COMPUESTOS BIFUNCIONALES DEL RECEPTOR DE ANDRÓGENOS

REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

[0001] La presente solicitud reivindica la prioridad a, y el beneficio de, la solicitud de patente provisional estadounidense N.° 63/589.861, presentada el 12 de octubre de 2023, y la solicitud de patente provisional estadounidense N.° 63/636.293, presentada el 19 de abril de 2024, cuyas divulgaciones se incorporan en la presente por referencia en su totalidad.

CAMPO DE LA INVENCIