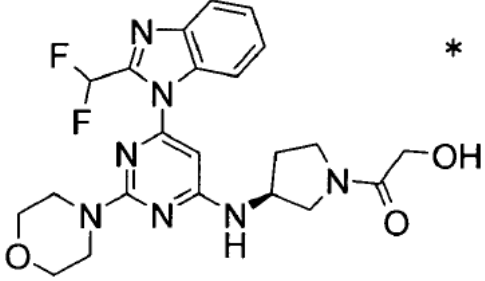
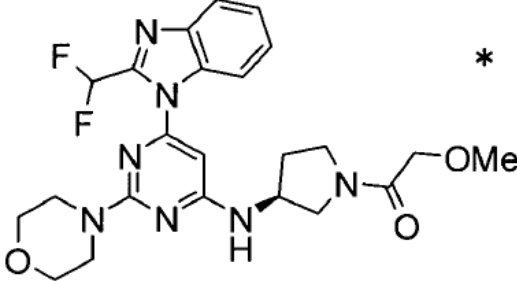
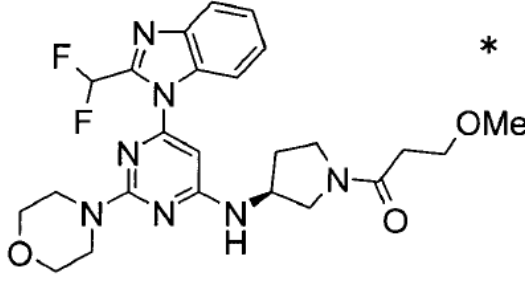
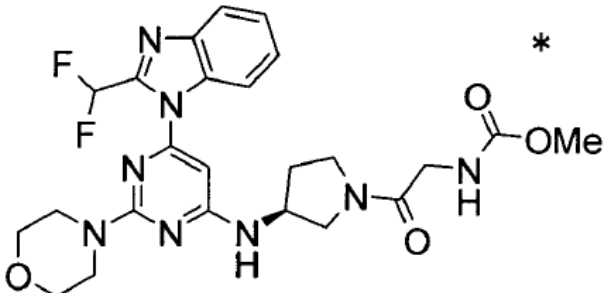
Ej	Estr	ESI+	TR
A273		529	2,72
A274		529	2,64
A275		543	2,7
A276		557	2,88
A277		556	2,5

[Tabla 219]

Ej	Estr	ESI+	TR
A278		570	2,55
A279		586	2,72
A280		529	2,74
A281		543	2,74
A282#		551	2,9

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 220]

Ej	Estr	ESI+	TR
A283#		552	2,83
A284#		474	2,4
A285#		488	2,51
A286#		502	2,59
A287#		531	2,49

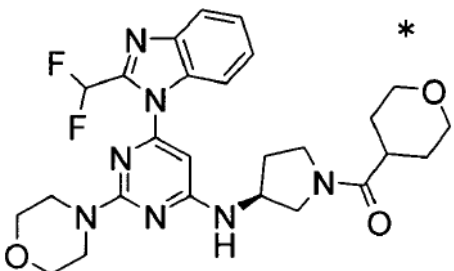
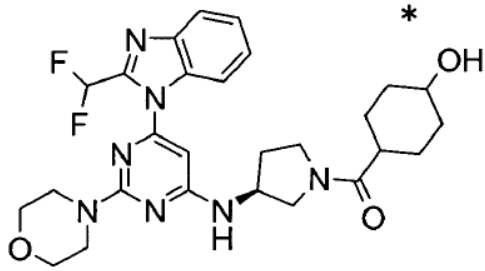
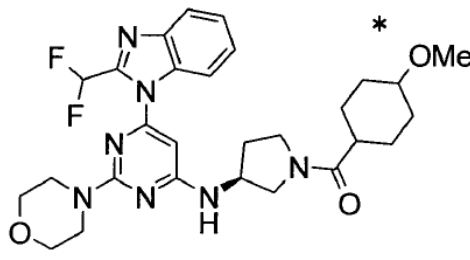
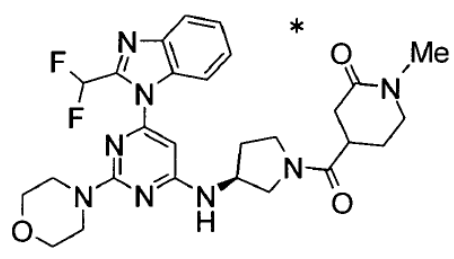
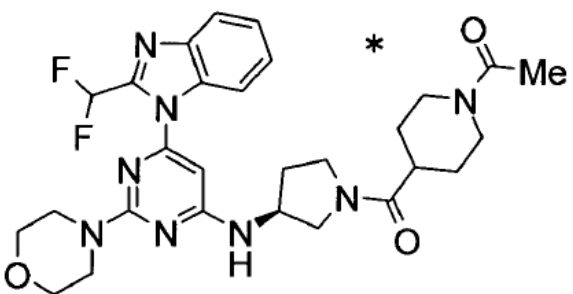
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 221]

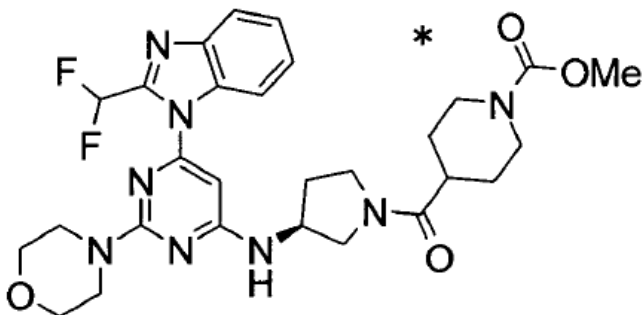
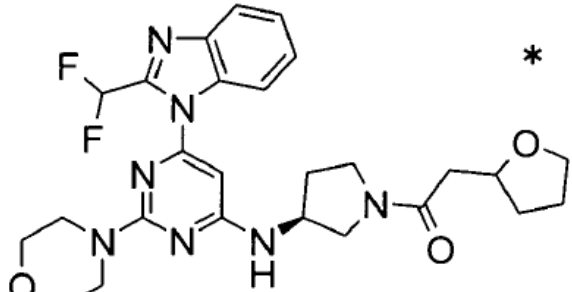
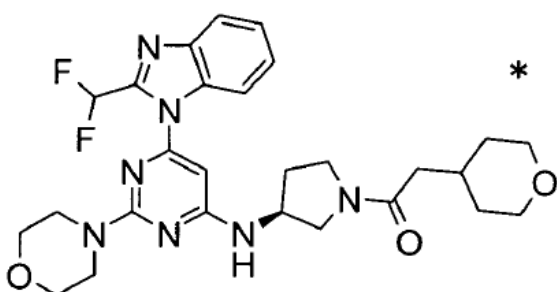
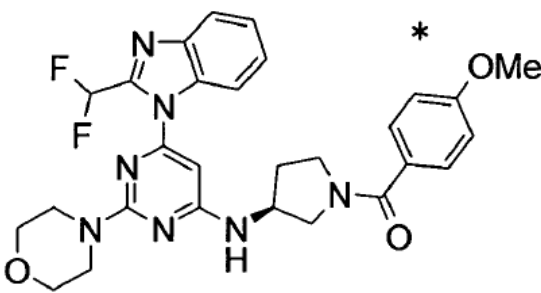
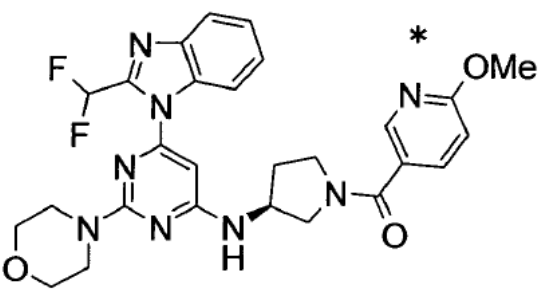
Ej	Estr	ESI+	TR
A288#	<p>Chemical structure of compound A288#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 1H-pyrazol-5-yl group at position 4, and a (S)-1-(dimethylamino)propan-2-yl group at position 6. The pyrazole ring has a difluoromethyl group at position 3. An asterisk (*) is present in the upper right of the structure.</p>	515	2,43
A289#	<p>Chemical structure of compound A289#: Similar to A288#, but the propan-2-yl group is replaced by a 3-(dimethylamino)propan-1-yl group. An asterisk (*) is present in the upper right of the structure.</p>	543	2,56
A290	<p>Chemical structure of compound A290#: Similar to A288#, but the propan-2-yl group is replaced by a (S)-1-(oxolan-2-yl)ethan-1-yl group. An asterisk (*) is present in the upper right of the structure.</p>	514	2,62
A291	<p>Chemical structure of compound A291#: Similar to A290, but the oxolan-2-yl group is attached to the propan-2-yl chain with a dashed bond, indicating a different stereochemistry. An asterisk (*) is present in the upper right of the structure.</p>	514	2,62
A292	<p>Chemical structure of compound A292#: Similar to A288#, but the propan-2-yl group is replaced by a (S)-1-(tetrahydro-2H-pyran-2-yl)ethan-1-yl group. An asterisk (*) is present in the upper right of the structure.</p>	528	2,66

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 222]

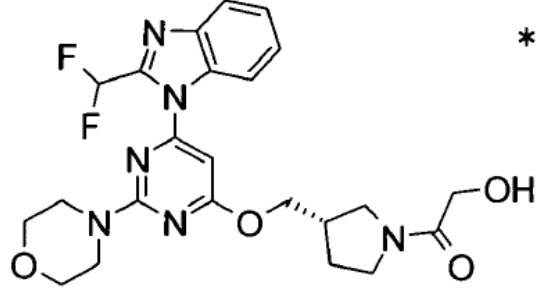
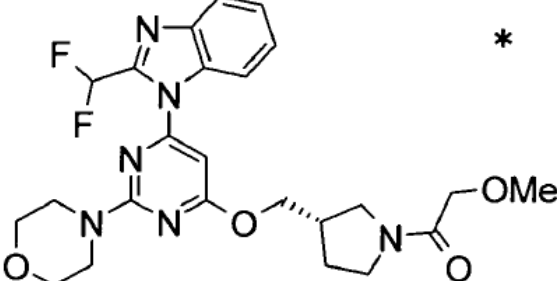
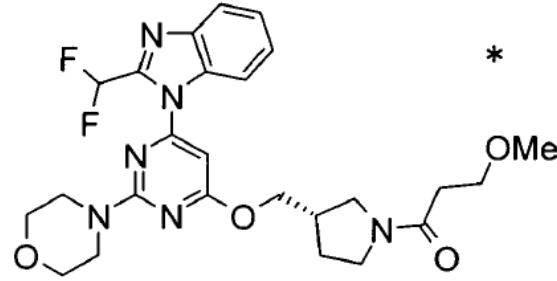
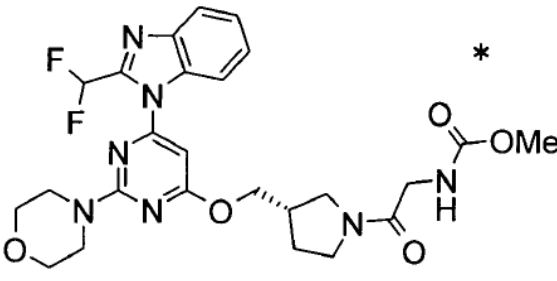
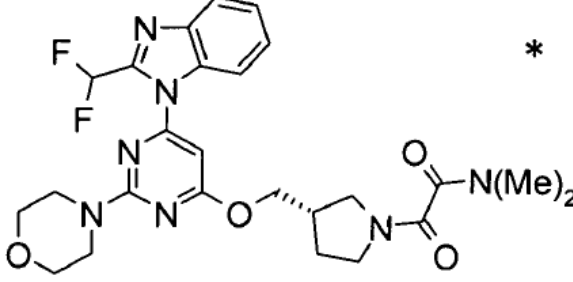
Ej	Estr	ESI+	TR
A293		528	2,59
A294		542	2,65
A295		556	2,83
A296		555	2,46
A297		569	2,5

[Tabla 223]

Ej	Estr	ESI+	TR
A298		585	2,68
A299		528	2,68
A300		542	2,66
A301#		550	2,83
A302#		551	2,76

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 224]

Ej	Estr	ESI+	TR
A303#		489	2,57
A304#		503	2,68
A305#		517	2,76
A306#		546	2,64
A307#		530	2,57

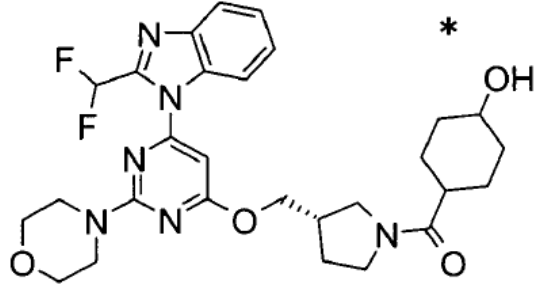
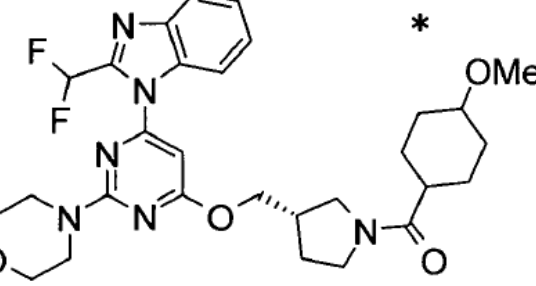
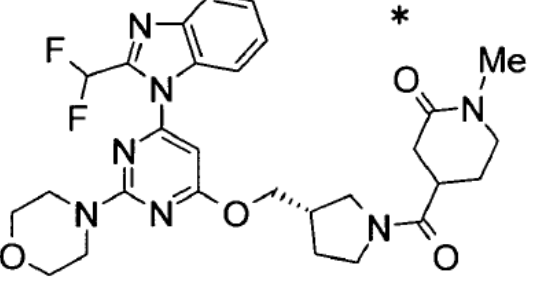
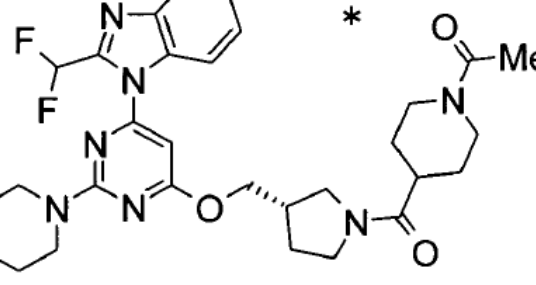
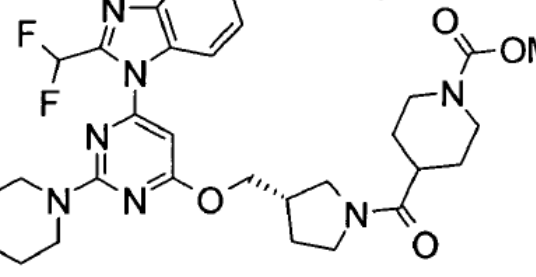
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 225]

Ej	Estr	ESI+	TR
A308#	<p>Chemical structure of compound A308#: A pyridine ring substituted with a morpholine group at the 2-position, a 1H-benzotriazol-2-ylidene group at the 3-position, and a 2-(dimethylamino)propyl ether group at the 4-position. The ether group is attached to the 2-position of a pyrrolidine ring. An asterisk (*) is present in the upper right of the structure.</p>	558	2,7
A309#	<p>Chemical structure of compound A309#: Similar to A308#, but the pyrrolidine ring is substituted with a tetrahydrofuran-2-yl group at the 2-position. An asterisk (*) is present in the upper right of the structure.</p>	529	2,78
A310#	<p>Chemical structure of compound A310#: Similar to A309#, but the tetrahydrofuran ring is substituted with a morpholine ring at the 2-position. An asterisk (*) is present in the upper right of the structure.</p>	529	2,78
A311#	<p>Chemical structure of compound A311#: Similar to A310#, but the morpholine ring is substituted with a piperidine ring at the 2-position. An asterisk (*) is present in the upper right of the structure.</p>	543	2,82
A312#	<p>Chemical structure of compound A312#: Similar to A311#, but the piperidine ring is substituted with a morpholine ring at the 2-position. An asterisk (*) is present in the upper right of the structure.</p>	543	2,75

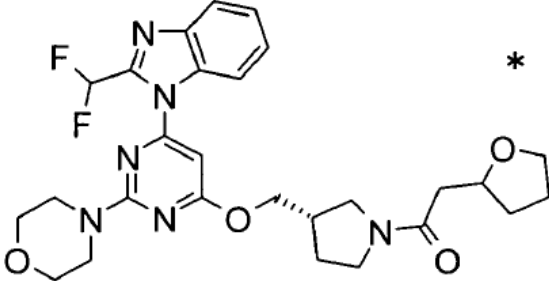
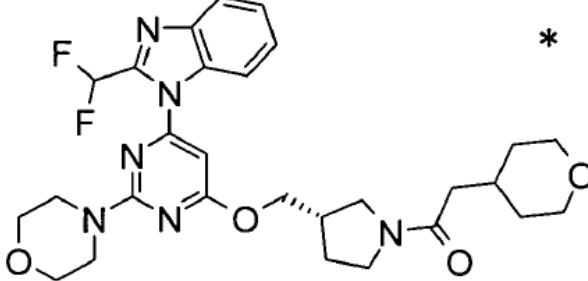
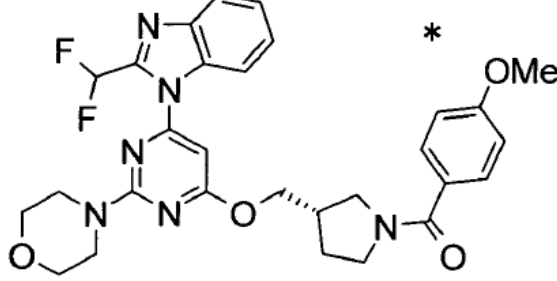
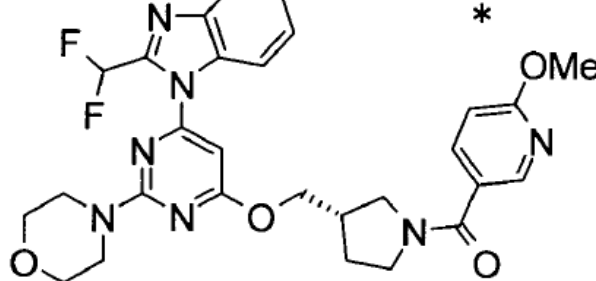
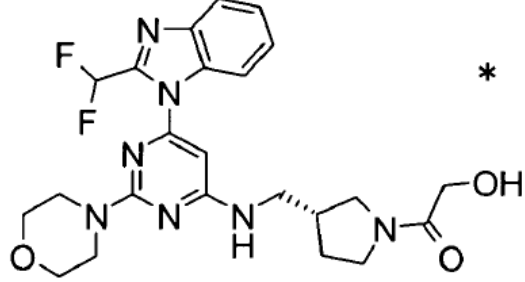
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 226]

Ej	Estr	ESI+	TR
A313#		557	2,8
A314#		571	2,97
A315#		570	2,61
A316#		584	2,65
A317#		600	2,82

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 227]

Ej	Estr	ESI+	TR
A318#		543	2,84
A319#		557	2,83
A320#		565	2,97
A321#		566	2,9
A322#		488	2,44

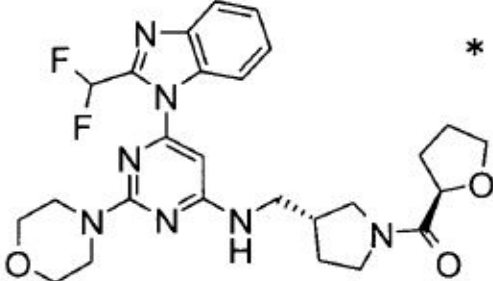
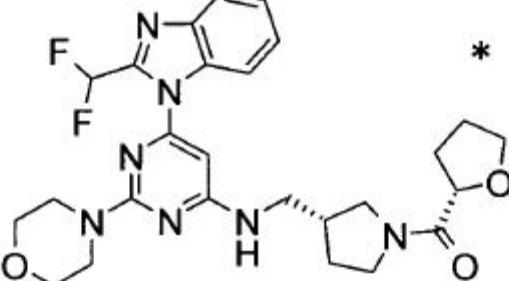
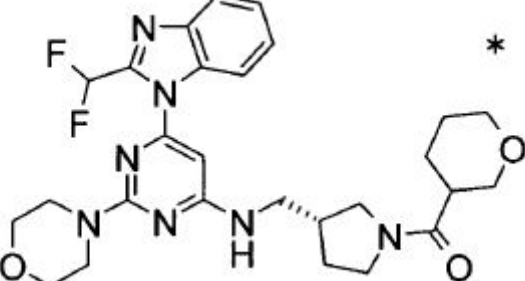
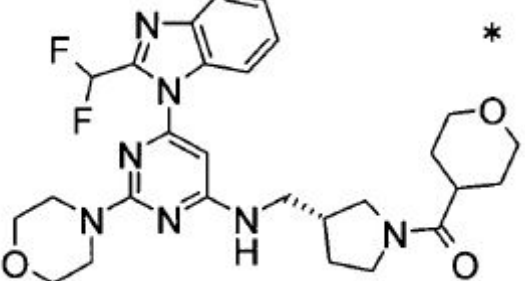
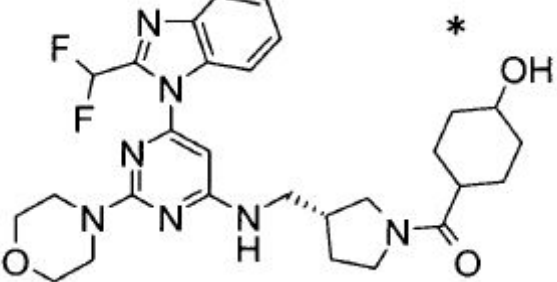
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 228]

Ej	Estr	ESI+	TR
A323#	<p>Chemical structure of compound A323#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-1-(methoxycarbonyl)pyrrolidin-2-ylamino group.</p>	502	2,54
A324#	<p>Chemical structure of compound A324#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-1-(3-methoxypropyl)pyrrolidin-2-ylamino group.</p>	516	2,62
A325#	<p>Chemical structure of compound A325#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-1-(methoxycarbonylamino)pyrrolidin-2-ylamino group.</p>	545	2,52
A326#	<p>Chemical structure of compound A326#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-1-(dimethylamino)pyrrolidin-2-ylamino group.</p>	529	2,45
A327#	<p>Chemical structure of compound A327#: A central pyrimidopyrimidine core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a (S)-1-(3-(dimethylamino)propyl)pyrrolidin-2-ylamino group.</p>	557	2,58

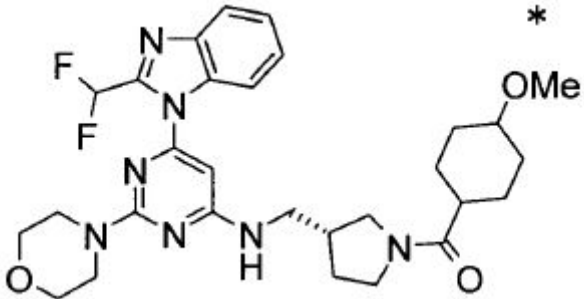
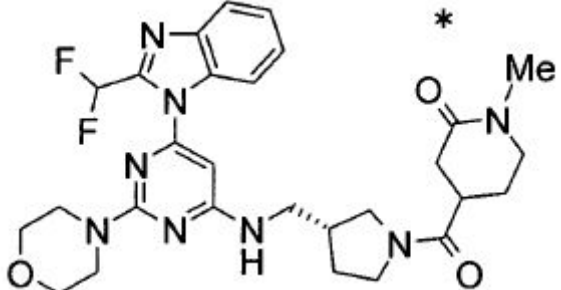
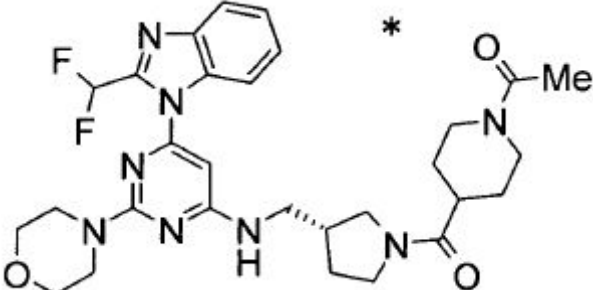
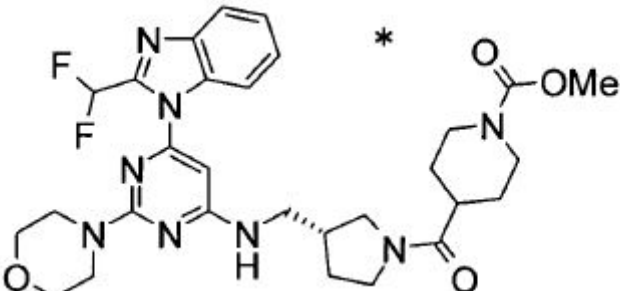
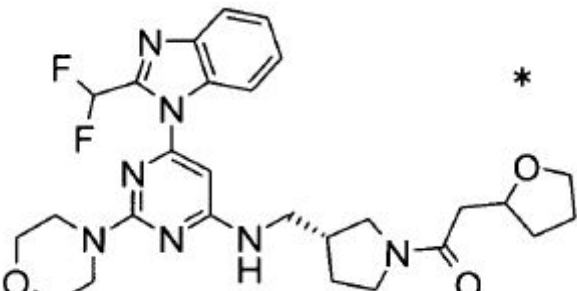
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 229]

Ej	Estr	ESI+	TR
A328#		528	2,65
A329#		528	2,65
A330#		542	2,69
A331#		542	2,62
A332#		556	2,66

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 230]

Ej	Estr	ESI+	TR
A333#		570	2,85
A334#		569	2,48
A335#		583	2,53
A336#		599	2,7
A337#		542	2,71

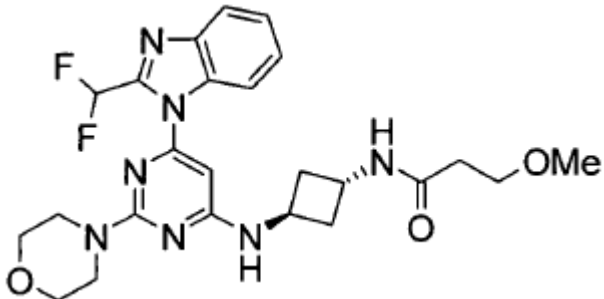
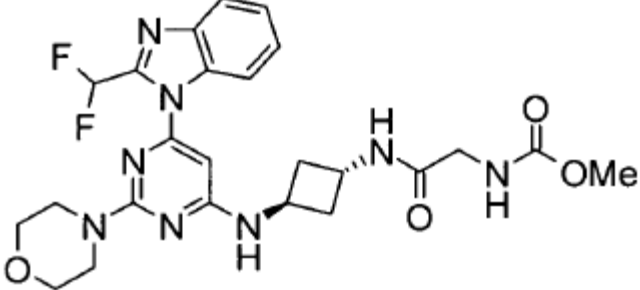
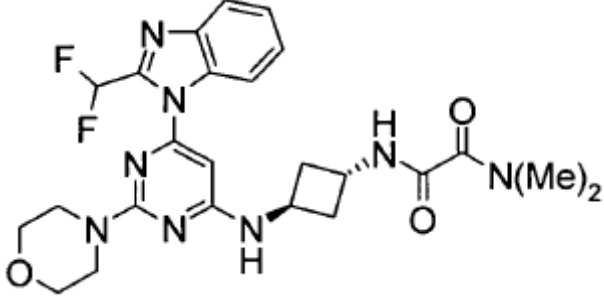
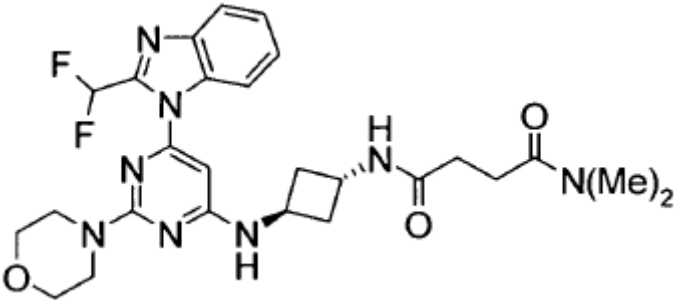
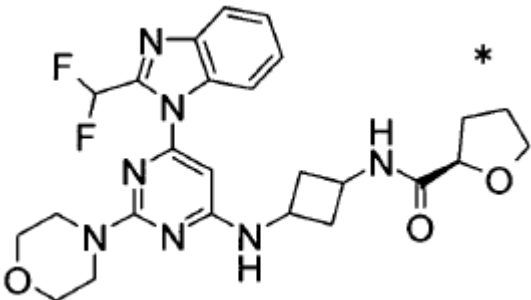
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 231]

Ej	Estr	ESI+	TR
A338#	<p>The structure of A338# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a phenyl ring at the 6-position. The 5-position is linked via an amide bond to a cyclopentane ring, which is further substituted with a morpholinepropyl chain. An asterisk (*) is placed above the structure.</p>	556	2,69
A339#	<p>The structure of A339# is similar to A338# but the morpholinepropyl chain is replaced by a 4-methoxyphenylpropyl chain. An asterisk (*) is placed above the structure.</p>	564	2,83
A340#	<p>The structure of A340# is similar to A338# but the morpholinepropyl chain is replaced by a 4-methoxypyridin-3-ylpropyl chain. An asterisk (*) is placed above the structure.</p>	565	2,76
A341#	<p>The structure of A341# is similar to A338# but the morpholinepropyl chain is replaced by a cyclobutane ring substituted with a hydroxyacetyl group. An asterisk (*) is placed above the structure.</p>	474	2,42
A342#	<p>The structure of A342# is similar to A338# but the morpholinepropyl chain is replaced by a cyclobutane ring substituted with a methoxyacetyl group. An asterisk (*) is placed above the structure.</p>	488	2,6

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 232]

Ej	Estr	ESI+	TR
A343#		502	2,58
A344#		531	2,47
A345#		515	2,49
A346#		543	2,53
A347#		514	2,68

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 233]

Ej	Estr	ESI+	TR
A348#	<p>The structure of A348# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. The 5-position of the core is linked via an amide bond to a cyclobutane ring, which is further substituted with an amide group connected to a tetrahydrofuran ring. An asterisk (*) is placed above the tetrahydrofuran ring, indicating it is not claimed.</p>	514	2,68
A349#	<p>The structure of A349# is similar to A348# but the tetrahydrofuran ring is replaced by a piperidine ring.</p>	528	2,69
A350#	<p>The structure of A350# is similar to A349# but the piperidine ring is substituted with a hydroxyl group (-OH).</p>	528	2,61
A351#	<p>The structure of A351# is similar to A350# but the piperidine ring is substituted with a methoxy group (-OMe).</p>	542	2,61
A352#	<p>The structure of A352# is similar to A351# but the piperidine ring is substituted with a methoxy group (-OMe).</p>	556	2,82

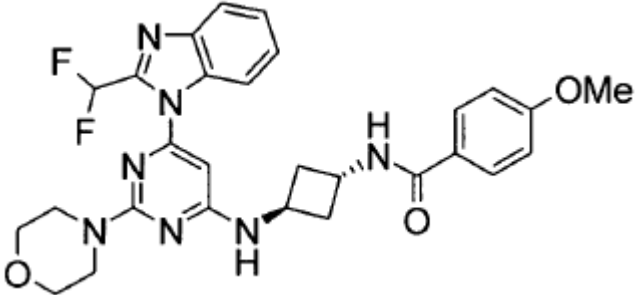
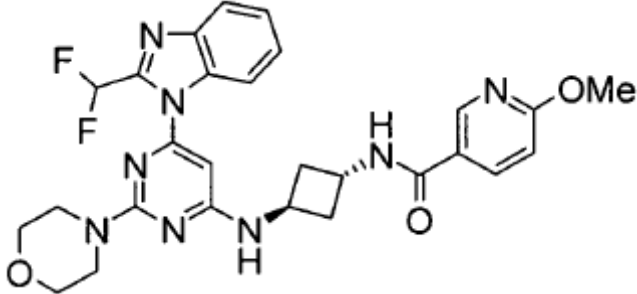
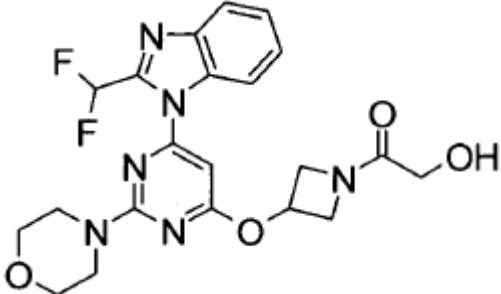
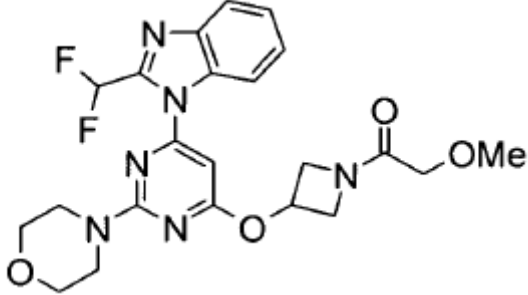
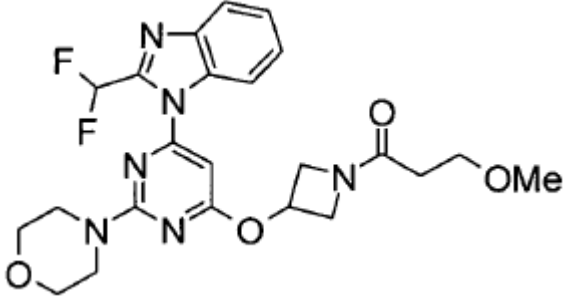
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 234]

Ej	Estr	ESI+	TR
A353#	<p>The structure of A353# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclobutylamino group at the 6-position. The cyclobutylamino group is further substituted with a piperidin-2-ylmethylcarbamoyl group.</p>	555	2,49
A354#	<p>The structure of A354# is similar to A353#, but the piperidin-2-ylmethylcarbamoyl group is replaced by a piperidin-1-ylmethylcarbamoyl group.</p>	596	2,53
A355#	<p>The structure of A355# is similar to A353#, but the piperidin-2-ylmethylcarbamoyl group is replaced by a methyl piperidin-1-ylmethylcarbamoyl group.</p>	585	2,71
A356#	<p>The structure of A356# is similar to A353#, but the piperidin-2-ylmethylcarbamoyl group is replaced by a (2S)-2-(oxolan-2-yl)acetamide group.</p>	528	2,68
A357#	<p>The structure of A357# is similar to A353#, but the piperidin-2-ylmethylcarbamoyl group is replaced by a (2S)-2-(piperidin-2-yl)acetamide group.</p>	542	2,66

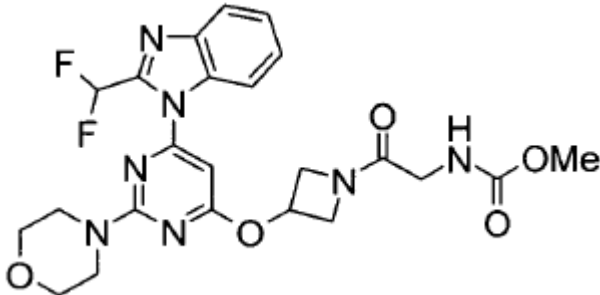
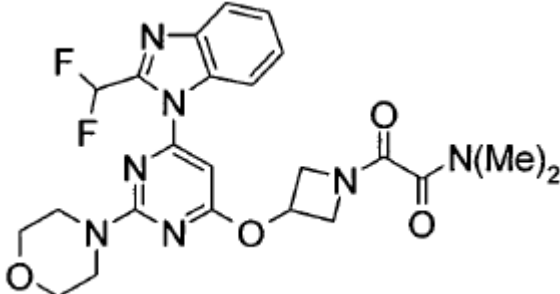
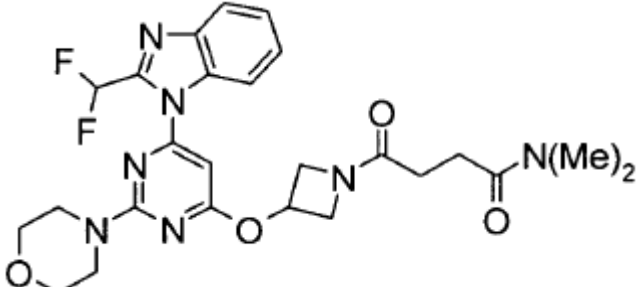
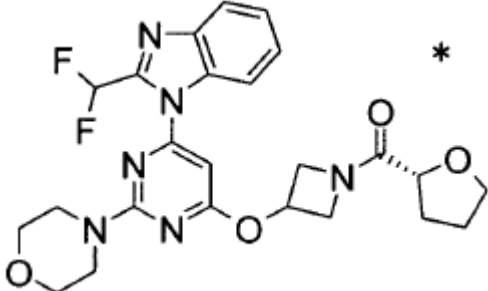
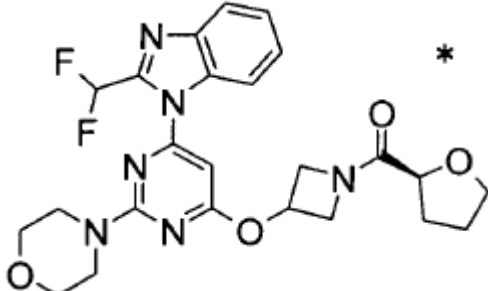
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 235]

Ej	Estr	ESI+	TR
A358#		550	2,87
A359#		551	2,84
A360#		461	2,4
A361#		475	2,58
A362#		489	2,61

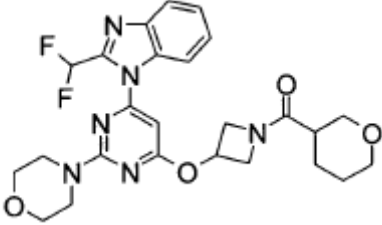
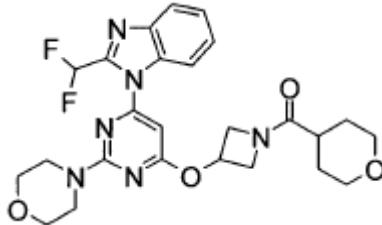
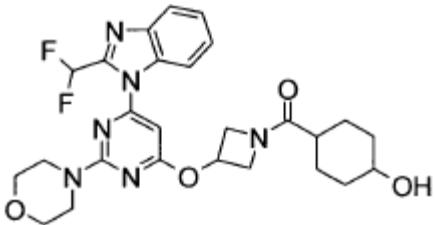
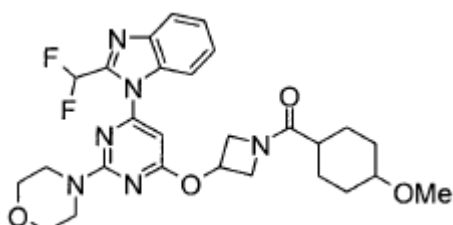
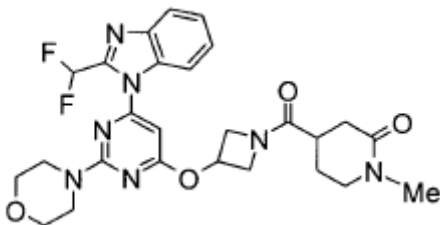
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 236]

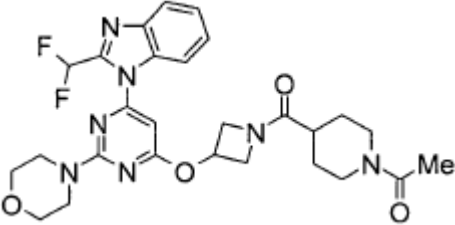
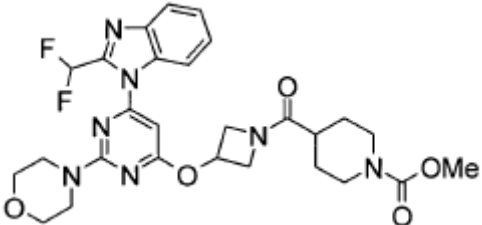
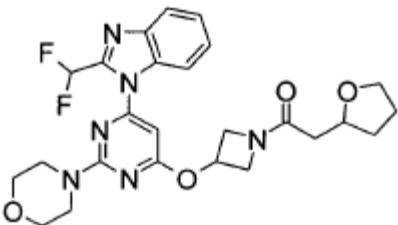
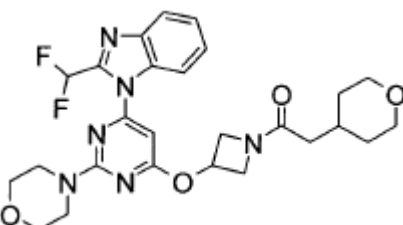
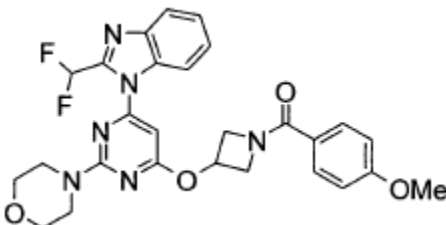
Ej	Estr	ESI+	TR
A363#		518	2,49
A364#		502	2,49
A365#		530	2,56
A366		501	2,7
A367		501	2,7

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 237]

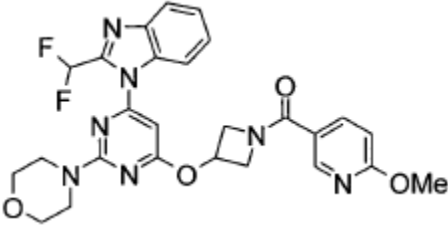
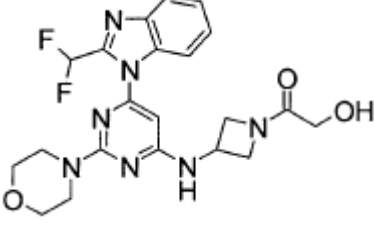
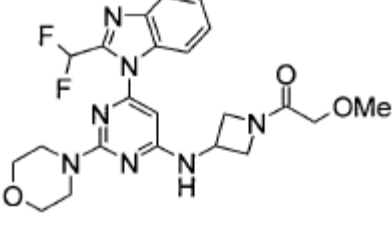
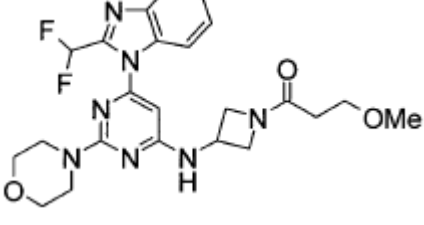
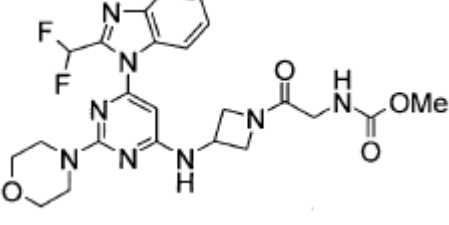
Ej	Estr	ESI+	TR
A368		515	2,69
A369		515	2,61
A370		529	2,66
A371		543	2,86
A372		542	2,46

[Tabla 238]

Ej	Estr	ESI+	TR
A373		556	2,51
A374		572	2,7
A375		515	2,7
A376		529	2,69
A377#		537	2,92

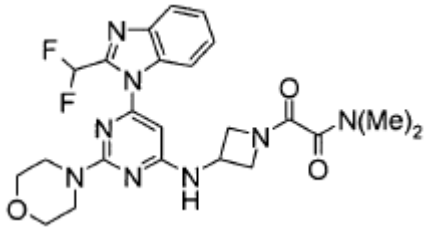
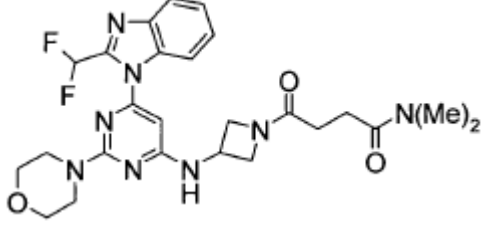
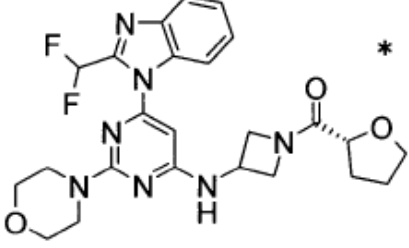
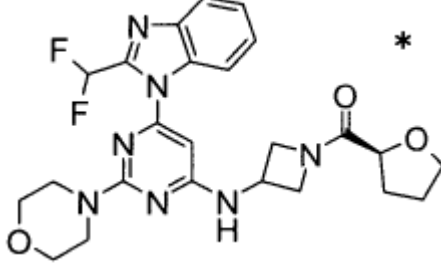
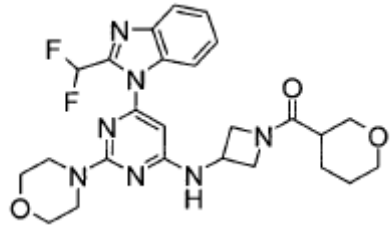
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 239]

Ej	Estr	ESI+	TR
A378#		538	2,85
A379#		460	2,32
A380#		474	2,49
A381#		488	2,54
A382#		517	2,43

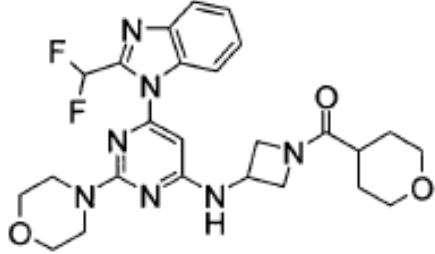
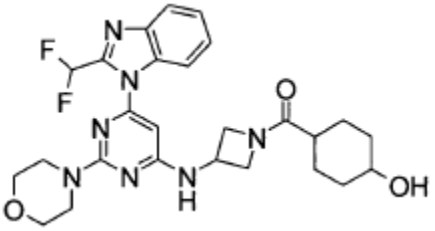
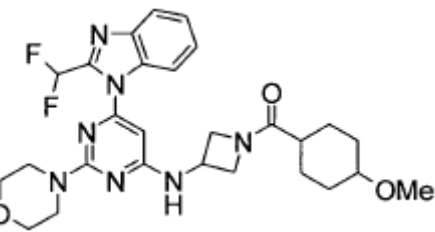
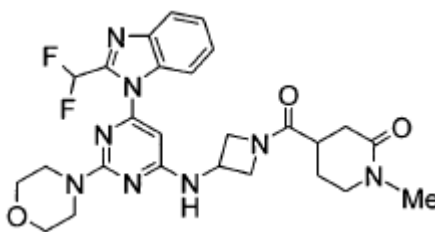
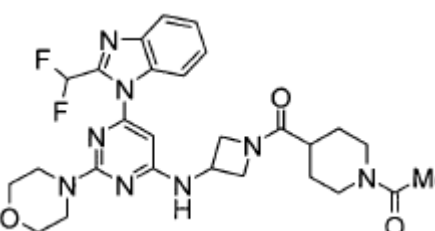
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 240]

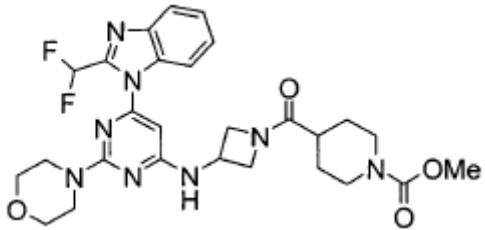
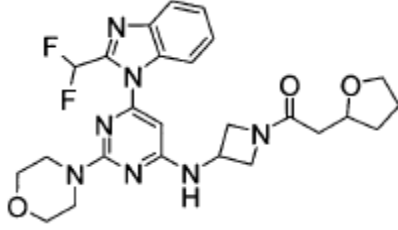
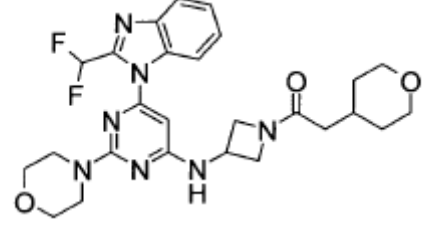
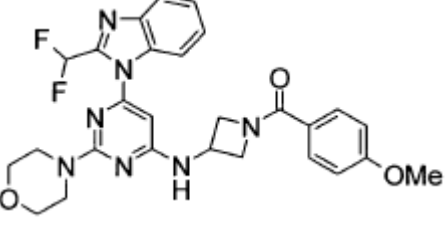
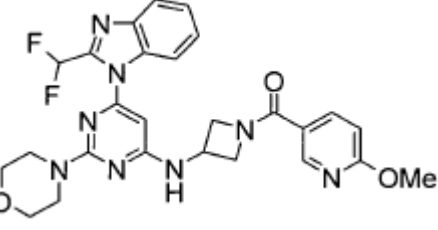
Ej	Estr	ESI+	TR
A383#		501	2,41
A384#		529	2,5
A385		500	2,61
A386		500	2,61
A387		514	2,62

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 241]

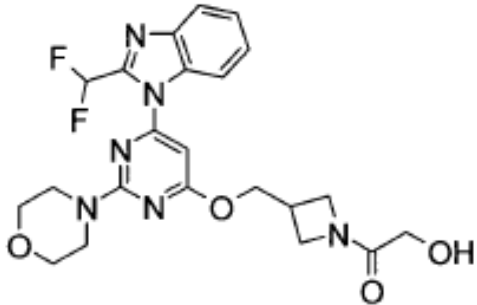
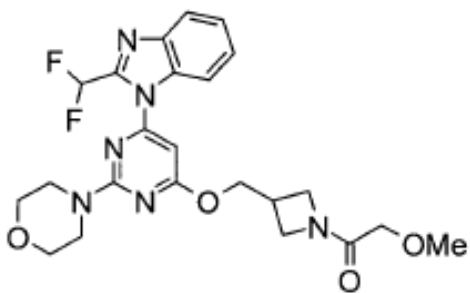
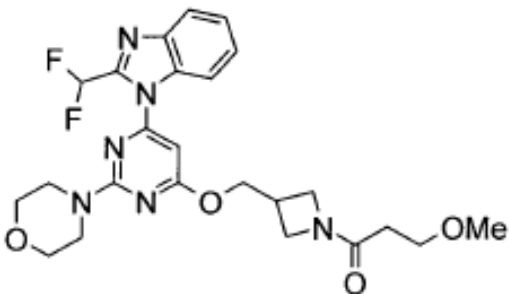
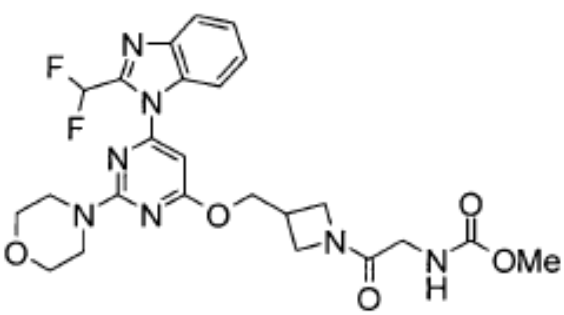
Ej	Estr	ESI+	TR
A388		514	2,53
A389		528	2,6
A390		542	2,8
A391		541	2,39
A392		555	2,44

[Tabla 242]

Ej	Estr	ESI+	TR
A393		571	2,63
A394		514	2,64
A395		528	2,62
A396#		536	2,83
A397#		537	2,77

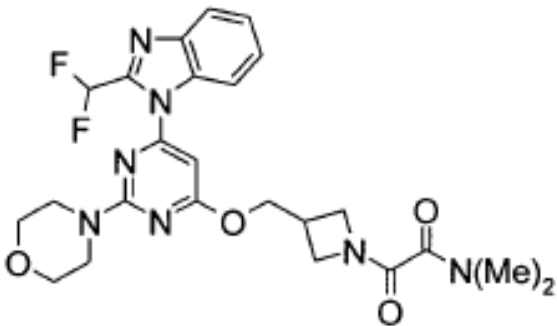
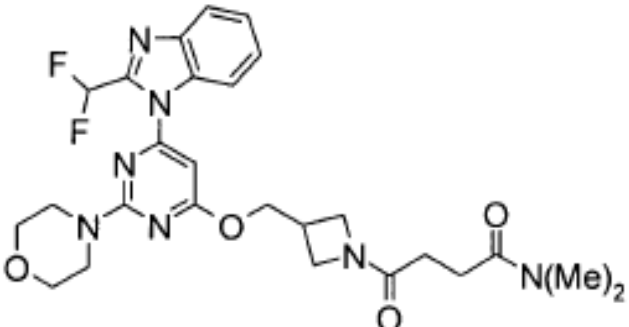
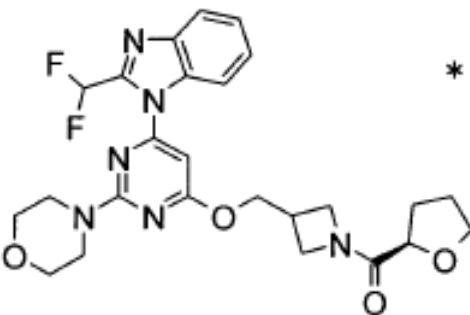
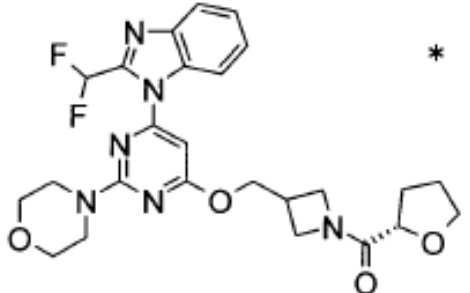
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 243]

Ej	Estr	ESI+	TR
A398#		475	2,45
A399#		489	2,61
A400#		503	2,64
A401#		532	2,53

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 244]

Ej	Estr	ESI+	TR
A402#		516	2,5
A403#		544	2,59
A404#		515	2,71
A405#		515	2,71

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 245]

Ej	Estr	ESI+	TR
A406#	<p>The structure of A406# features a central pyrimidopyrimidine core. At position 2, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂-). At position 4, there is a morpholine ring. At position 6, there is a 2-(4-morpholinyl)ethyl ether group (-O-CH₂-CH₂-N(CH₂)₄-H).</p>	529	2,71
A407#	<p>The structure of A407# is identical to A406#.</p>	529	5,64
A408#	<p>The structure of A408# is identical to A406#, but the morpholine ring is substituted with a hydroxyl group (-OH) at the 4-position.</p>	543	2,69
A409#	<p>The structure of A409# is identical to A406#, but the morpholine ring is substituted with a methoxy group (-OMe) at the 4-position.</p>	557	2,88

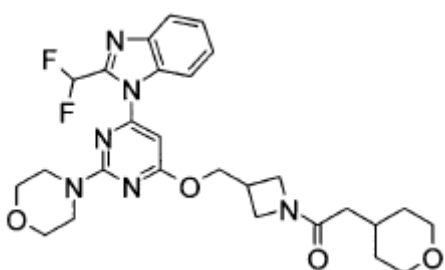
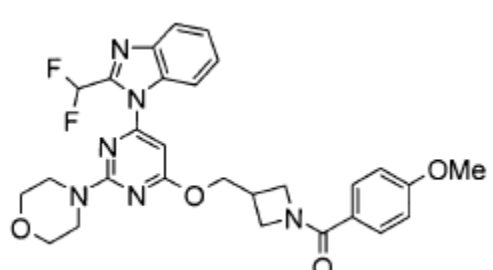
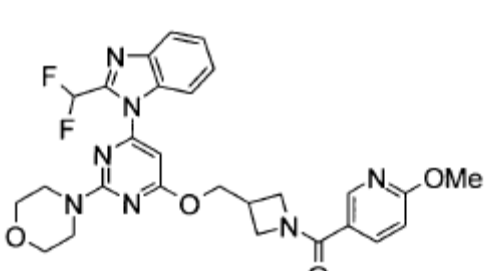
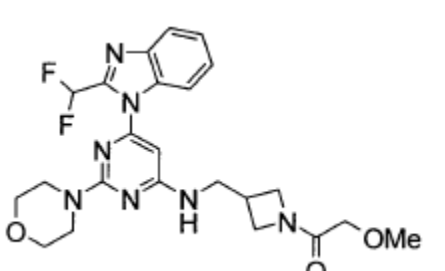
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 246]

Ej	Estr	ESI+	TR
A410#	<p>The structure of A410# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a 2-(2-methyl-1,4-piperidyl)ethyl ether group at the 6-position.</p>	556	2,49
A411#	<p>The structure of A411# is identical to A410#, but the methyl group on the piperidine ring is attached to the nitrogen atom, forming an N-methyl-1,4-piperidine-2-carboxamide moiety.</p>	570	2,54
A412#	<p>The structure of A412# is identical to A411#, but the methyl group on the piperidine ring is replaced by a methoxy group, forming an N-methoxy-1,4-piperidine-2-carboxamide moiety.</p>	586	2,72
A413#	<p>The structure of A413# is identical to A410#, but the methyl group on the piperidine ring is replaced by a tetrahydrofuran-2-ylmethyl group, forming a 2-(2-(tetrahydrofuran-2-ylmethyl)ethyl)ethyl ether moiety.</p>	529	2,73

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 247]

Ej	Estr	ESI+	TR
A414#		543	2,71
A415#		551	2,92
A416#		552	2,86
A417#		488	2,5

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 248]

Ej	Estr	ESI+	TR
A418#	<p>The structure of A418# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluorophenyl group at the 4-position, and a 2-(3-methoxypropyl)pyrrolidin-1-yl group at the 6-position.</p>	502	2,54
A419#	<p>The structure of A419# is similar to A418# but includes an additional methylene group in the side chain, resulting in a 2-(4-methoxybutyl)pyrrolidin-1-yl group at the 6-position of the core.</p>	531	2,44
A420#	<p>The structure of A420# features a morpholine ring at the 2-position and a 2,2-difluorophenyl group at the 4-position of the core. The side chain at the 6-position is a 2-(4-morpholinylbutyl)pyrrolidin-1-yl group.</p>	528	2,61
A421#	<p>The structure of A421# is identical to A420#, featuring a morpholine ring at the 2-position, a 2,2-difluorophenyl group at the 4-position, and a 2-(4-morpholinylbutyl)pyrrolidin-1-yl group at the 6-position of the core.</p>	528	2,53

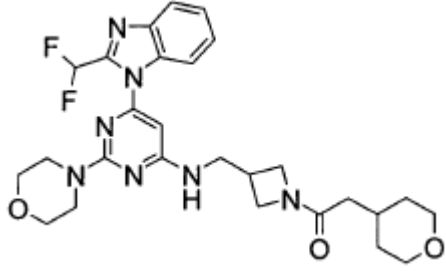
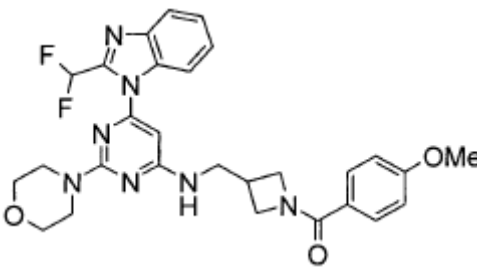
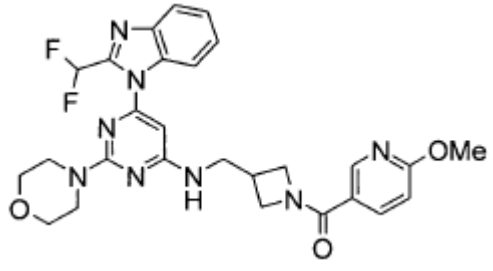
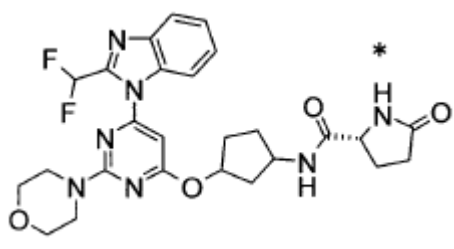
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 249]

Ej	Estr	ESI+	TR
A422#	<p>The structure of A422# features a central pyrimidopyrimidine core. At position 2, there is a morpholine ring. At position 4, there is a 1H-imidazole ring substituted with a 2,2-difluoroethyl group. At position 6, there is a secondary amine group (-NH-) connected to a 2-pyrrolidine ring, which is further linked via a carbonyl group to a 4-methoxy-1,4-dihydropyridin-2(1H)-one ring.</p>	556	2,78
A423#	<p>The structure of A423# is similar to A422#, but the terminal ring is a 1-methyl-2,6-dihydropyridin-4(1H)-one instead of a 4-methoxy-1,4-dihydropyridin-2(1H)-one.</p>	555	2,41
A424#	<p>The structure of A424# is similar to A423#, but the terminal ring is a 1-methyl-2,6-dihydropyridin-4(1H)-one with a methyl group on the nitrogen atom.</p>	569	2,44
A425#	<p>The structure of A425# is similar to A424#, but the terminal ring is a 1-methoxy-2,6-dihydropyridin-4(1H)-one instead of a 1-methyl-2,6-dihydropyridin-4(1H)-one.</p>	585	2,62

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 250]

Ej	Estr	ESI+	TR
A426#		542	2,6
A427#		550	2,8
A428#		551	2,75
A429#		542	2,65

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 251]

Ej	Estr	ESI+	TR
A430#	<p>Chemical structure of compound A430#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a cyclopentane ring. The cyclopentane ring is further substituted with a piperidine-2-carboxamide group, where the piperidine ring has an asterisk (*) indicating a specific stereocenter.</p>	542	2,65
A431#	<p>Chemical structure of compound A431#: Similar to A430#, but the piperidine ring is replaced by a morpholine ring.</p>	557	3
A432#	<p>Chemical structure of compound A432#: Similar to A430#, but the piperidine ring is substituted with a methyl group (Me) on the nitrogen atom.</p>	598	2,79
A433#	<p>Chemical structure of compound A433#: Similar to A430#, but the piperidine ring is replaced by a tetrahydrofuran ring.</p>	529	2,79
A434#	<p>Chemical structure of compound A434#: Similar to A432#, but the piperidine ring is substituted with a methyl group (Me) on the nitrogen atom.</p>	570	2,74

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 252]

Ej	Estr	ESI+	TR
A435#	<p>The structure of A435# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1-phenyl-1H-benzotriazol-5-yl group at the 4-position, and a 2-(methylamino)propanoate group at the 6-position. The propanoate group is linked to the core via an ether bridge through its 2-position.</p>	556	2,69
A436#	<p>The structure of A436# is similar to A435#, but the propanoate group is linked to the core via an ether bridge through its 3-position.</p>	543	2,82
A437#	<p>The structure of A437# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1-phenyl-1H-benzotriazol-5-yl group at the 4-position, and a 2-(morpholin-2-yl)propanoate group at the 6-position. The propanoate group is linked to the core via an ether bridge through its 2-position.</p>	600	2,75
A438#	<p>The structure of A438# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1-phenyl-1H-benzotriazol-5-yl group at the 4-position, and a 2-azepanone group at the 6-position. The azepanone group is linked to the core via an ether bridge through its 2-position.</p>	556	2,71
A439#	<p>The structure of A439# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1-phenyl-1H-benzotriazol-5-yl group at the 4-position, and a 2-(tetrahydro-2H-pyran-2-yl)propanoate group at the 6-position. The propanoate group is linked to the core via an ether bridge through its 2-position.</p>	587	3,1

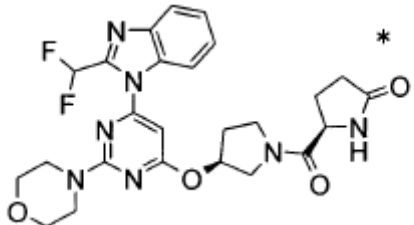
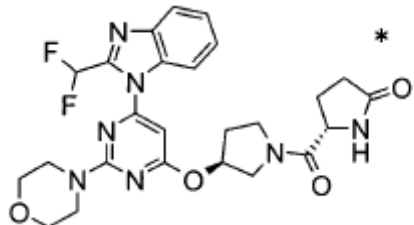
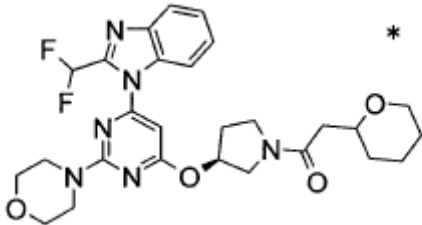
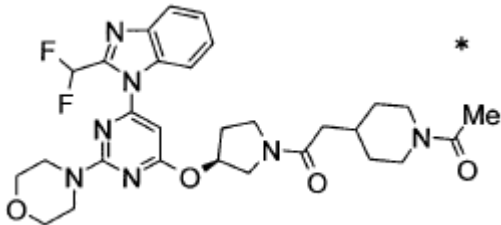
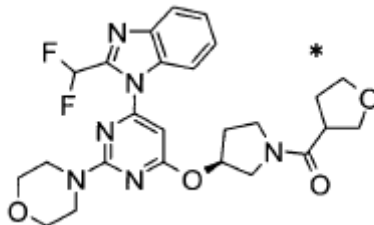
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 253]

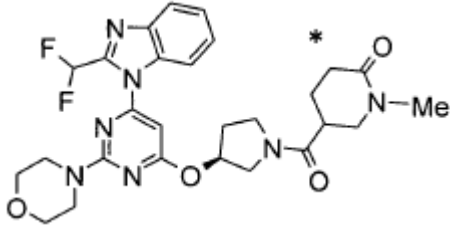
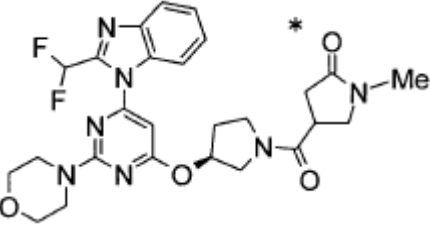
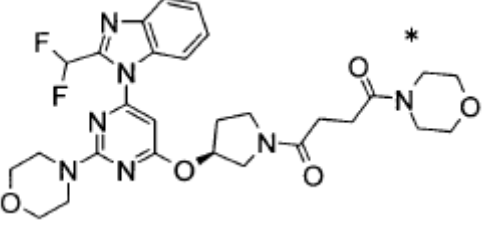
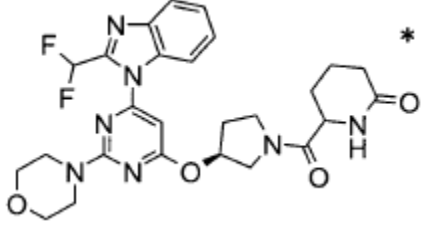
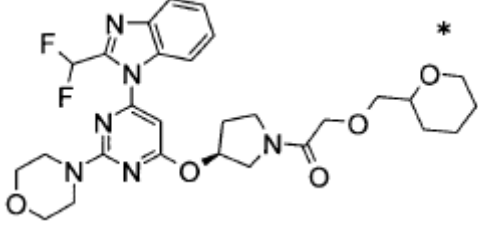
Ej	Estr	ESI+	TR
A440#	<p>The structure of A440# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,6-difluorophenyl group at the 4-position, and a 2-pyridyl group at the 6-position. A cyclopentane ring is attached to the 5-position of the core via an oxygen atom. This cyclopentane ring is further substituted with an amide group (-NH-C(=O)-) which is linked to a 2-pyridyl ring.</p>	536	3,03
A441#	<p>The structure of A441# is identical to A440#, but the amide group is linked to a 3-pyridyl ring instead of a 2-pyridyl ring.</p>	536	2,84
A442#	<p>The structure of A442# is identical to A440#, but the amide group is linked to a 2-pyridylmethyl group (-CH₂-2-pyridyl).</p>	550	2,67
A443#	<p>The structure of A443# is identical to A440#, but the amide group is linked to a 2-piperidinylmethyl group (-CH₂-2-piperidinyl).</p>	570	2,23
A444#	<p>The structure of A444# is identical to A440#, but the amide group is linked to a 2-piperidinylethyl group (-CH₂-CH₂-2-piperidinyl).</p>	584	2,26

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 254]

Ej	Estr	ESI+	TR
A445		528	2,44
A446		528	2,43
A447		543	2,9
A448		584	2,63
A449		515	2,62

[Tabla 255]

Ej	Estr	ESI+	TR
A450		556	2,52
A451		542	2,48
A452#		586	2,6
A453		542	2,5
A454#		573	2,85

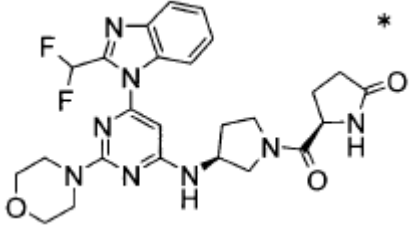
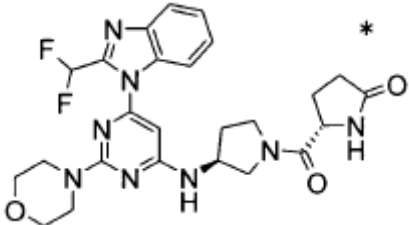
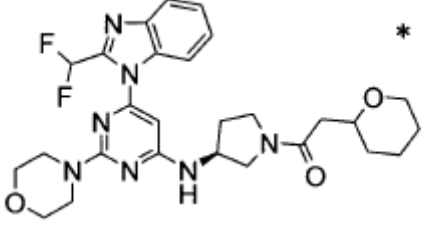
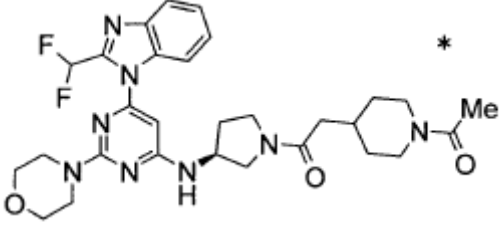
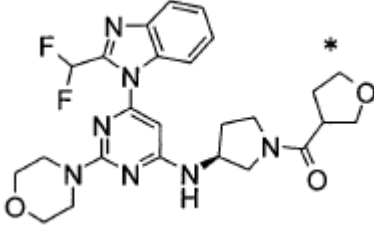
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 256]

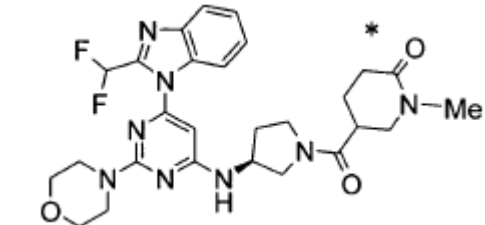
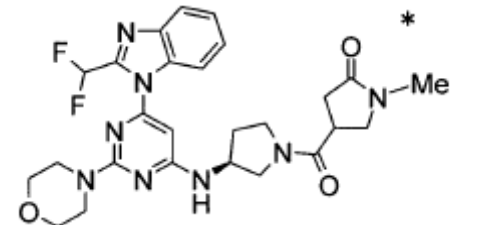
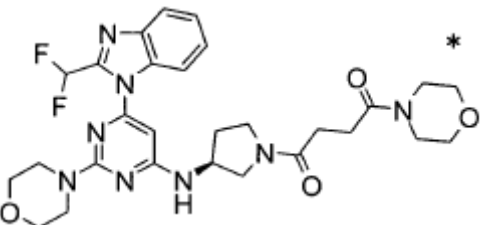
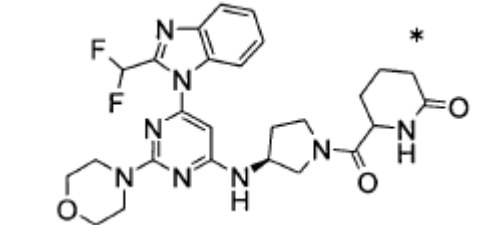
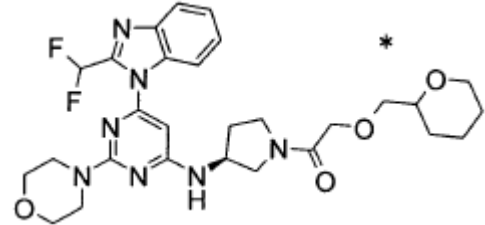
Ej	Estr	ESI+	TR
A455#	<p>Chemical structure of compound A455#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a 2-pyrrolidinyl group. The 2-pyrrolidinyl group is further substituted with a 2-pyridyl group. An asterisk (*) is placed above the pyridine ring.</p>	522	2,75
A456#	<p>Chemical structure of compound A456#: Similar to A455#, but the pyridine ring is substituted at the 3-position. An asterisk (*) is placed above the pyridine ring.</p>	522	2,56
A457#	<p>Chemical structure of compound A457#: Similar to A455#, but the pyridine ring is substituted at the 4-position. An asterisk (*) is placed above the pyridine ring.</p>	536	2,46
A458	<p>Chemical structure of compound A458: Similar to A455#, but the 2-pyrrolidinyl group is substituted with a propyl chain ending in a piperidine ring. An asterisk (*) is placed above the piperidine ring.</p>	556	2,05
A459	<p>Chemical structure of compound A459: Similar to A458, but the piperidine ring is substituted with a propyl chain ending in a piperidine ring. An asterisk (*) is placed above the piperidine ring.</p>	570	2,11

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 257]

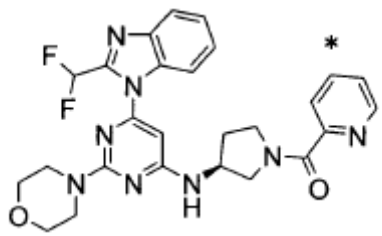
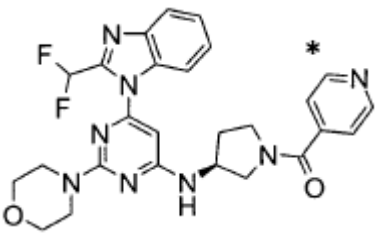
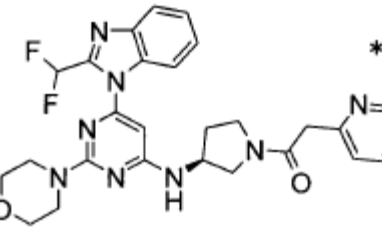
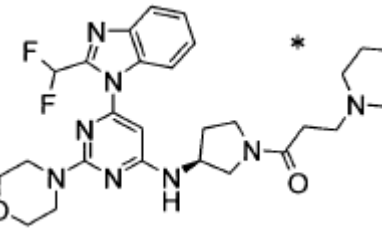
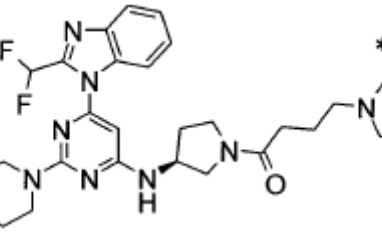
Ej	Estr	ESI+	TR
A460		527	2,39
A461		527	2,39
A462		542	2,85
A463		583	2,57
A464		514	2,56

[Tabla 258]

Ej	Estr	ESI+	TR
A465		555	2,47
A466		541	2,43
A467#		585	2,56
A468		541	2,45
A469#		572	2,8

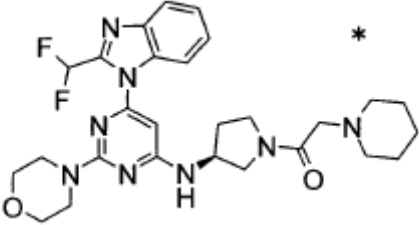
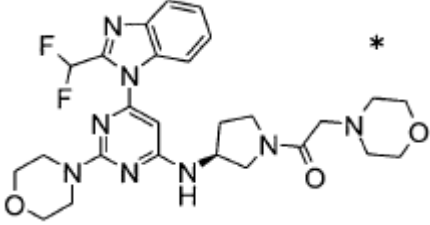
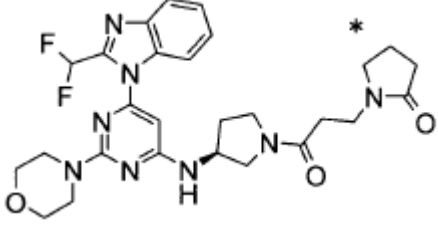
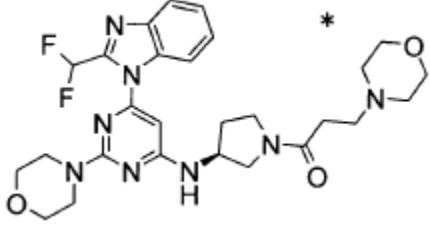
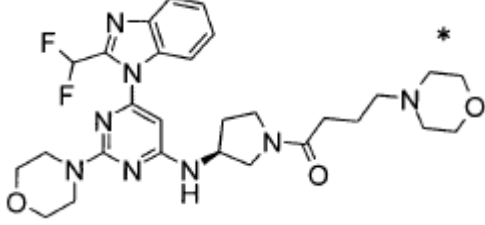
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 259]

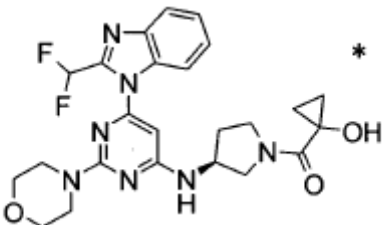
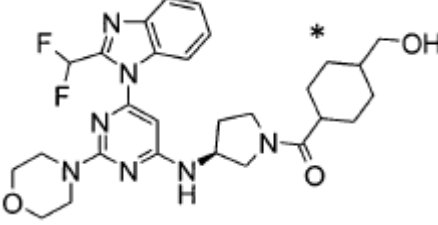
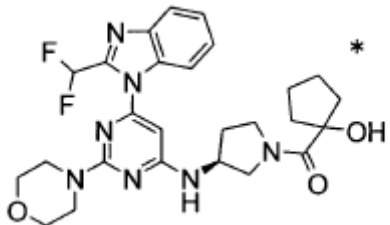
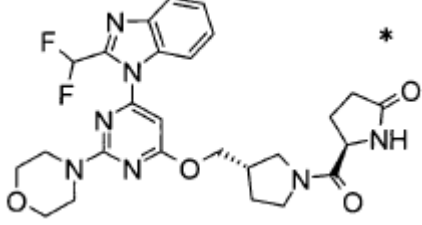
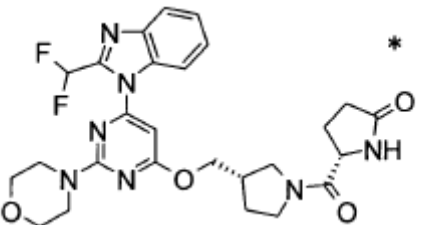
Ej	Estr	ESI+	TR
A470#		521	2,67
A471#		521	2,49
A472#		535	2,41
A473		535	2
A474		569	2,05

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 260]

Ej	Estr	ESI+	TR
A475		541	1,97
A476		543	1,94
A477		555	2,52
A478		557	1,94
A479		571	1,98

[Tabla 261]

Ej	Estr	ESI+	TR
A480		500	2,58
A481		556	2,72
A482		528	2,76
A483#		542	2,54
A484#		542	2,54

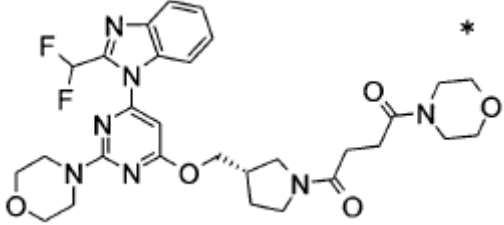
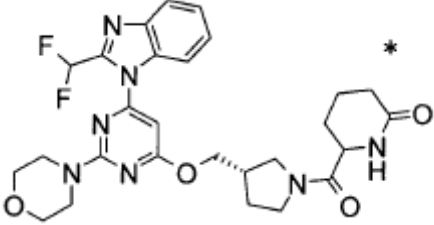
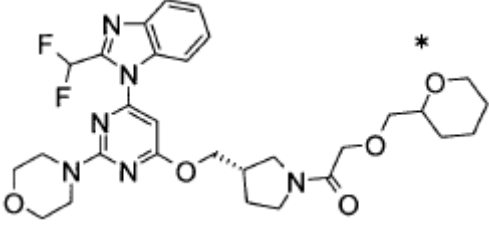
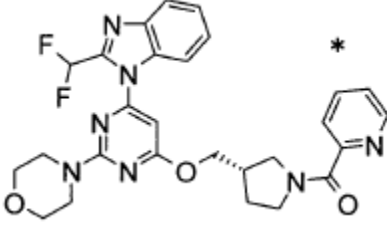
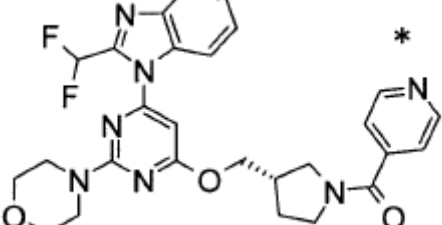
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 262]

Ej	Estr	ESI+	TR
A485#	<p>The structure of A485# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,6-difluorophenyl group at the 4-position, and a 2-(morpholin-2-yl)ethyl ester group at the 6-position. An asterisk (*) is placed above the morpholine ring of the ester group.</p>	557	2,99
A486#	<p>The structure of A486# is similar to A485# but the ester group is a 2-(N-methylpiperidin-2-yl)ethyl ester. An asterisk (*) is placed above the piperidine ring.</p>	598	2,73
A487#	<p>The structure of A487# is similar to A485# but the ester group is a 2-(morpholin-2-yl)ethyl ester. An asterisk (*) is placed above the morpholine ring.</p>	529	2,73
A488#	<p>The structure of A488# is similar to A485# but the ester group is a 2-(N-methylpiperidin-2-yl)ethyl ester. An asterisk (*) is placed above the piperidine ring.</p>	570	2,62
A489#	<p>The structure of A489# is similar to A485# but the ester group is a 2-(N-methylpyrrolidin-2-yl)ethyl ester. An asterisk (*) is placed above the pyrrolidine ring.</p>	556	2,58

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 263]

Ej	Estr	ESI+	TR
A490#		600	2,7
A491#		556	2,6
A492#		587	2,93
A493#		536	2,83
A494#		536	2,65

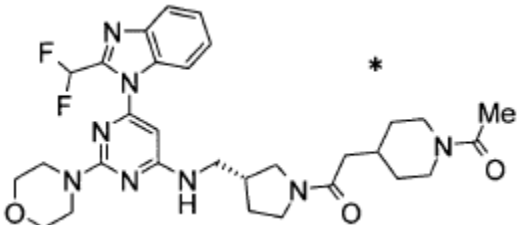
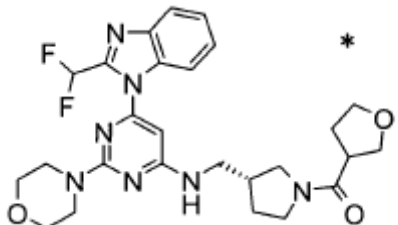
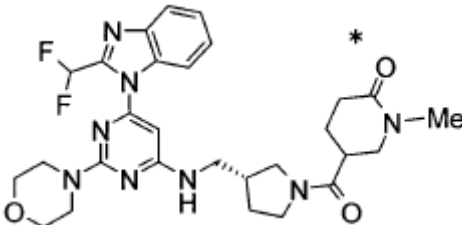
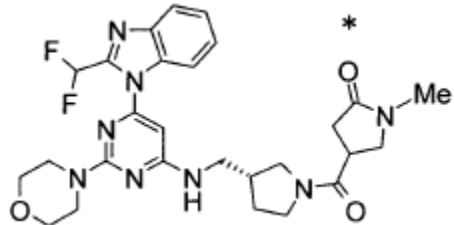
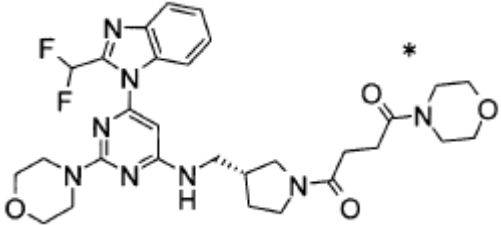
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 264]

Ej	Estr	ESI+	TR
A495#	<p>Chemical structure of compound A495#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a piperidine ring connected via an ether linkage to a piperidine ring, which is further substituted with a piperidine ring marked with an asterisk.</p>	570	2,14
A496#	<p>Chemical structure of compound A496#: Similar to A495#, but the piperidine ring is connected to the morpholine ring via a propyl chain.</p>	584	2,2
A497#	<p>Chemical structure of compound A497#: Similar to A495#, but the piperidine ring is connected to the morpholine ring via a propyl chain, and the piperidine ring is substituted with a pyrrolidine ring marked with an asterisk.</p>	541	2,42
A498#	<p>Chemical structure of compound A498#: Similar to A497#, but the piperidine ring is connected to the morpholine ring via a propyl chain, and the piperidine ring is substituted with a pyrrolidine ring marked with an asterisk.</p>	541	2,42
A499#	<p>Chemical structure of compound A499#: Similar to A495#, but the piperidine ring is connected to the morpholine ring via a propyl chain, and the piperidine ring is substituted with a morpholine ring marked with an asterisk.</p>	556	2,87

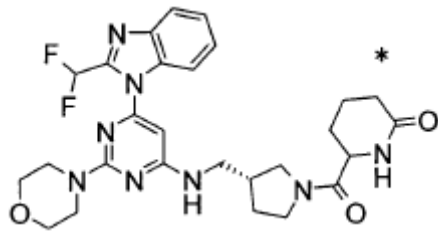
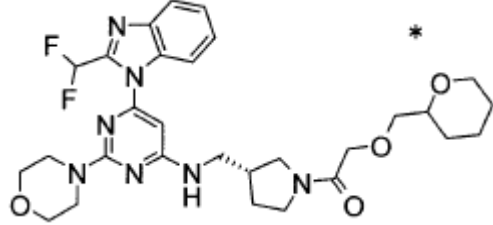
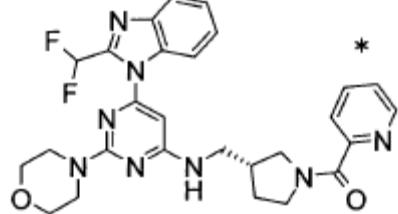
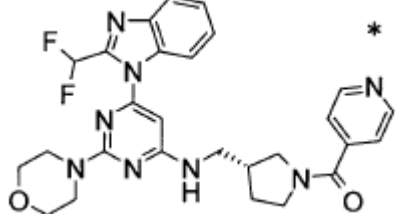
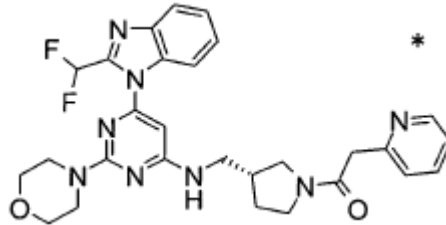
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 265]

Ej	Estr	ESI+	TR
A500#		597	2,6
A501#		528	2,6
A502#		569	2,5
A503#		555	2,46
A504#		599	2,58

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 266]

Ej	Estr	ESI+	TR
A505#		555	2,48
A506#		586	2,82
A507#		535	2,67
A508#		535	2,5
A509#		549	2,42

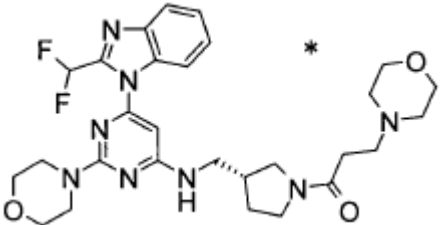
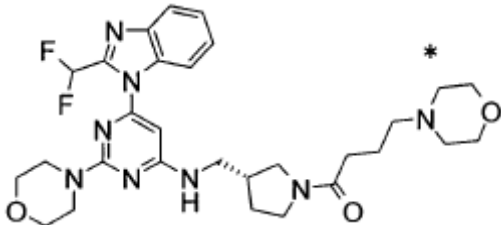
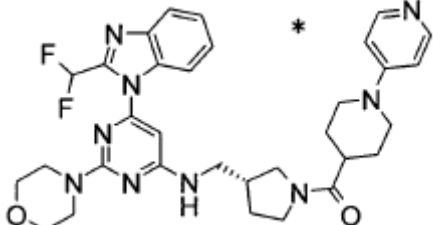
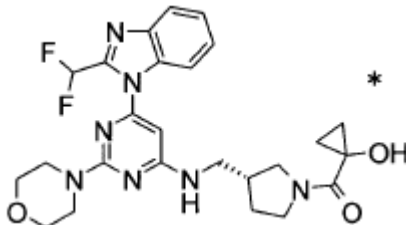
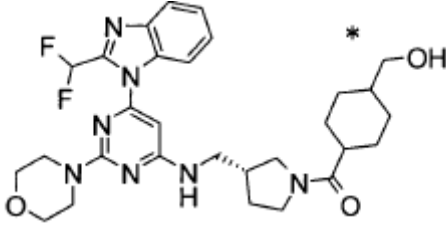
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 267]

Ej	Estr	ESI+	TR
A510#	<p>The structure of A510# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,6-difluorophenyl group at the 4-position, and a 2,6-difluorophenyl group at the 6-position. A piperidine ring is attached to the 5-position of the core via a dashed bond. This piperidine ring is further substituted with a propyl chain that terminates in a piperidine ring, marked with an asterisk (*).</p>	569	2,04
A511#	<p>The structure of A511# is similar to A510#, but the piperidine ring attached to the core is substituted with a propyl chain that terminates in a piperidine ring, marked with an asterisk (*).</p>	583	2,08
A512#	<p>The structure of A512# is similar to A510#, but the piperidine ring attached to the core is substituted with a propyl chain that terminates in a piperidine ring, marked with an asterisk (*).</p>	555	2,02
A513#	<p>The structure of A513# is similar to A510#, but the piperidine ring attached to the core is substituted with a propyl chain that terminates in a morpholine ring, marked with an asterisk (*).</p>	557	1,98
A514#	<p>The structure of A514# is similar to A510#, but the piperidine ring attached to the core is substituted with a propyl chain that terminates in a piperidine ring, marked with an asterisk (*).</p>	569	2,55

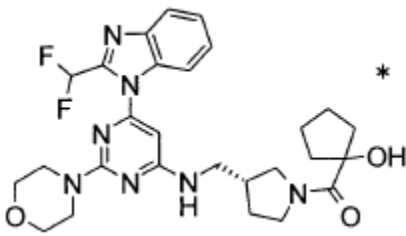
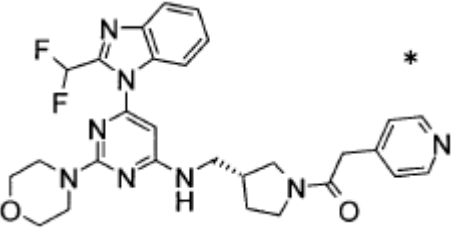
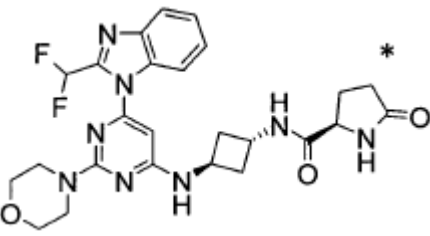
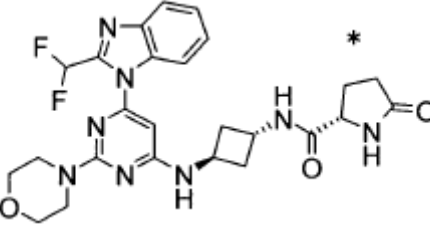
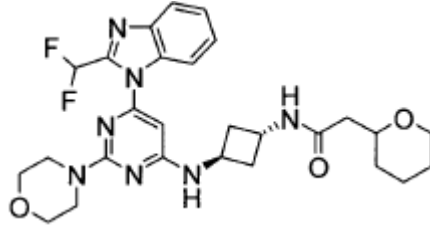
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 268]

Ej	Estr	ESI+	TR
A515#		571	1,99
A516#		585	2,02
A517#		618	2,12
A518#		514	2,62
A519#		570	2,74

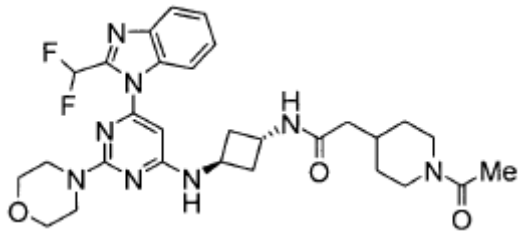
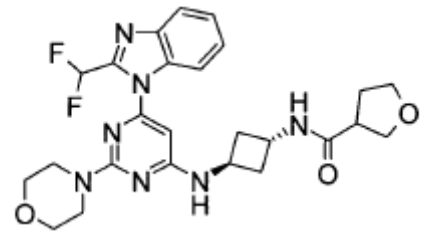
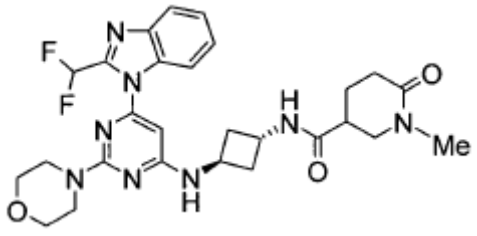
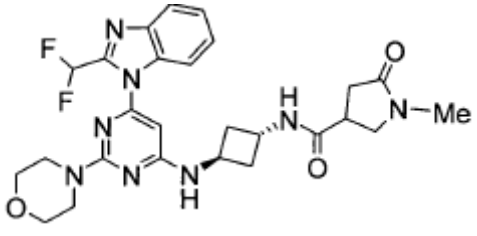
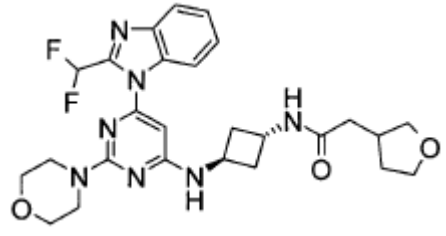
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 269]

Ej	Estr	ESI+	TR
A520#		542	2,79
A521#		549	2,17
A522#		527	2,42
A523#		527	2,42
A524#		542	2,83

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 270]

Ej	Estr	ESI+	TR
A525#		583	2,58
A526#		514	2,59
A527#		555	2,52
A528#		541	2,47
A529#		528	2,62

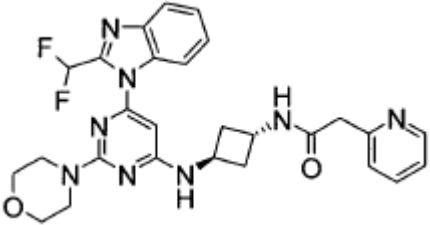
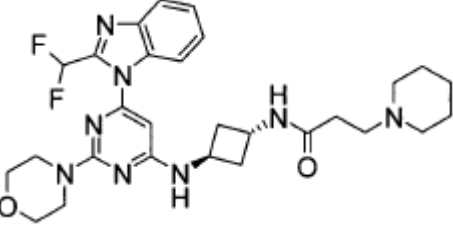
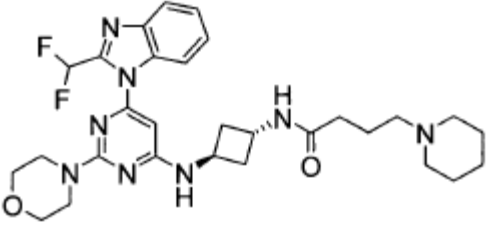
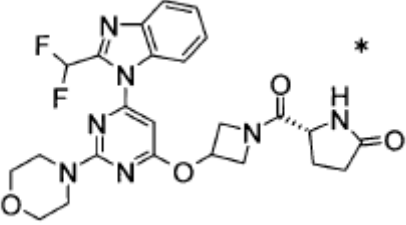
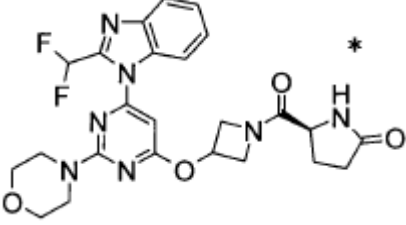
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 271]

Ej	Estr	ESI+	TR
A530#	<p>The structure of A530# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a cyclopropylamino group at the 6-position. The cyclopropylamino group is further substituted with a propanoic acid derivative, which is in turn linked to a morpholine ring via an amide bond.</p>	585	2,53
A531#	<p>The structure of A531# is similar to A530#, but the propanoic acid derivative is replaced by a piperidine-2-carboxamide group.</p>	541	2,49
A532#	<p>The structure of A532# is similar to A530#, but the propanoic acid derivative is replaced by a 2-(2-morpholinoethyl)acetic acid derivative.</p>	572	2,94
A533#	<p>The structure of A533# is similar to A530#, but the propanoic acid derivative is replaced by a pyridine-2-carboxamide group.</p>	521	2,85
A534#	<p>The structure of A534# is similar to A530#, but the propanoic acid derivative is replaced by a pyridine-3-carboxamide group.</p>	521	2,62

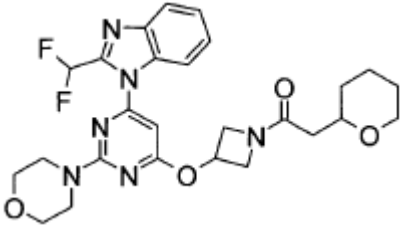
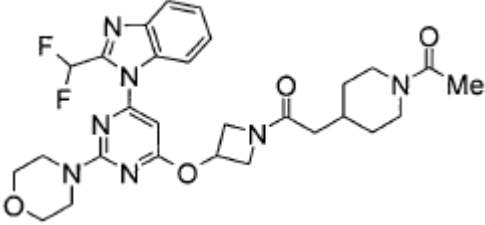
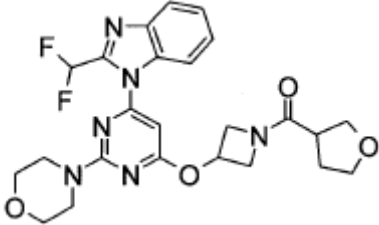
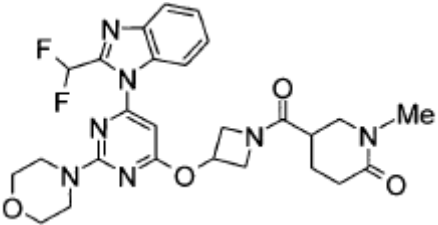
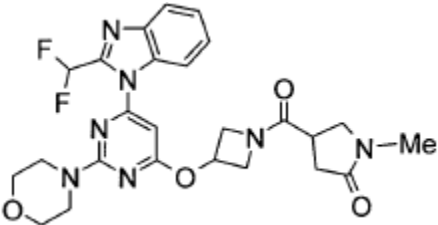
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 272]

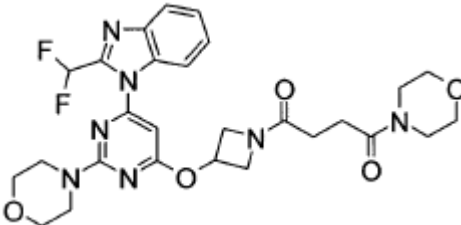
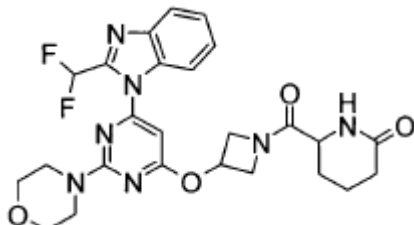
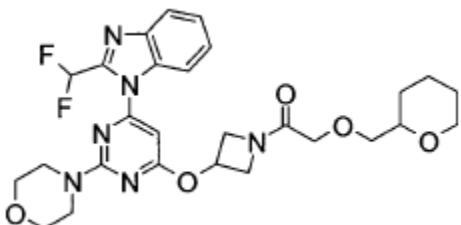
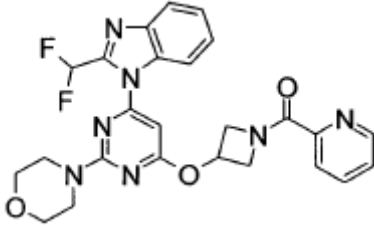
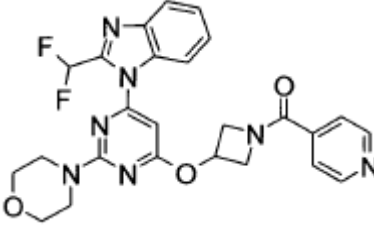
Ej	Estr	ESI+	TR
A535#		535	2,43
A536#		555	2,01
A537#		569	2,06
A538		514	2,39
A539		514	2,39

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 273]

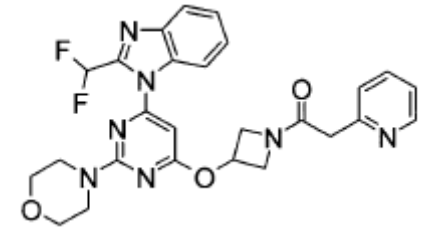
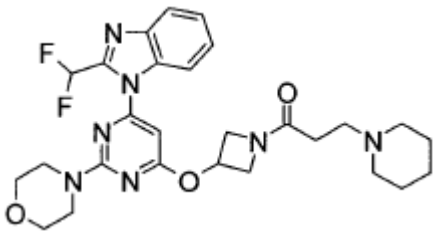
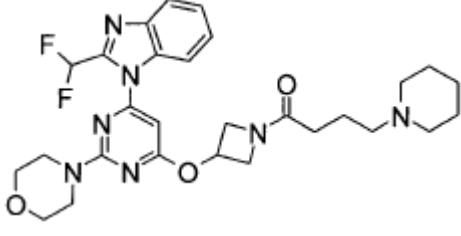
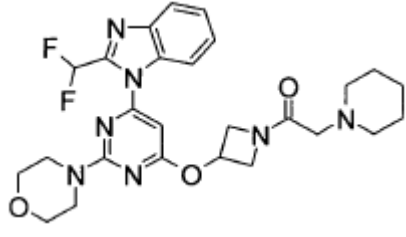
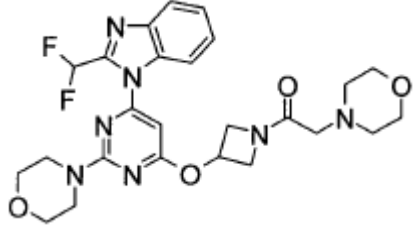
Ej	Estr	ESI+	TR
A540		529	2,88
A541		570	2,59
A542		501	2,59
A543		542	2,48
A544		528	2,44

[Tabla 274]

Ej	Estr	ESI+	TR
A545#		572	2,56
A546		528	2,46
A547#		559	2,88
A548#		508	2,88
A549#		508	2,58

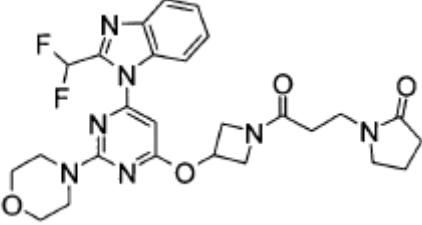
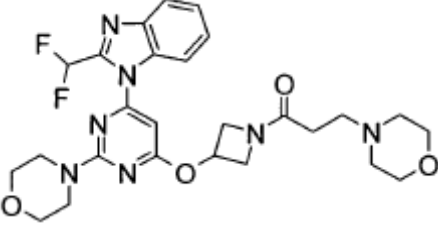
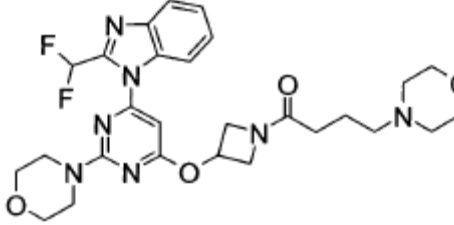
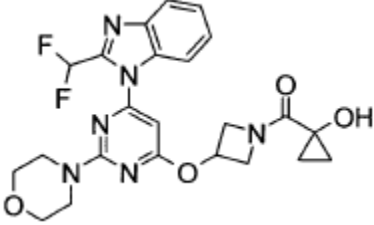
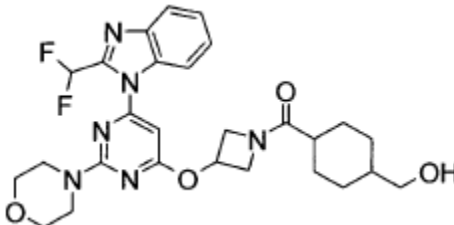
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 275]

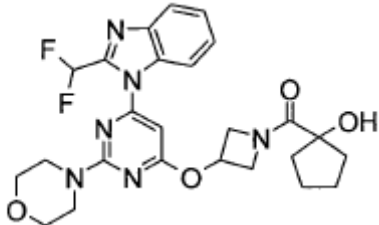
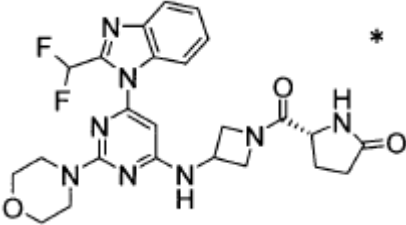
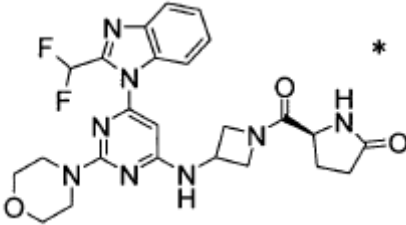
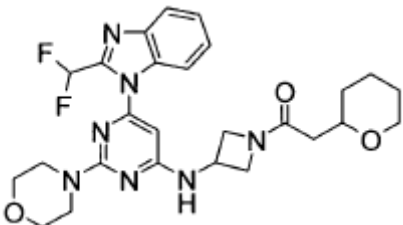
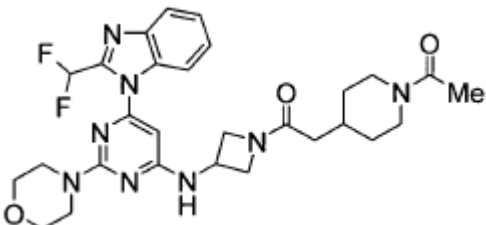
Ej	Estr	ESI+	TR
A550#		522	2,48
A551		542	1,99
A552		556	2,04
A553		528	1,96
A554		530	1,98

los compuestos marcados no están englobados en las reivindicaciones

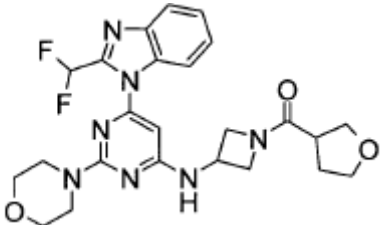
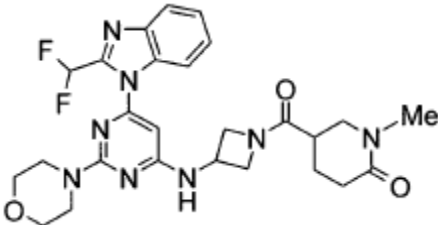
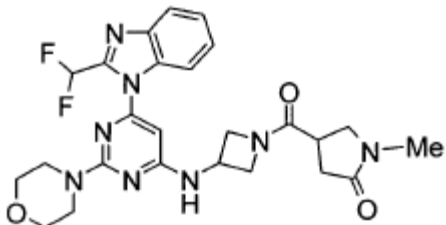
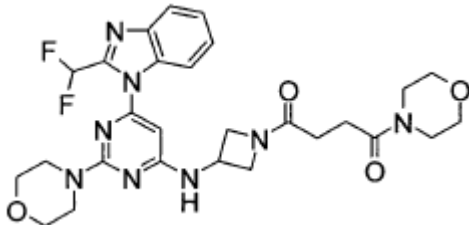
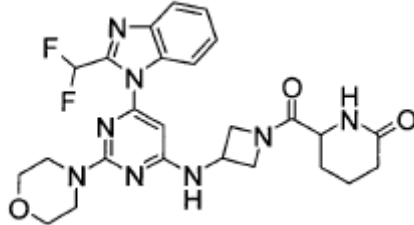
[Tabla 276]

Ej	Estr	ESI+	TR
A555		542	2,52
A556		544	1,93
A557		558	1,97
A558		487	2,59
A559		543	2,75

[Tabla 277]

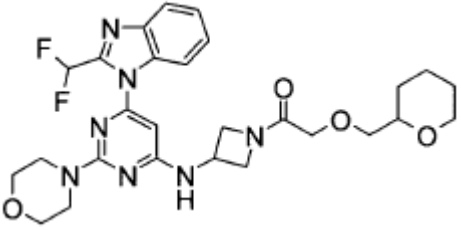
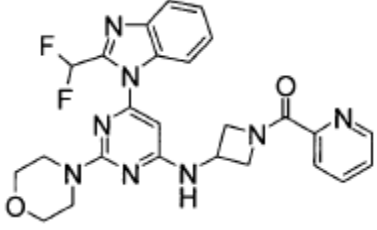
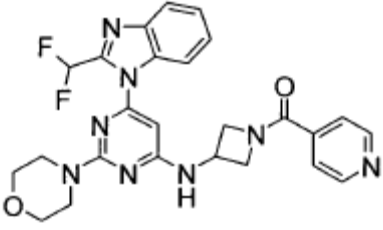
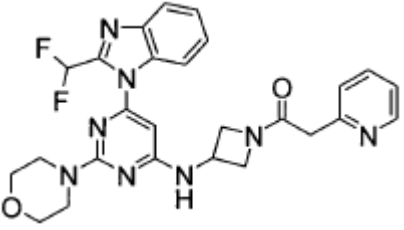
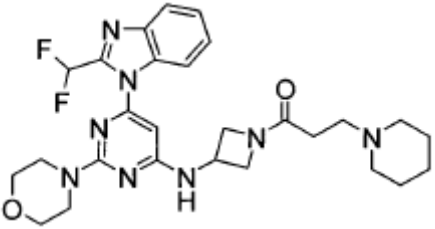
Ej	Estr	ESI+	TR
A560		515	2,77
A561		513	2,33
A562		513	2,33
A563		528	2,81
A564		569	2,52

[Tabla 278]

Ej	Estr	ESI+	TR
A565		500	2,51
A566		541	2,41
A567		527	2,37
A568#		571	2,5
A569		527	2,4

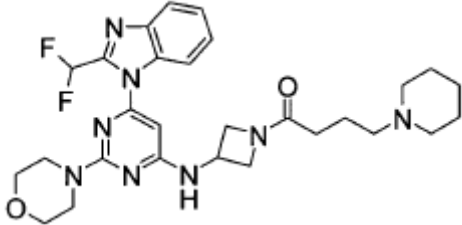
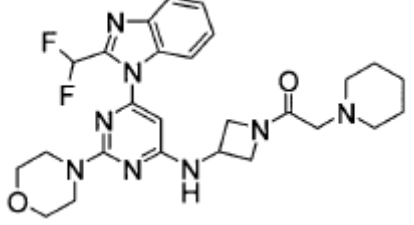
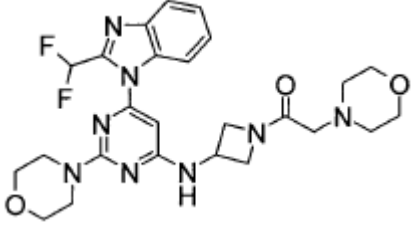
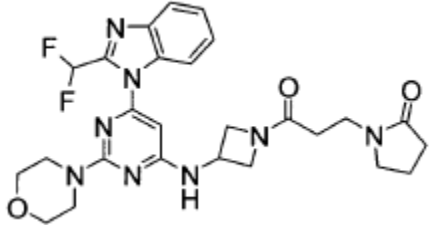
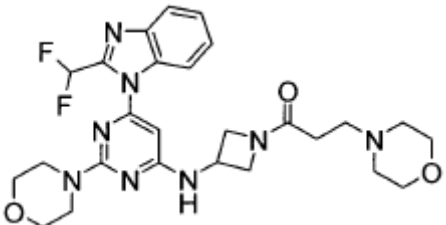
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 279]

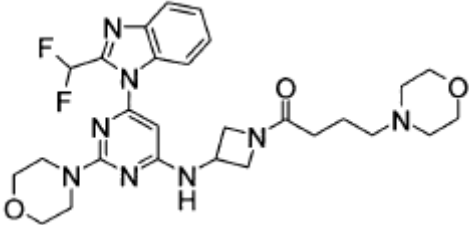
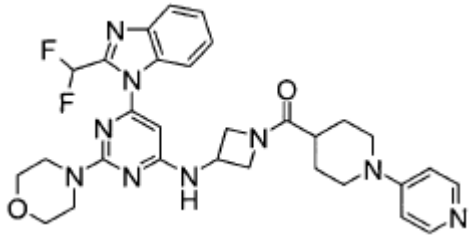
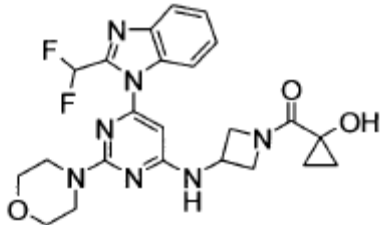
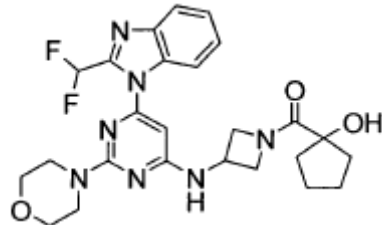
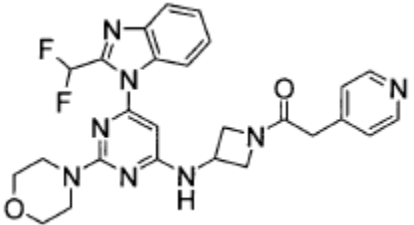
Ej	Estr	ESI+	TR
A570#		558	2,8
A571#		507	2,75
A572#		507	2,49
A573#		521	2,39
A574		541	1,96

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 280]

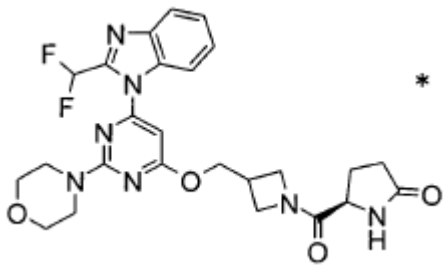
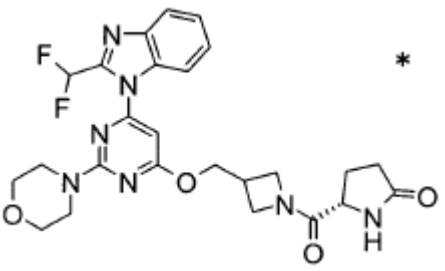
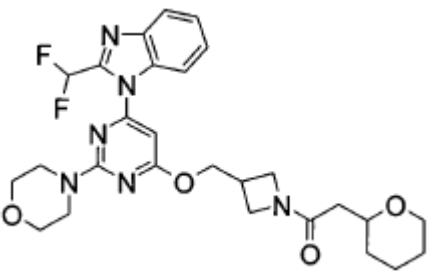
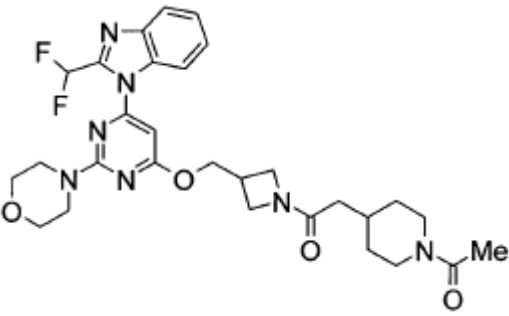
Ej	Estr	ESI+	TR
A575		555	1,99
A576		527	1,94
A577		529	1,93
A578		541	2,45
A579		543	1,9

[Tabla 281]

Ej	Estr	ESI+	TR
A580		557	1,93
A581#		590	2,04
A582		486	2,49
A583		514	2,68
A584#		521	2,09

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 282]

Ej	Estr	ESI+	TR
A585#		528	2,43
A586#		528	2,43
A587#		543	2,89
A588#		584	2,61

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 283]

Ej	Estr	ESI+	TR
A589#	<p>The structure of A589# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a 2-(oxolan-2-yl)ethylamino group at the 6-position.</p>	515	2,61
A590#	<p>The structure of A590# is similar to A589# but features a 2-(2-methylpiperidin-1-yl)ethylamino group at the 6-position instead of the oxolan ring.</p>	556	2,51
A591#	<p>The structure of A591# is similar to A590# but features a 2-(2-methylimidazolidin-1-yl)ethylamino group at the 6-position.</p>	542	2,47
A592#	<p>The structure of A592# is similar to A590# but features a 2-piperidinylethylamino group at the 6-position.</p>	542	2,49

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 284]

Ej	Estr	ESI+	TR
A593#	The chemical structure of A593# features a central pyrimidopyrimidine core. At position 2, there is a benzimidazole ring substituted with two fluorine atoms. At position 4, there is a morpholine ring. At position 6, there is a 4-oxo-1,2,3,4-tetrahydropyridin-1-yl group. At position 8, there is a 2-(tetrahydro-2H-pyran-2-yloxy)ethyl group. <chem>Fc1nc2c(nc1)c3ccccc3n2C4=CN(C5CCOCC5)C=C(C6=CN(C7CCOCC7)C=O)C=C6C8=CCOCC8</chem>	573	2,87
A594#	The chemical structure of A594# features a central pyrimidopyrimidine core. At position 2, there is a benzimidazole ring substituted with two fluorine atoms. At position 4, there is a morpholine ring. At position 6, there is a 4-oxo-1,2,3,4-tetrahydropyridin-1-yl group. At position 8, there is a 2-(pyridin-2-yl)ethyl group. <chem>Fc1nc2c(nc1)c3ccccc3n2C4=CN(C5CCOCC5)C=C(C6=CN(C7CCOCC7)C=O)C=C6C8=CC=CN8</chem>	522	2,87
A595#	The chemical structure of A595# features a central pyrimidopyrimidine core. At position 2, there is a benzimidazole ring substituted with two fluorine atoms. At position 4, there is a morpholine ring. At position 6, there is a 4-oxo-1,2,3,4-tetrahydropyridin-1-yl group. At position 8, there is a 2-(pyridin-3-yl)ethyl group. <chem>Fc1nc2c(nc1)c3ccccc3n2C4=CN(C5CCOCC5)C=C(C6=CN(C7CCOCC7)C=O)C=C6C8=CC=CN8</chem>	522	2,6
A596#	The chemical structure of A596# features a central pyrimidopyrimidine core. At position 2, there is a benzimidazole ring substituted with two fluorine atoms. At position 4, there is a morpholine ring. At position 6, there is a 4-oxo-1,2,3,4-tetrahydropyridin-1-yl group. At position 8, there is a 2-(pyridin-4-yl)ethyl group. <chem>Fc1nc2c(nc1)c3ccccc3n2C4=CN(C5CCOCC5)C=C(C6=CN(C7CCOCC7)C=O)C=C6C8=CC=CN8</chem>	536	2,5

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 285]

Ej	Estr	ESI+	TR
A597#	<p>The structure of A597# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a 2-(2-(2-(piperidin-1-yl)ethyl)ethylamino)ethyl ether group at the 6-position.</p>	556	2,04
A598#	<p>The structure of A598# is similar to A597# but with a longer alkyl chain in the ether linkage, specifically a 2-(2-(2-(2-(piperidin-1-yl)ethyl)ethyl)ethylamino)ethyl ether group.</p>	570	2,07
A599#	<p>The structure of A599# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a 2-(2-(2-(2-(2-hydroxyethyl)amino)ethyl)cyclohexyl)ethyl ether group at the 6-position.</p>	517	2,73
A600#	<p>The structure of A600# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a 2-(2-(2-(2-(2-hydroxy-1-cyclopropylethyl)amino)ethyl)cyclohexyl)ethyl ether group at the 6-position.</p>	543	2,85

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 286]

Ej	Estr	ESI+	TR
A601#	<p>The structure of A601# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a methoxycarbonyl group (-COOCH₃) and a propyl methoxy group (-CH₂CH₂CH₂OMe).</p>	531	2,88
A602#	<p>The structure of A602# is similar to A601#, but the propyl methoxy group is replaced by a butyl methoxy group (-CH₂CH₂CH₂CH₂OMe).</p>	545	2,93
A603#	<p>The structure of A603# is similar to A601#, but the propyl methoxy group is replaced by a 1,3-dimethoxypropyl group (-CH₂(OMe)CH₂CH₂OMe).</p>	575	2,96
A604#	<p>The structure of A604# is similar to A601#, but the propyl methoxy group is replaced by a 2-methoxypropyl group (-CH₂(OH)CH₂OMe).</p>	561	2,8

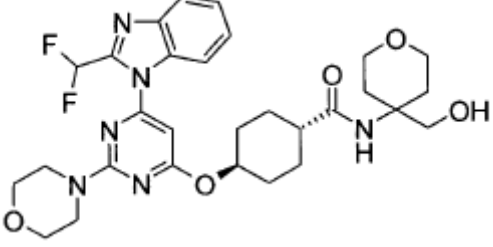
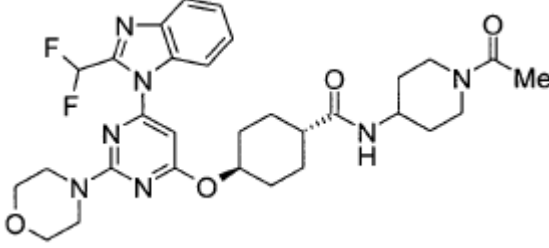
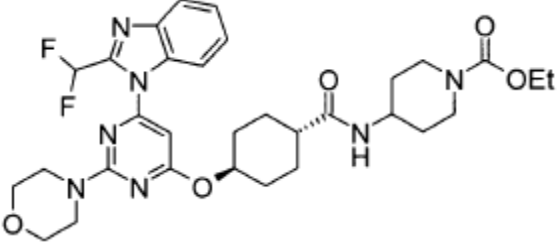
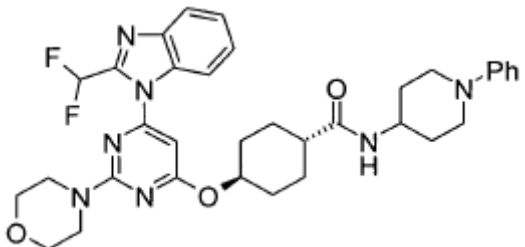
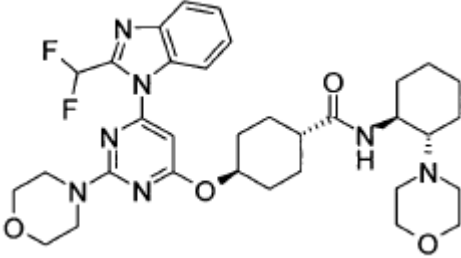
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 287]

Ej	Estr	ESI+	TR
A605#	<p>The structure of A605# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a dimethylacetamide group (-NHCOCH₂NMe₂) at the 1-position.</p>	558	2,8
A606#	<p>The structure of A606# is similar to A605#, but the dimethylacetamide group is replaced by a cyclohexylamino group (-NH-cyclohexane).</p>	555	3,21
A607#	<p>The structure of A607# is similar to A605#, but the dimethylacetamide group is replaced by a cyclohexylamino group with a hydroxyl group (-NH-cyclohexane-OH).</p>	571	2,87
A608#	<p>The structure of A608# is similar to A605#, but the dimethylacetamide group is replaced by a morpholine ring (-NH-morpholine).</p>	557	2,92

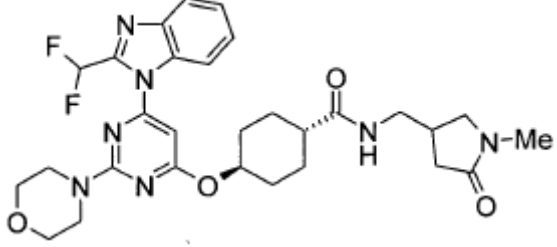
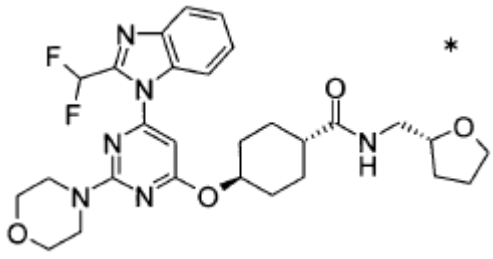
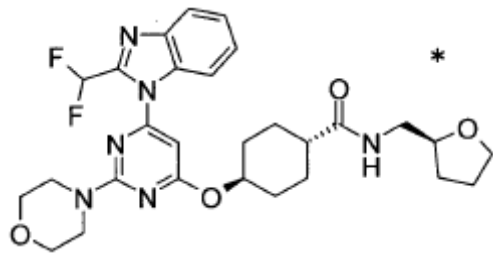
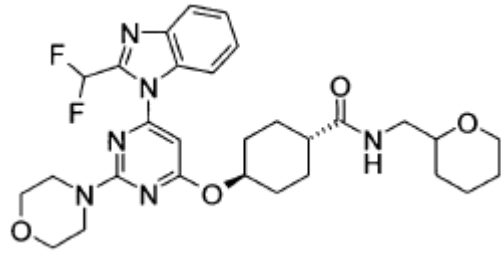
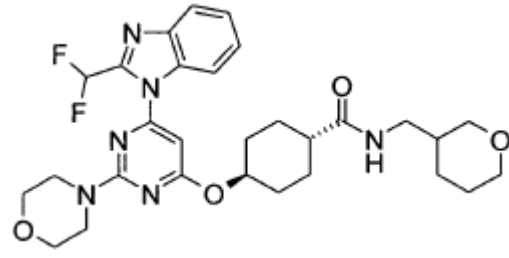
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 288]

Ej	Estr	ESI+	TR
A609#		587	2,83
A610#		598	2,84
A611#		628	3,07
A612#		632	3,14
A613#		640	2,48

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 289]

Ej	Estr	ESI+	TR
A614#		584	2,78
A615#		557	2,96
A616#		557	2,97
A617#		571	3,08
A618#		571	2,98

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 290]

Ej	Estr	ESI+	TR
A619#	<p>The structure of A619# features a central pyrimidopyrimidine ring system. It is substituted with a 2,2-difluoro-1-phenyl-1H-imidazole-4-yl group at the 2-position, a morpholine ring at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a morpholine ring and an amide group (-NH-CH2-CH2-morpholine).</p>	571	2,94
A620#	<p>The structure of A620# is similar to A619# but the amide group is substituted with a propyl chain ending in a morpholine ring (-NH-CH2-CH2-CH2-morpholine).</p>	585	3,01
A621#	<p>The structure of A621# is similar to A619# but the amide group is substituted with a 2-hydroxyethyl group (-NH-CH2-CH2-OH).</p>	601	2,81
A622#	<p>The structure of A622# is similar to A619# but the amide group is substituted with a 2-(4-hydroxypiperidin-1-yl)ethyl group (-NH-CH2-CH2-N(piperidine)-OH).</p>	600	2,3
A623#	<p>The structure of A623# is similar to A619# but the amide group is substituted with a 2-(4-morpholinyl)ethyl group (-NH-CH2-CH2-N(morpholine)).</p>	586	2,31

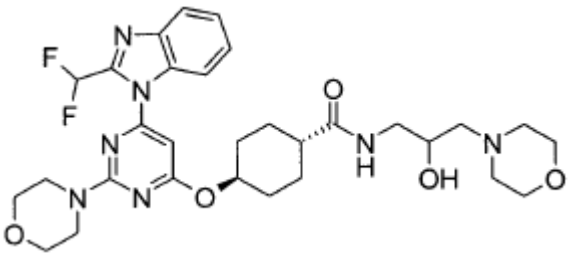
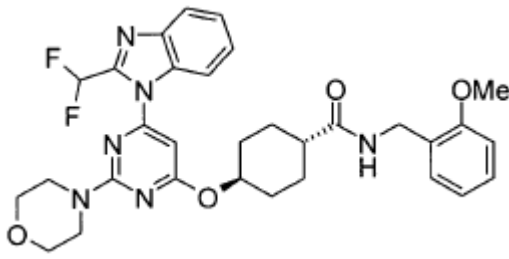
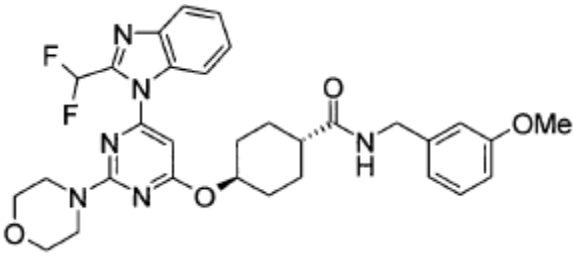
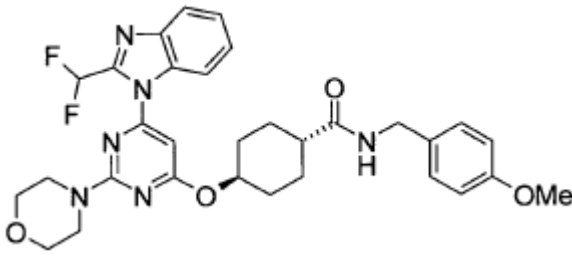
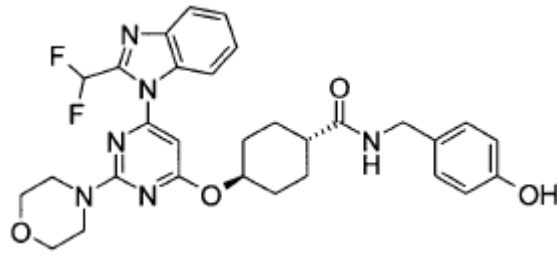
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 291]

Ej	Estr	ESI+	TR
A624#	<p>The structure of A624# features a central pyrimidopyridine ring system. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. A cyclohexane ring is attached to the 5-position of the pyrimidopyridine core via an oxygen atom. This cyclohexane ring is further substituted with a methyl group and a carbonyl group. The carbonyl group is part of an amide linkage to a 2,2-dimethylpropanoic acid derivative, which is in turn linked to a morpholine ring.</p>	614	2,33
A625#	<p>The structure of A625# is similar to A624# but lacks the methyl groups on the propanoic acid derivative. It consists of the same pyrimidopyridine core with morpholine, difluoroethyl, and benzimidazole substituents, and a cyclohexane ring attached at the 5-position. The cyclohexane ring is substituted with a carbonyl group that forms an amide linkage to a morpholine ring.</p>	600	2,79
A626#	<p>The structure of A626# features the same pyrimidopyridine core and substituents as the previous compounds. The cyclohexane ring attached at the 5-position is substituted with a carbonyl group that forms an amide linkage to a 2-(2-oxo-2H-tetrahydrofuran-3-yl)ethyl group.</p>	585	3
A627#	<p>The structure of A627# is similar to A625# but includes a morpholine ring at the end of the propanoic acid derivative chain. It consists of the same pyrimidopyridine core with morpholine, difluoroethyl, and benzimidazole substituents, and a cyclohexane ring attached at the 5-position. The cyclohexane ring is substituted with a carbonyl group that forms an amide linkage to a morpholine ring.</p>	600	2,31

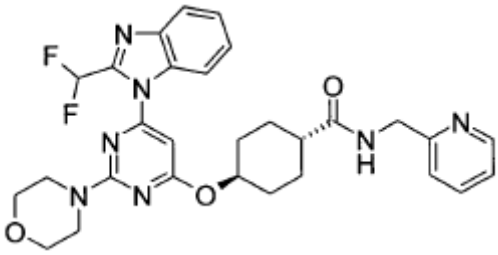
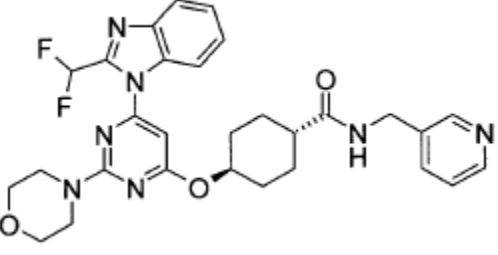
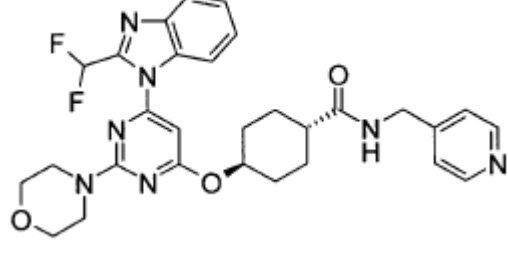
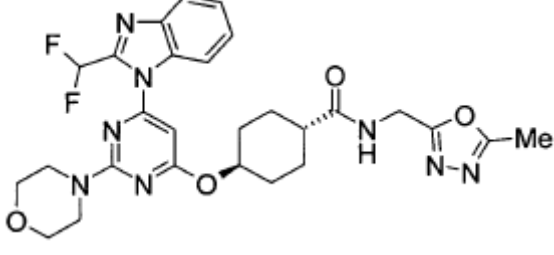
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 292]

Ej	Estr	ESI+	TR
A628#		616	2,32
A629#		593	3,12
A630#		593	3,09
A631#		593	3,08
A632#		579	2,87

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 293]

Ej	Estr	ESI+	TR
A633#		564	2,8
A634#		564	2,64
A635#		564	2,5
A636#		569	2,75

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 294]

Ej	Estr	ESI+	TR
A637#	<p>The structure of A637# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a morpholine ring and an amide group (-NH-CH2-CH2-C6H4-N-morpholine).</p>	648	3,03
A638#	<p>The structure of A638# is similar to A637# but the amide group is substituted with a 4-methoxyphenyl group (-NH-CH2-CH2-C6H4-OMe).</p>	607	3,14
A639#	<p>The structure of A639# is similar to A637# but the amide group is substituted with a 3-pyridyl group (-NH-CH2-CH2-pyridine).</p>	578	2,62
A640#	<p>The structure of A640# is identical to A639#.</p>	578	2,59

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 295]

Ej	Estr	ESI+	TR
A641#	<p>The structure of A641# features a central pyrimidine ring substituted with a morpholine group at the 2-position, a 1H-benzotriazol-2-ylidene group at the 4-position, and a 2-(2,2-difluoroethyl)amino group at the 6-position. This pyrimidine ring is linked via an oxygen atom to a cyclohexane ring. The cyclohexane ring is further substituted with a dimethylamino group at the 1-position and a propyl chain at the 4-position, which is terminated by a pyridine ring.</p>	578	2,47
A642#	<p>The structure of A642# is similar to A641# but the propyl chain on the cyclohexane ring is extended to a butyl chain, which is terminated by a 4-methoxyphenyl ring.</p>	621	3,2
A643#	<p>The structure of A643# is similar to A641# but the propyl chain on the cyclohexane ring is replaced by a dimethylamino group.</p>	501	2,94
A644#	<p>The structure of A644# is similar to A641# but the propyl chain on the cyclohexane ring is replaced by a 2-methoxyethyl chain.</p>	545	2,99

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 296]

Ej	Estr	ESI+	TR
A645#	<p>The structure of A645# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a dimethylamino group (-N(CH₃)₂) and a methoxymethyl group (-CH₂OMe).</p>	589	3,07
A646#	<p>The structure of A646# is similar to A645# but the dimethylamino group on the cyclohexane ring is replaced by a dimethylacetamide group (-N(CH₃)₂COCH₃).</p>	572	2,81
A647#	<p>The structure of A647# is similar to A645# but the dimethylamino group on the cyclohexane ring is replaced by a cyclohexyl group.</p>	599	3,19
A648#	<p>The structure of A648# is similar to A645# but the dimethylamino group on the cyclohexane ring is replaced by a morpholine ring.</p>	571	3

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 297]

Ej	Estr	ESI+	TR
A649#	<p>The structure of A649# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a methyl group and a piperidine ring, which is in turn substituted with an ethyl ester group.</p>	642	3,12
A650#	<p>The structure of A650# is similar to A649#, but the piperidine ring is substituted with a morpholine ring instead of an ethyl ester group.</p>	585	3,22
A651#	<p>The structure of A651# is similar to A650#, but the morpholine ring is substituted with a piperidine ring.</p>	585	3,03
A652#	<p>The structure of A652# is similar to A651#, but the piperidine ring is substituted with a morpholine ring.</p>	598	2,37

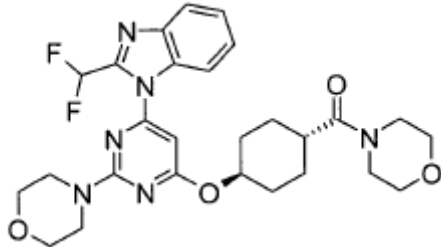
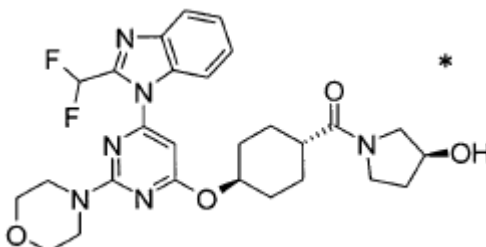
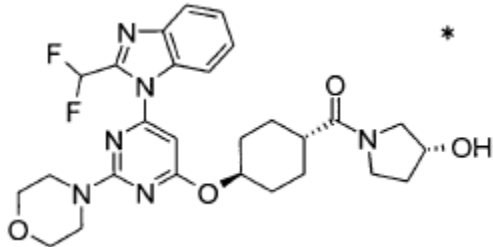
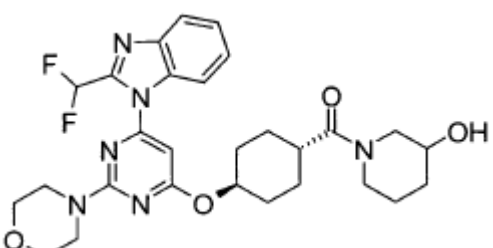
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 298]

Ej	Estr	ESI+	TR
A653#	<p>Chemical structure of compound A653#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a cyclohexane ring. The cyclohexane ring is further substituted with a methylamino group and a morpholine ring.</p>	614	2,81
A654#	<p>Chemical structure of compound A654#: Similar to A653#, but the methylamino group is substituted with a 4-methoxyphenyl group.</p>	607	3,2
A655#	<p>Chemical structure of compound A655#: Similar to A653#, but the methylamino group is substituted with a 3-pyridyl group.</p>	578	2,63
A656#	<p>Chemical structure of compound A656#: Similar to A653#, but the methylamino group is substituted with a 3-pyridyl group via a propyl chain.</p>	592	2,58
A657#	<p>Chemical structure of compound A657#: Similar to A653#, but the methylamino group is substituted with a piperidine ring.</p>	541	3,18

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 299]

Ej	Estr	ESI+	TR
A658#		543	2,91
A659#		543	2,8
A660#		543	2,8
A661#		557	2,89

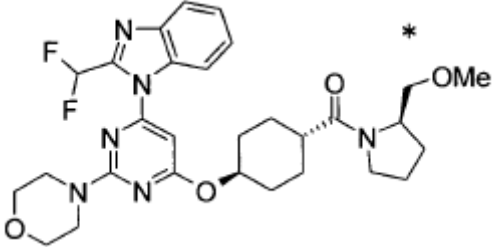
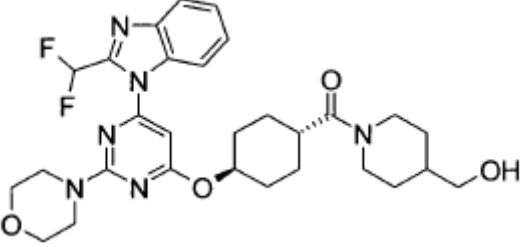
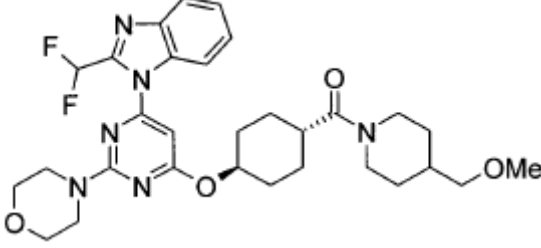
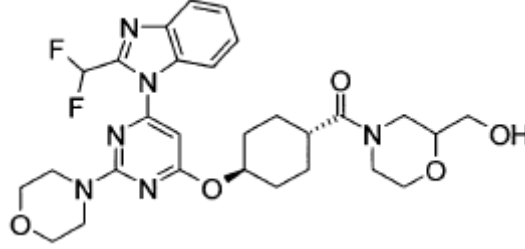
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 300]

Ej	Estr	ESI+	TR
A662#	<p>The structure of A662# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-4-yl group at the 4-position, and a 4-(4-hydroxypiperidin-1-yl)cyclohexyloxy group at the 6-position.</p>	557	2,84
A663#	<p>The structure of A663# is similar to A662#, but the hydroxyl group on the piperidine ring is replaced by a methoxy (OMe) group.</p>	571	3,07
A664#	<p>The structure of A664# is identical to A663#.</p>	571	3,04
A665#	<p>The structure of A665# is similar to A663#, but the piperidine ring is replaced by a pyrrolidine ring. The methoxy (OMe) group is attached to the pyrrolidine ring with a dashed bond, and an asterisk (*) is placed above it, indicating it is not part of the claims.</p>	571	3,13

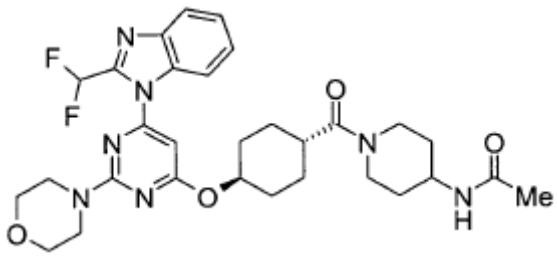
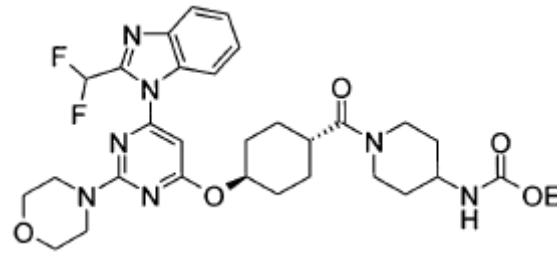
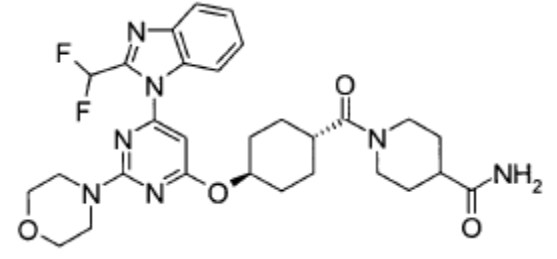
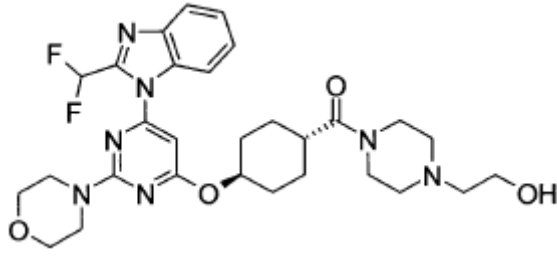
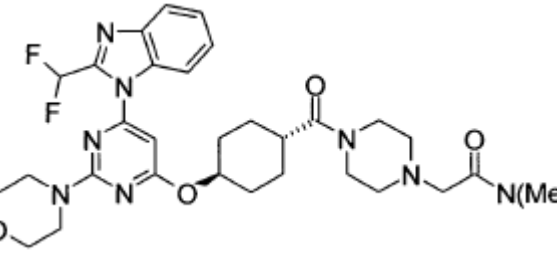
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 301]

Ej	Estr	ESI+	TR
A666#		571	3,13
A667#		571	2,9
A668#		585	3,12
A669#		573	2,79

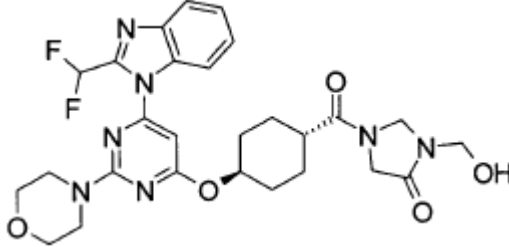
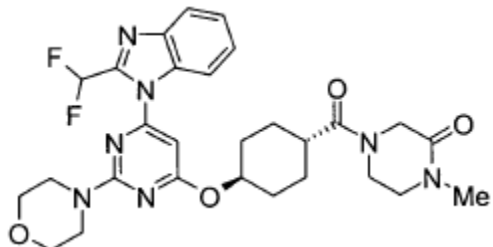
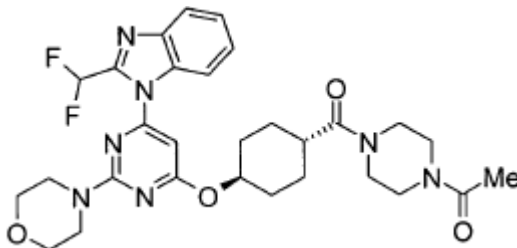
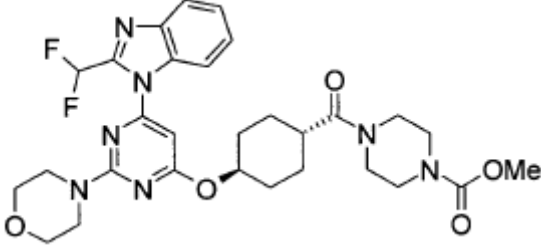
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 302]

Ej	Estr	ESI+	TR
A670#		598	2,81
A671#		628	2,99
A672#		584	2,74
A673#		586	2,27
A674#		627	2,33

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 303]

Ej	Estr	ESI+	TR
A675#		572	2,69
A676#		570	2,76
A677#		584	2,79
A678#		600	2,95

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 304]

Ej	Estr	ESI+	TR
A679#	<p>Chemical structure of compound A679#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzimidazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with a carbonyl group linked to a piperidine ring, which is in turn linked to a 2-methylpyrrolidine ring.</p>	624	2,87
A680#	<p>Chemical structure of compound A680#: Similar to A679#, but the 2-methylpyrrolidine ring is replaced by a piperidine ring.</p>	582	2,3
A681#	<p>Chemical structure of compound A681#: Similar to A679#, but the piperidine ring is substituted with a 4-methoxyphenyl group (OMe).</p>	619	3,28
A682#	<p>Chemical structure of compound A682#: Similar to A679#, but the piperidine ring is substituted with a quinoline ring system.</p>	590	2,97
A683#	<p>Chemical structure of compound A683#: Similar to A679#, but the piperidine ring is substituted with a morpholine ring.</p>	626	2,32

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 305]

Ej	Estr	ESI+	TR
A684#	<p>The structure of A684# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzotriazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a carbonyl group, which is linked to a piperidine ring. The piperidine ring is substituted with a pyridine ring.</p>	604	2,66
A685#	<p>The structure of A685# is similar to A684#, but the piperidine ring is substituted with a morpholine ring instead of a pyridine ring.</p>	640	2,35
A686#	<p>The structure of A686# is similar to A684#, but the piperidine ring is substituted with a morpholine ring and a pyrrolidine ring.</p>	626	2,35
A687#	<p>The structure of A687# is similar to A684#, but the piperidine ring is substituted with a morpholine ring and a pyridine ring.</p>	634	2,44
A688#	<p>The structure of A688# is similar to A684#, but the piperidine ring is substituted with a morpholine ring and a morpholine ring.</p>	655	2,33

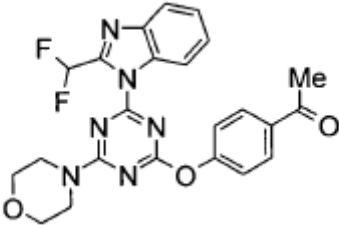
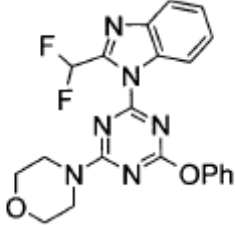
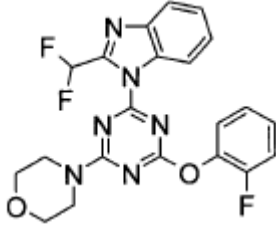
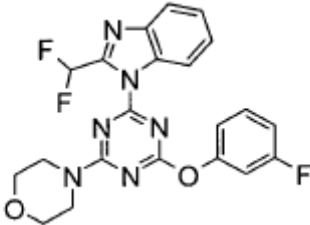
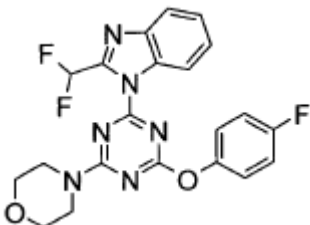
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 306]

Ej	Estr	ESI+	TR
A689#	<p>Chemical structure of compound A689#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,6-difluorophenyl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a dimethylcarbamoyl group (-NH-C(=O)-NMe₂) at position 1.</p>	636	3,11
A690#	<p>Chemical structure of compound A690#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,6-difluorophenyl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 4-methoxyphenylamino group (-NH-C(=O)-C₆H₄-OMe) at position 1.</p>	580	3,09
A691#	<p>Chemical structure of compound A691#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,6-difluorophenyl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 2-phenylethylamino group (-NH-C(=O)-CH₂-CH₂-Ph) at position 1.</p>	593	3,32
A692#	<p>Chemical structure of compound A692#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,6-difluorophenyl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 2-(4-hydroxyphenyl)ethylamino group (-NH-C(=O)-CH₂-CH₂-C₆H₄-OH) at position 1.</p>	607	3,24
A693#	<p>Chemical structure of compound A693#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,6-difluorophenyl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 2-(2-hydroxyphenyl)ethylamino group (-NH-C(=O)-CH₂-CH₂-C₆H₄-OH) at position 1.</p>	621	3,27

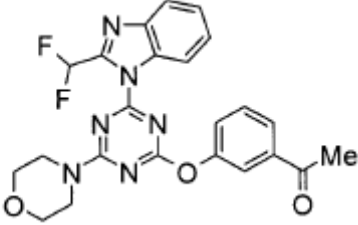
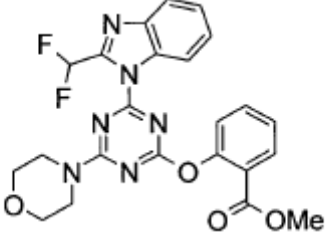
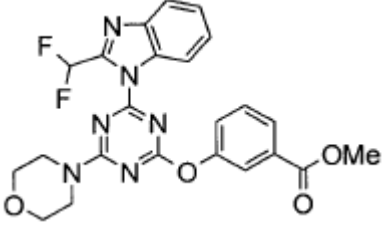
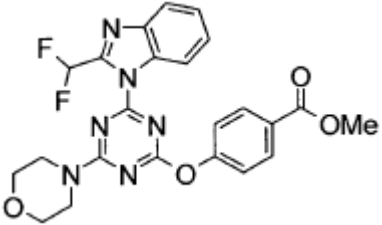
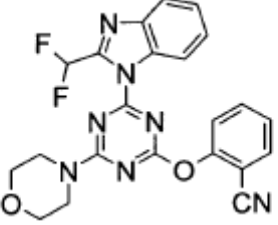
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 307]

Ej	Estr	ESI+	TR
B1#		467	3,1
B2#		425	3,32
B3#		443	3,32
B4#		443	3,37
B5#		443	3,35

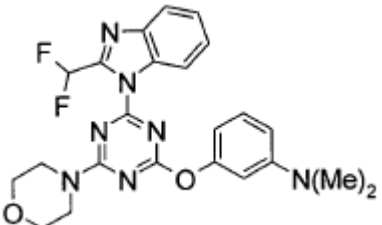
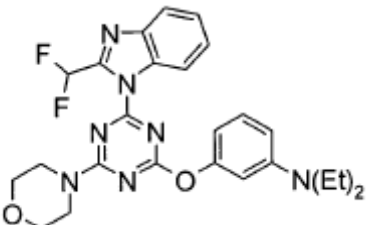
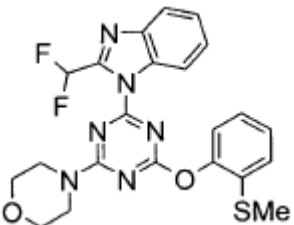
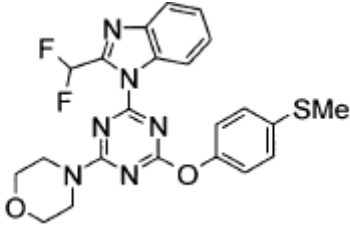
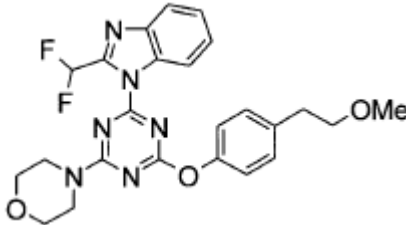
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 308]

Ej	Estr	ESI+	TR
B6#		467	3,09
B7#		483	3,14
B8#		483	3,28
B9#		483	3,31
B10#		450	2,96

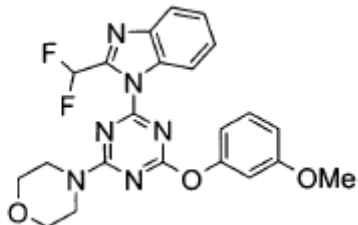
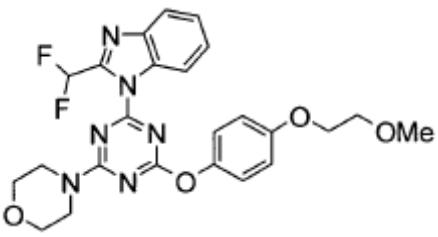
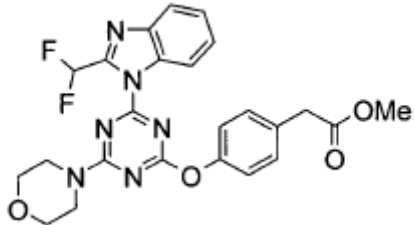
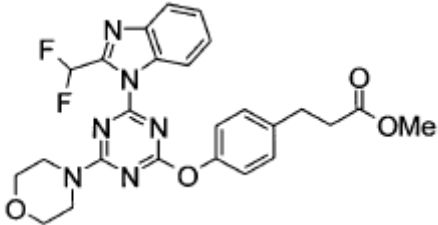
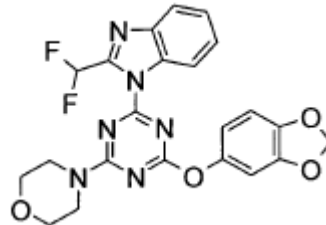
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 309]

Ej	Estr	ESI+	TR
B11#		468	3,27
B12#		496	2,86
B13#		471	3,36
B14#		471	3,51
B15#		483	3,37

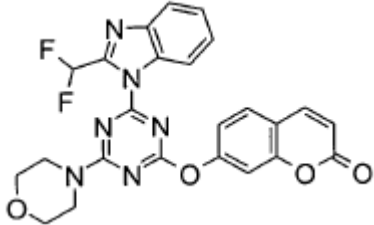
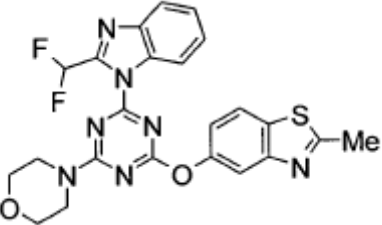
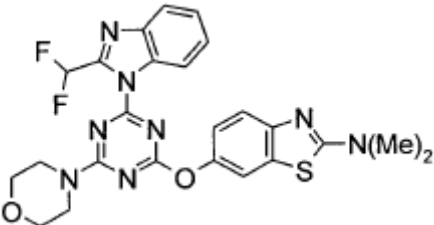
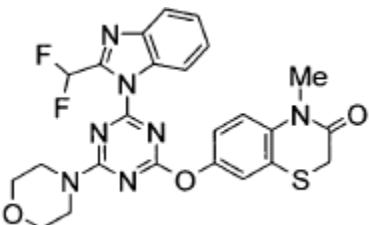
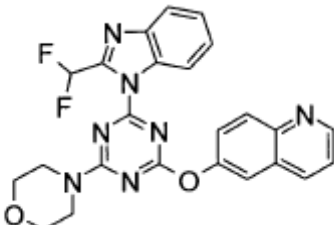
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 310]

Ej	Estr	ESI+	TR
B16#		455	3,34
B17#		499	2,95
B18#		497	3,24
B19#		511	3,37
B20#		469	3,28

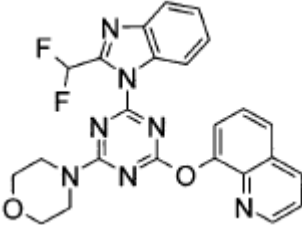
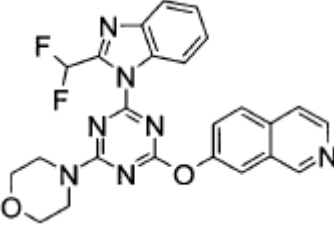
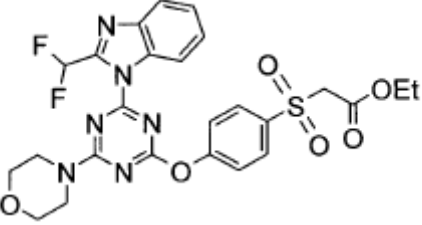
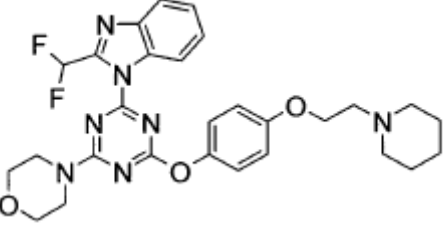
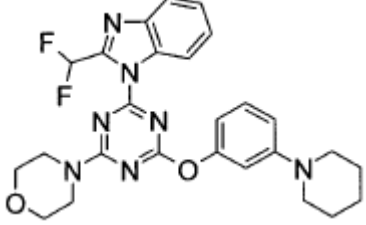
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 311]

Ej	Estr	ESI+	TR
B21#		493	2,97
B22#		496	3,24
B23#		525	3,12
B24#		526	3,17
B25#		476	2,73

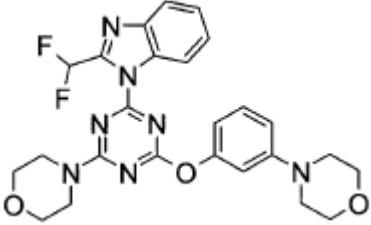
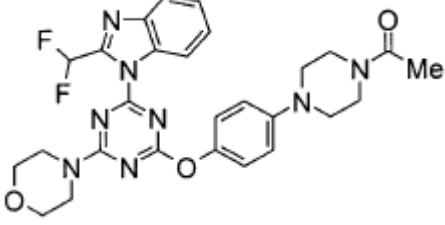
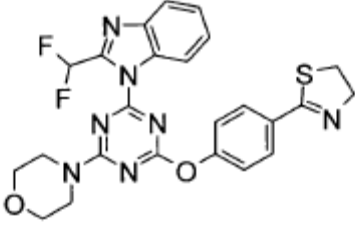
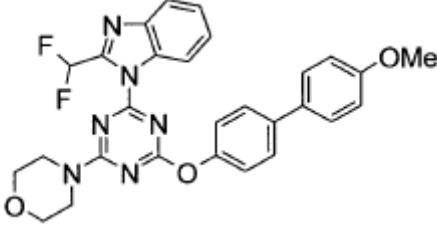
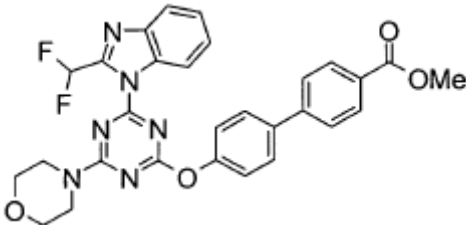
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 312]

Ej	Estr	ESI+	TR
B26#		476	2,98
B27#		476	2,46
B28#		575	2,88
B29#		552	2,62
B30#		508	3

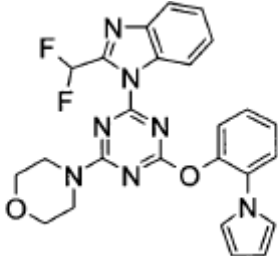
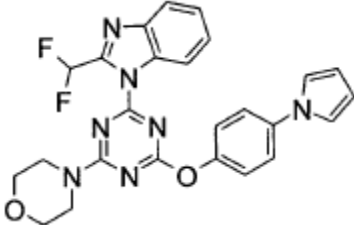
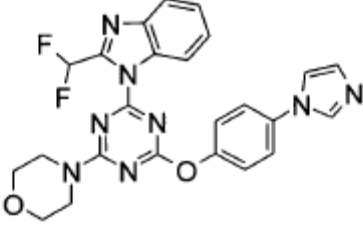
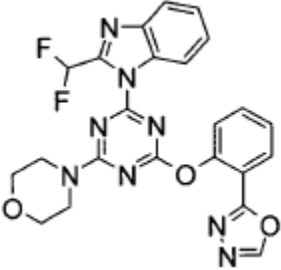
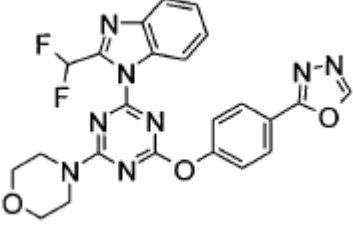
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 313]

Ej	Estr	ESI+	TR
B31#		510	3,25
B32#		551	3,02
B33#		510	3,23
B34#		531	3,84
B35#		559	3,82

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 314]

Ej	Estr	ESI+	TR
B36#		490	3,43
B37#		490	3,62
B38#		491	2,35
B39#		493	2,88
B40#		493	2,95

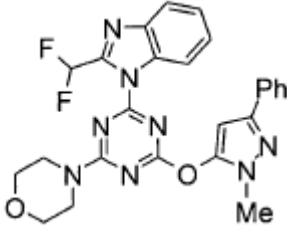
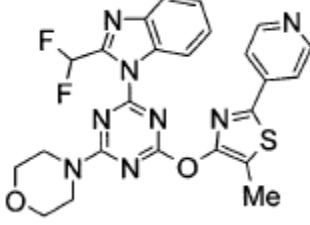
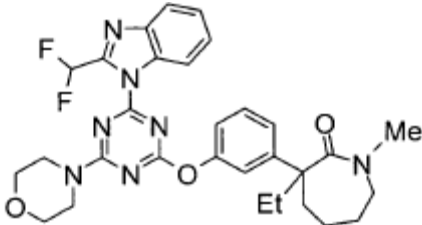
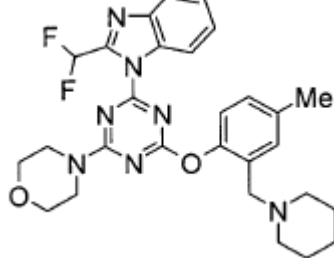
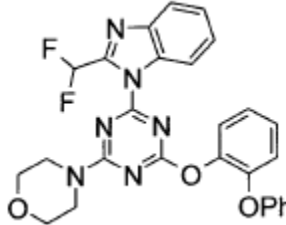
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 315]

Ej	Estr	ESI+	TR
B41#	<p>Chemical structure of compound B41#: A central 1,3,5-triazine ring is substituted with a morpholine group at position 4, a 2,6-difluorophenyl group at position 2, and a 4-(methylisoxazol-5-yl)phenoxy group at position 6.</p>	507	3,36
B42#	<p>Chemical structure of compound B42#: A central 1,3,5-triazine ring is substituted with a morpholine group at position 4, a 2,6-difluorophenyl group at position 2, and a 4-(1,2,4-triazol-5-yl)phenoxy group at position 6.</p>	492	3
B43#	<p>Chemical structure of compound B43#: A central 1,3,5-triazine ring is substituted with a morpholine group at position 4, a 2,6-difluorophenyl group at position 2, and a 4-(quinoline-2-yl)phenoxy group at position 6.</p>	552	3,58
B44#	<p>Chemical structure of compound B44#: A central 1,3,5-triazine ring is substituted with a morpholine group at position 4, a 2,6-difluorophenyl group at position 2, and a 4-(2-benzofuran-5-yl)phenoxy group at position 6.</p>	542	3,51
B45#	<p>Chemical structure of compound B45#: A central 1,3,5-triazine ring is substituted with a morpholine group at position 4, a 2,6-difluorophenyl group at position 2, and a 4-(1H-imidazo[4,5-b]pyridine-2-yl)phenoxy group at position 6.</p>	541	2,54

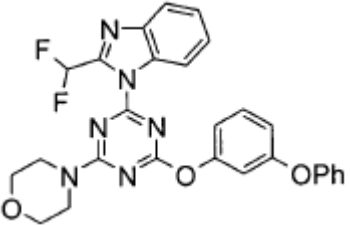
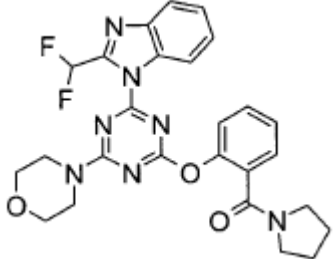
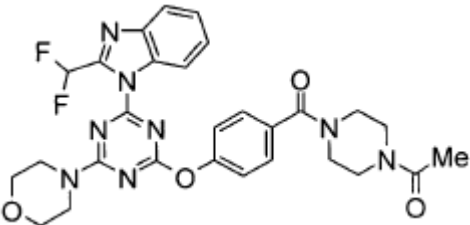
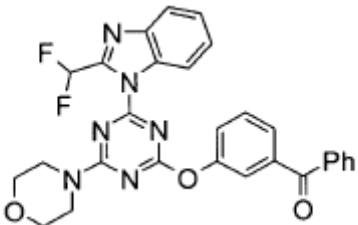
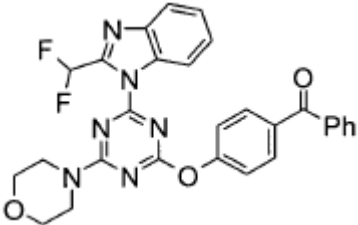
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 316]

Ej	Estr	ESI+	TR
B46#		505	3,31
B47#		523	2,73
B48#		578	3,52
B49#		536	3,57
B50#		517	3,59

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 317]

Ej	Estr	ESI+	TR
B51#		517	3,78
B52#		522	3,06
B53#		579	2,76
B54#		529	3,56
B55#		529	3,54

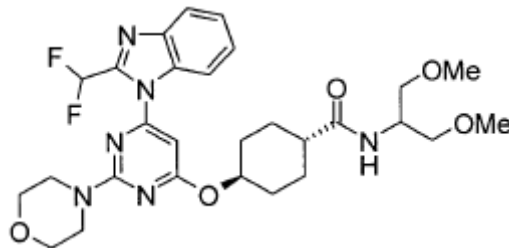
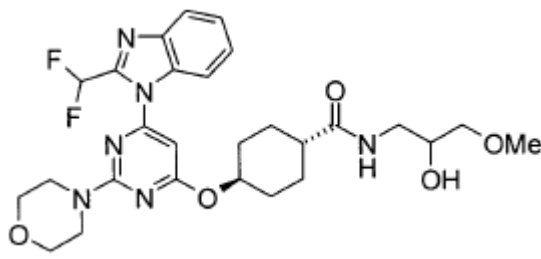
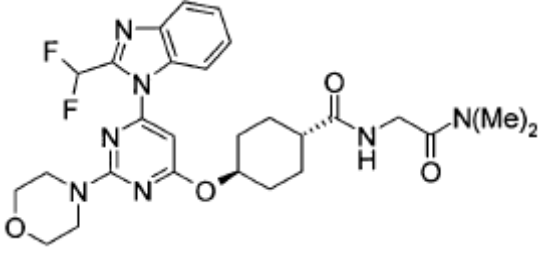
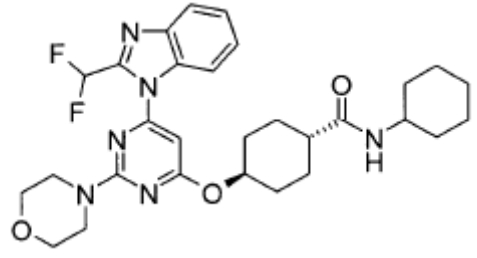
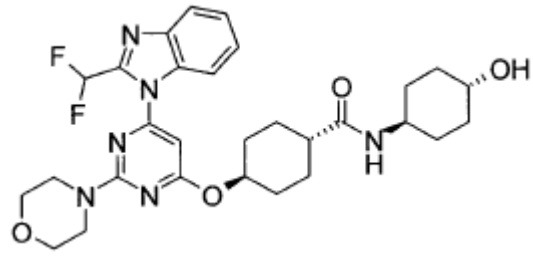
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 318]

Ej	Estr	ESI+	TR
B56#	<p>Chemical structure of B56#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a 4-(2,6-dimethylpyridin-2-ylsulfanyl)phenoxy group.</p>	563	3,54
B57#	<p>Chemical structure of B57#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring which is further substituted with a hydroxyethylcarbamoyl group.</p>	517	2,73
B58#	<p>Chemical structure of B58#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring which is further substituted with a (1-hydroxyethyl)carbamoyl group.</p>	543	2,85
B59#	<p>Chemical structure of B59#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring which is further substituted with a methoxyethylcarbamoyl group.</p>	531	2,88
B60#	<p>Chemical structure of B60#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring which is further substituted with a methoxypropylcarbamoyl group.</p>	545	2,93

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 319]

Ej	Estr	ESI+	TR
B61#		575	2,96
B62#		561	2,8
B63#		558	2,8
B64#		555	3,21
B65#		571	2,87

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 320]

Ej	Estr	ESI+	TR
B66#	<p>The structure of B66# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoro-1H-benzimidazol-5-yl group at the 4-position, and a cyclohexane ring at the 6-position. The cyclohexane ring is further substituted with a morpholine ring and an amide group (-NH-C(=O)-morpholine).</p>	557	2,92
B67#	<p>The structure of B67# is similar to B66#, but the amide group is attached to a morpholine ring that also has a hydroxyl group (-OH) on the adjacent carbon.</p>	587	2,83
B68#	<p>The structure of B68# is similar to B66#, but the amide group is attached to a morpholine ring that is substituted with a methyl group (-Me) on the nitrogen atom.</p>	598	2,84
B69#	<p>The structure of B69# is similar to B66#, but the amide group is attached to a morpholine ring that is substituted with an ethyl ester group (-COOEt) on the nitrogen atom.</p>	628	3,07
B70#	<p>The structure of B70# is similar to B66#, but the amide group is attached to a morpholine ring that is substituted with a phenyl group (-Ph) on the nitrogen atom.</p>	632	3,14

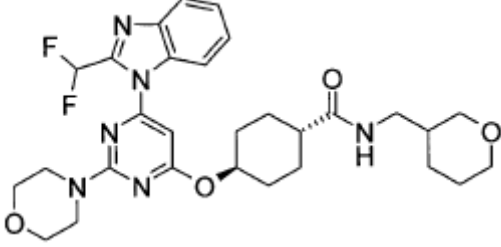
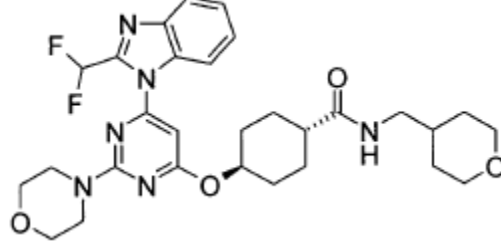
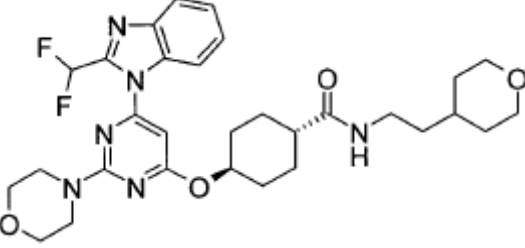
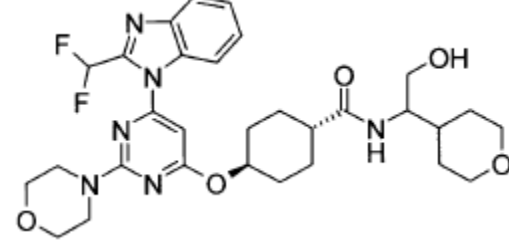
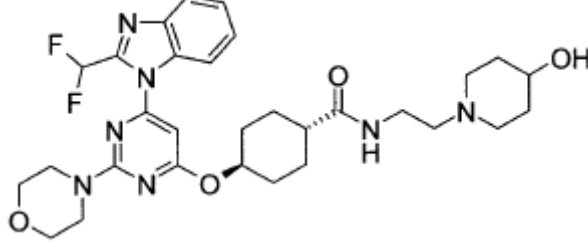
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 321]

Ej	Estr	ESI+	TR
B71#	<p>Chemical structure of compound B71#: A central pyrimidine ring substituted with a morpholine group at position 2, a 2,6-difluorophenyl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a morpholine group and an amide linkage to a piperidine ring.</p>	640	2,48
B72#	<p>Chemical structure of compound B72#: Similar to B71#, but the amide linkage connects to a 2-methyl-2-oxoimidazolidine ring.</p>	584	2,78
B73#	<p>Chemical structure of compound B73#: Similar to B71#, but the amide linkage connects to a morpholine ring. An asterisk (*) is placed above the morpholine ring, indicating it is not claimed.</p>	557	2,96
B74#	<p>Chemical structure of compound B74#: Similar to B71#, but the amide linkage connects to a morpholine ring. An asterisk (*) is placed above the morpholine ring, indicating it is not claimed.</p>	557	2,97
B75#	<p>Chemical structure of compound B75#: Similar to B71#, but the amide linkage connects to a morpholine ring.</p>	571	3,08

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 322]

Ej	Estr	ESI+	TR
B76#		571	2,98
B77#		571	2,94
B78#		585	3,01
B79#		601	2,81
B80#		600	2,3

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 323]

Ej	Estr	ESI+	TR
B81#	<p>Chemical structure of B81#: A pyrimidopyrimidinone core substituted with a morpholine ring, a 2,6-difluorophenyl group, and a cyclohexane ring. The cyclohexane ring is linked via an ether oxygen to a carbonyl group, which is further connected to a morpholine ring.</p>	586	2,31
B82#	<p>Chemical structure of B82#: Similar to B81#, but the morpholine ring is substituted with two methyl groups (Me).</p>	614	2,33
B83#	<p>Chemical structure of B83#: Similar to B81#, but the morpholine ring is substituted with a carbonyl group and another morpholine ring.</p>	600	2,79
B84#	<p>Chemical structure of B84#: Similar to B81#, but the morpholine ring is substituted with a 2,5-dihydrofuran ring.</p>	585	3
B85#	<p>Chemical structure of B85#: Similar to B81#, but the morpholine ring is substituted with a propyl chain.</p>	600	2,31

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 324]

Ej	Estr	ESI+	TR
B86#	<p>Chemical structure of compound B86#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoroethyl group, and a benzimidazole ring. It is linked via an ether bridge to a cyclohexane ring, which is further substituted with a morpholine ring and a hydroxyethylamino group.</p>	616	2,32
B87#	<p>Chemical structure of compound B87#: Similar to B86#, but the hydroxyethylamino group is replaced by a 3-methoxybenzylamino group.</p>	593	3,12
B88#	<p>Chemical structure of compound B88#: Similar to B86#, but the hydroxyethylamino group is replaced by a 4-methoxybenzylamino group.</p>	593	3,09
B89#	<p>Chemical structure of compound B89#: Similar to B86#, but the hydroxyethylamino group is replaced by a 3,5-dimethoxybenzylamino group.</p>	593	3,08
B90#	<p>Chemical structure of compound B90#: Similar to B86#, but the hydroxyethylamino group is replaced by a 4-hydroxybenzylamino group.</p>	579	2,87

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 325]

Ej	Estr	ESI+	TR
B91#	<p>Chemical structure of B91#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,2-difluoro-1H-benzimidazol-5-yl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 2-pyridylmethylcarbamoyl group.</p>	564	2,8
B92#	<p>Chemical structure of B92#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,2-difluoro-1H-benzimidazol-5-yl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 2-pyridylmethylcarbamoyl group.</p>	564	2,64
B93#	<p>Chemical structure of B93#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,2-difluoro-1H-benzimidazol-5-yl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 2-pyridylmethylcarbamoyl group.</p>	564	2,5
B94#	<p>Chemical structure of B94#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,2-difluoro-1H-benzimidazol-5-yl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 1-methyl-1H-tetrazol-5-ylmethylcarbamoyl group.</p>	569	2,75
B95#	<p>Chemical structure of B95#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 2,2-difluoro-1H-benzimidazol-5-yl group at position 4, and a cyclohexane ring at position 6. The cyclohexane ring is further substituted with a 4-(morpholin-2-yl)benzylcarbamoyl group.</p>	648	3,03

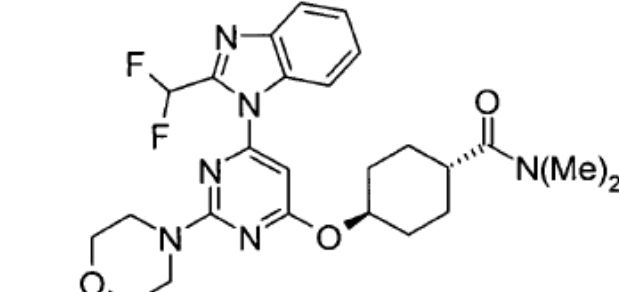
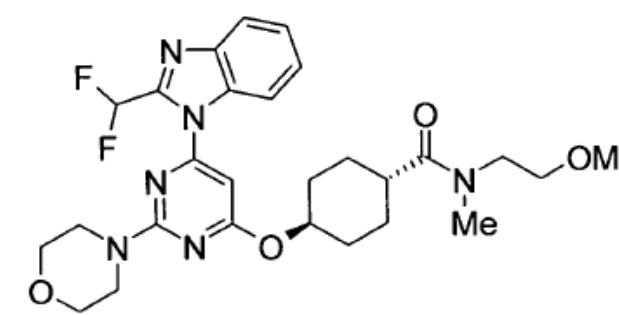
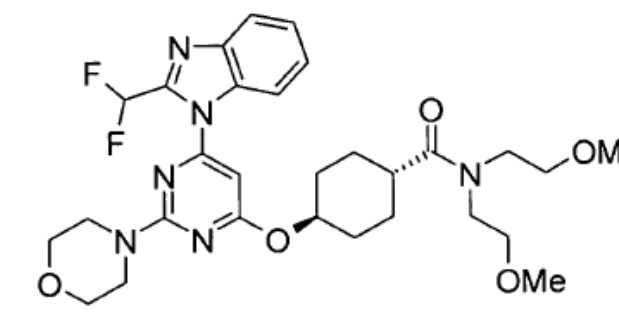
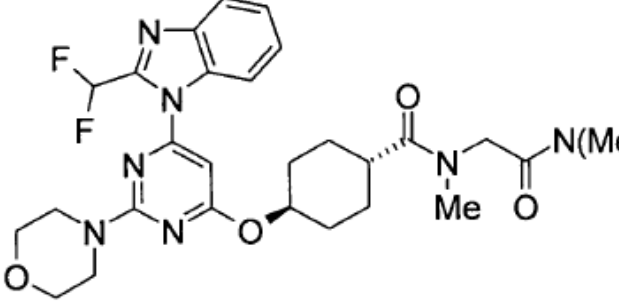
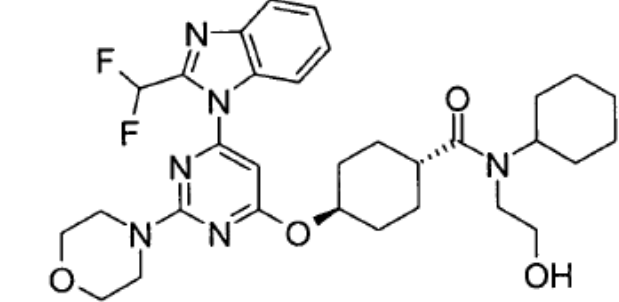
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 326]

Ej	Estr	ESI+	TR
B96#	<p>Chemical structure of B96#: A central pyrimidine ring is substituted with a morpholine group at position 2, a 1H-benzotriazol-2-ylidene group at position 4, and a 4-methoxyphenyl group at position 6. The pyrimidine ring is linked via an oxygen atom to a cyclohexane ring. The cyclohexane ring is further substituted with a 4-methoxyphenylacetamide group.</p>	607	3,14
B97#	<p>Chemical structure of B97#: Similar to B96#, but the 4-methoxyphenylacetamide group is replaced by a 2-pyridylacetamide group.</p>	578	2,62
B98#	<p>Chemical structure of B98#: Similar to B97#, but the 2-pyridylacetamide group is replaced by a 3-pyridylacetamide group.</p>	578	2,59
B99#	<p>Chemical structure of B99#: Similar to B97#, but the 2-pyridylacetamide group is replaced by a 4-pyridylacetamide group.</p>	578	2,47
B100#	<p>Chemical structure of B100#: Similar to B96#, but the 4-methoxyphenylacetamide group is replaced by a 4-methoxyphenylpropylacetamide group.</p>	621	3,2

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 327]

Ej	Estr	ESI+	TR
B101#		501	2,94
B102#		545	2,99
B103#		589	3,07
B104#		572	2,81
B105#		599	3,19

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 328]

Ej	Estr	ESI+	TR
B106#	<p>The structure of B106# features a central pyrimidopyrimidinone core. It is substituted with a morpholine ring at the 2-position, a 2-fluorophenyl group at the 4-position, and a 2,2-difluoroethyl group at the 6-position. A cyclohexane ring is attached to the 5-position of the core via an oxygen atom. This cyclohexane ring is further substituted with a methyl group and a carbonyl group, which is linked to a morpholine ring.</p>	571	3
B107#	<p>The structure of B107# is similar to B106#, but the morpholine ring attached to the carbonyl group is substituted with an ethyl ester group (-COOEt).</p>	642	3,12
B108#	<p>The structure of B108# is similar to B106#, but the morpholine ring attached to the carbonyl group is substituted with a methyl group and a morpholine ring.</p>	585	3,22
B109#	<p>The structure of B109# is similar to B106#, but the morpholine ring attached to the carbonyl group is substituted with a methyl group and a morpholine ring.</p>	585	3,03
B110#	<p>The structure of B110# is similar to B106#, but the morpholine ring attached to the carbonyl group is substituted with a methyl group and a morpholine ring.</p>	598	2,37

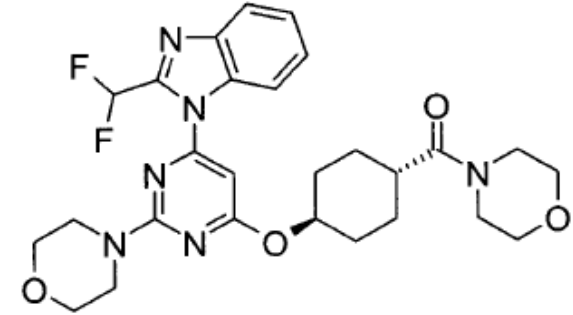
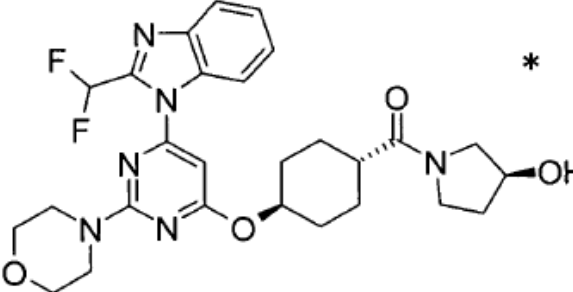
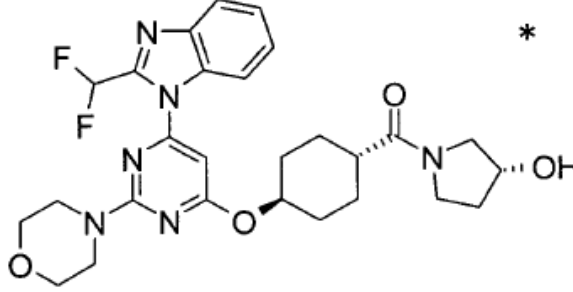
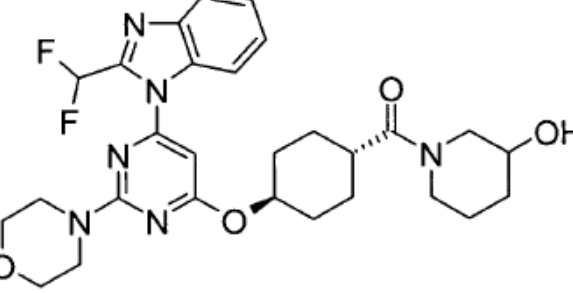
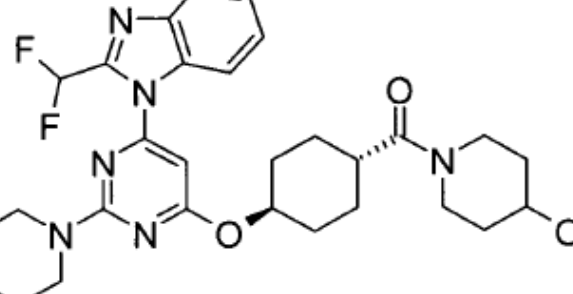
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 329]

Ej	Estr	ESI+	TR
B111#	<p>Chemical structure of B111#: A central pyrimidine ring is substituted at the 2-position with a morpholine ring, at the 4-position with a 2-(2-fluorophenyl)imidazole-1-yl group, and at the 6-position with a cyclohexane ring. The cyclohexane ring is further substituted at the 1-position with a methylcarbamoyl group and at the 2-position with a morpholine ring.</p>	614	2,81
B112#	<p>Chemical structure of B112#: Similar to B111#, but the cyclohexane ring is substituted at the 2-position with a 4-methoxybenzyl group instead of a morpholine ring.</p>	607	3,2
B113#	<p>Chemical structure of B113#: Similar to B111#, but the cyclohexane ring is substituted at the 2-position with a 3-pyridylmethyl group instead of a morpholine ring.</p>	578	2,63
B114#	<p>Chemical structure of B114#: Similar to B111#, but the cyclohexane ring is substituted at the 2-position with a 3-pyridylpropyl group instead of a morpholine ring.</p>	592	2,58
B115#	<p>Chemical structure of B115#: Similar to B111#, but the cyclohexane ring is substituted at the 2-position with a piperidine ring instead of a morpholine ring.</p>	541	3,18

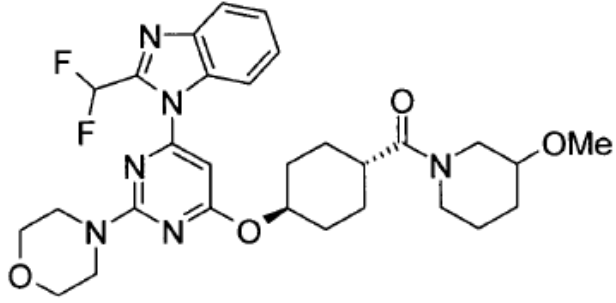
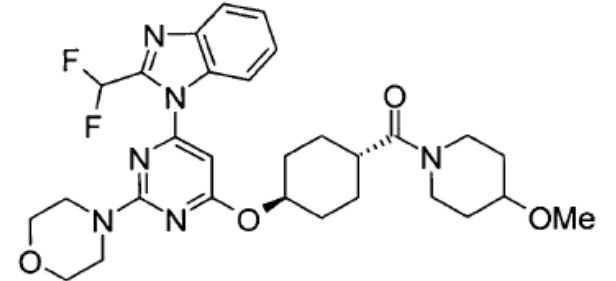
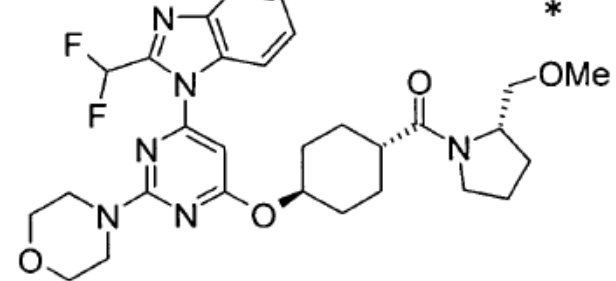
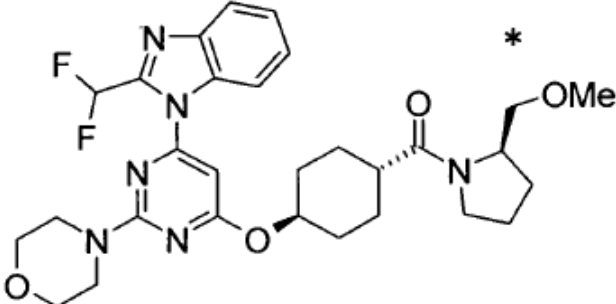
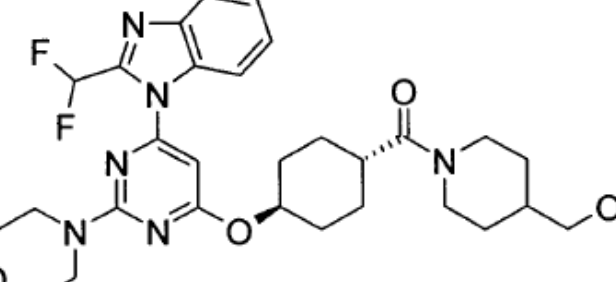
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 330]

Ej	Estr	ESI+	TR
B116#		543	2,91
B117#		543	2,8
B118#		543	2,8
B119#		557	2,89
B120#		557	2,84

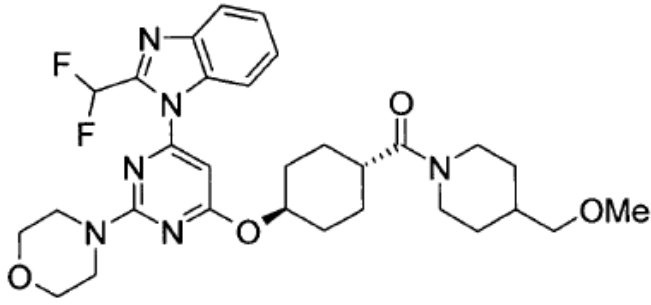
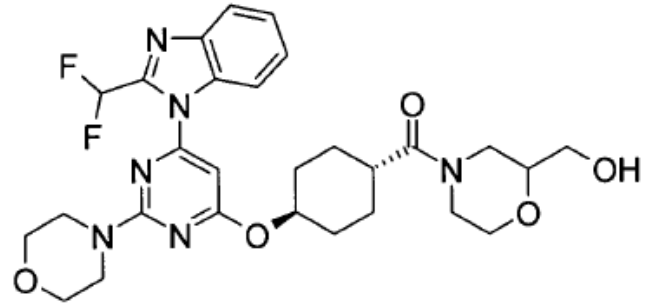
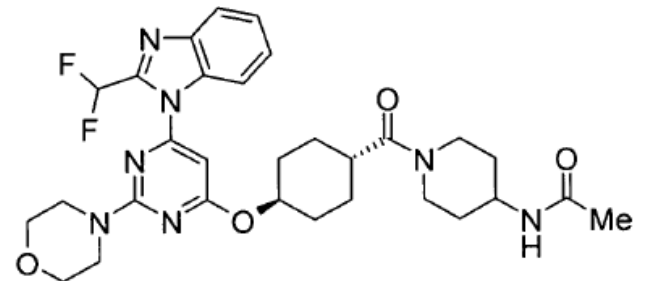
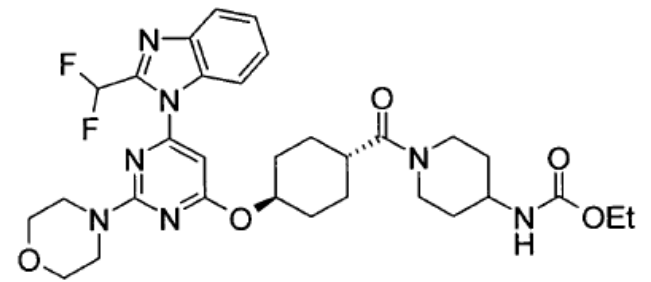
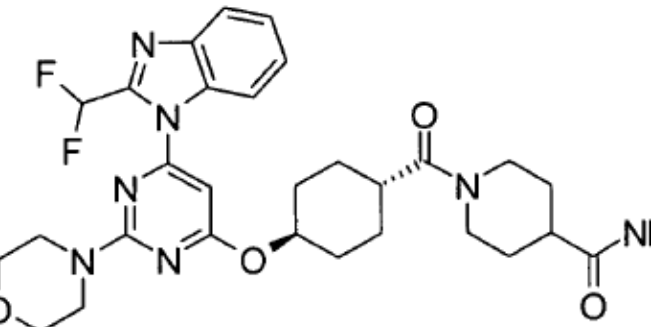
los compuestos marcados no están englobados en las reivindicaciones

[Tabla 331]

Ej	Estr	ESI+	TR
B121#		571	3,07
B122#		571	3,04
B123#		571	3,13
B124#		571	3,13
B125#		571	2,9

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 332]

Ej	Estr	ESI+	TR
B126#		585	3,12
B127#		573	2,79
B128		598	2,81
B129#		628	2,99
B130#		584	2,74

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 333]

Ej	Estr	ESI+	TR
B131#	<p>The structure of B131# features a central pyrimidopyrimidine core. At position 2, there is a morpholine ring. At position 4, there is a benzimidazole ring substituted with a difluoromethyl group (-CF₂H). At position 6, there is a cyclohexane ring connected via an oxygen atom. The cyclohexane ring is further substituted with a piperazine ring, which is in turn connected to a hydroxyethyl group (-CH₂CH₂OH).</p>	586	2,27
B132#	<p>The structure of B132# is similar to B131#, but the hydroxyethyl group is replaced by a dimethylacetamide group (-CH₂CO-NMe₂).</p>	627	2,33
B133#	<p>The structure of B133# is similar to B131#, but the piperazine ring is replaced by a 5-membered cyclic urea derivative with a hydroxyl group (-OH).</p>	572	2,69
B134#	<p>The structure of B134# is similar to B131#, but the piperazine ring is replaced by a 6-membered cyclic urea derivative with a methyl group (-Me).</p>	570	2,76
B135#	<p>The structure of B135# is similar to B131#, but the piperazine ring is replaced by a 6-membered cyclic urea derivative with a methyl group (-Me) and a carbonyl group (=O).</p>	584	2,79

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 334]

Ej	Estr	ESI+	TR
B136#	<p>The structure of B136# features a central pyrimidopyrimidine core. It is substituted with a morpholine ring at the 2-position, a 2,2-difluoroethyl group at the 4-position, and a benzimidazole ring at the 6-position. The 5-position is linked via an ether oxygen to a cyclohexane ring, which is further substituted with a piperazine ring containing a methyl ester group.</p>	600	2,95
B137#	<p>The structure of B137# is similar to B136# but the piperazine ring is fused to a pyrrolidine ring, which has a methyl group attached to its nitrogen atom.</p>	624	2,87
B138#	<p>The structure of B138# is similar to B136# but the piperazine ring is fused to a pyrrolidine ring without a methyl group on the nitrogen.</p>	582	2,3
B139#	<p>The structure of B139# is similar to B136# but the piperazine ring is fused to a benzene ring, which has a methoxy group attached to it.</p>	619	3,28
B140#	<p>The structure of B140# is similar to B136# but the piperazine ring is fused to a pyridine ring.</p>	590	2,97

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 335]

Ej	Estr	ESI+	TR
B141#	<p>Chemical structure of B141#: A central pyrimidopyrimidine core substituted with a 2,2-difluoro-1H-benzotriazol-4-yl group, a morpholine ring, and a cyclohexane ring. The cyclohexane ring is further substituted with a carbonyl group linked to a piperidine ring, which is in turn linked to a morpholine ring.</p>	626	2,32
B142#	<p>Chemical structure of B142#: Similar to B141#, but the piperidine ring is substituted with a pyridine ring instead of a morpholine ring.</p>	604	2,66
B143#	<p>Chemical structure of B143#: Similar to B141#, but the piperidine ring is substituted with a morpholine ring via a methylene bridge.</p>	640	2,35
B144#	<p>Chemical structure of B144#: Similar to B141#, but the piperidine ring is substituted with a morpholine ring via a methylene bridge, and the morpholine ring is further substituted with a pyrrolidine ring.</p>	626	2,35
B145#	<p>Chemical structure of B145#: Similar to B141#, but the piperidine ring is substituted with a morpholine ring via a methylene bridge, and the morpholine ring is further substituted with a pyridine ring.</p>	634	2,44

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 336]

Ej	Estr	ESI+	TR
B146#	<p>Chemical structure of B146#: A central pyrimidopyrimidinone core substituted with a morpholine ring, a 2,2-difluoro-1H-benzotriazol-5-yl group, and a cyclohexane ring. The cyclohexane ring is further substituted with a piperazine ring and a morpholine ring.</p>	655	2,33
B147#	<p>Chemical structure of B147#: Similar to B146#, but the cyclohexane ring is substituted with a benzamide group (N,N-dimethyl-4-aminobenzamide) instead of the piperazine and morpholine rings.</p>	636	3,11
B148#	<p>Chemical structure of B148#: Similar to B146#, but the cyclohexane ring is substituted with a 4-methoxybenzamide group instead of the piperazine and morpholine rings.</p>	580	3,09
B149#	<p>Chemical structure of B149#: Similar to B146#, but the cyclohexane ring is substituted with a benzamide group (N-phenylethanolamide) instead of the piperazine and morpholine rings.</p>	593	3,32
B150#	<p>Chemical structure of B150#: Similar to B146#, but the cyclohexane ring is substituted with a morpholine ring and a 4-hydroxyphenyl group instead of the piperazine and morpholine rings.</p>	607	3,24

los compuestos marcados no están englobados en las reivindicaciones

[Tabla 337]

Ej	Estr	ESI+	TR
B151#	<p>The chemical structure of compound B151# is a complex molecule. It features a central pyrimidine ring system. One nitrogen of the pyrimidine is substituted with a morpholine ring. The other nitrogen is substituted with a benzimidazole ring system, which has a difluoromethyl group (-CF₂H) attached to its 2-position. The 4-position of the pyrimidine ring is linked via an oxygen atom to a cyclohexane ring. This cyclohexane ring is further substituted with a carbonyl group (-C(=O)-) and a nitrogen atom. The nitrogen atom is part of a side chain that includes a benzene ring with a hydroxyl group (-OH) and a methylene group (-CH₂-).</p>	621	3,27

los compuestos marcados no están englobados en las reivindicaciones

Aplicabilidad industrial

5

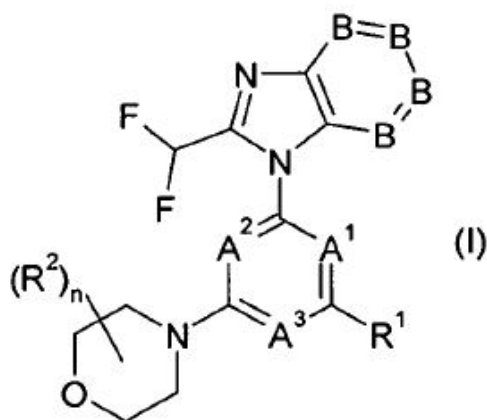
El compuesto, que es el principio activo del fármaco de la presente invención, tiene una acción inhibidora selectiva de PI3K δ y/o una acción inhibidora de la producción de IL-2 y/o una acción inhibidora de la proliferación de linfocitos B (incluyendo una acción inhibidora de la activación), así como una buena acción farmacológica basada en las mismas. Por tanto, la composición farmacéutica de la presente invención se puede usar como agente para la

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prevención o tratamiento de las reacciones de rechazo en varios de trasplantes de órganos, enfermedades de alergia (asma, dermatitis atópica, y similares), enfermedades autoinmunitarias (artritis reumatoide, psoriasis, colitis ulcerosa, enfermedad de Crohn, lupus eritematoso sistémico, y similares), y tumor hemático (leucemia y similares).

REIVINDICACIONES

1. Un compuesto de fórmula (I) o una sal del mismo:



- 5 (en la que
 A² y A³ son N y A¹ es CH o A¹ y A³ son N y A² es CH, todos los B son CH y n es 0,
 10 R¹ es -L¹-L²-Y, en el que -L¹-L²-es -NH- u -O-,
 Y es un heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo D1, y el grupo D1 consiste en:
 15 (1) -L^{5a}-(heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado, -NH-C(O)-O-[alquilo C₁₋₆ lineal o ramificado], -C(O)O-[alquilo C₁₋₆ lineal o ramificado], -C(O)-[alquilo C₁₋₆ lineal o ramificado], y oxo), en el que L^{5a} representa un enlace, -C(O)-[alquilenos C₁₋₆ lineal o ramificado-], o -C(O)-, y
 20 (2) -C(O)-(cicloalquilo que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado que puede estar sustituido con -OH, -OH y -O-[alquilo C₁₋₆ lineal o ramificado]).
 2. El compuesto o una sal del mismo de acuerdo con la reivindicación 1, en el que A² y A³ son N y A¹ es CH.
 25 3. El compuesto o sal del mismo de acuerdo con la reivindicación 1, en el que -L¹-L²- es -NH-.
 4. El compuesto o sal del mismo de acuerdo con la reivindicación 1, en el que Y es piperidinilo, pirrolidinilo, o azetidínulo que pueden estar respectivamente sustituidos con uno o más sustituyentes seleccionados del grupo D1.
 30 5. El compuesto o una sal del mismo de acuerdo con la reivindicación 1, en el que el grupo D1 consiste en:
 -L^{5a}-(heterociclo no aromático que puede estar sustituido con uno o más sustituyentes seleccionados del grupo que consiste en alquilo C₁₋₆ lineal o ramificado, -C(O)O-[alquilo C₁₋₆ lineal o ramificado], -C(O)-[alquilo C₁₋₆ lineal o ramificado] y oxo), en el que L^{5a} representa un enlace o -C(O)-.
 35 6. El compuesto o una sal del mismo de acuerdo con la reivindicación 1, en el que el compuesto es
 40 [(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il)][(2R)-tetrahidrofuran-2-il]metanona,
 [(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il](tetrahidro-
 2H-piran-4-il)metanona,
 45 4-[[[(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il]carbonil]piperidin-1-carboxilato de metilo,
 [(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxi)pirrolidin-1-il](tetrahidrofuran-
 3-il)metanona,
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- 4-[[{(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxi)pirrolidin-1-il]carbonil)-1-metilpirrolidin-2-ona,
- 5 [(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il](tetrahidrofuran-3-il)metanona,
- 10 4-[[{(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il]carbonil)-1-metilpirrolidin-2-ona,
- 15 7. El compuesto o una sal del mismo de acuerdo con la reivindicación 6, en el que el compuesto es [(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}amino)pirrolidin-1-il](tetrahidro-2H-piran-4-il)metanona.
- 20 8. El compuesto o una sal del mismo de acuerdo con la reivindicación 6, en el que el compuesto es [(3S)-3-({6-[2-(difluorometil)-1H-benzimidazol-1-il]-2-(morfolin-4-il)pirimidin-4-il}oxi)pirrolidin-1-il](tetrahidrofuran-3-il)metanona.
9. Una composición farmacéutica, que comprende el compuesto o una sal del mismo de acuerdo con una cualquiera de las reivindicaciones 1 a 8 y un excipiente farmacéuticamente aceptable.
- 25 10. Una composición farmacéutica para su uso en un procedimiento para la prevención o tratamiento de las reacciones de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias o tumor hemático, que comprende el compuesto o una sal del mismo de acuerdo con una cualquiera de las reivindicaciones 1 a 8 y un excipiente farmacéuticamente aceptable.
- 30 11. El compuesto o una sal del mismo de acuerdo con una cualquiera de las reivindicaciones 1 a 8, para su uso en un procedimiento para la prevención o tratamiento de las reacciones de rechazo en varios trasplantes de órganos, enfermedades de alergia, enfermedades autoinmunitarias o tumor hemático.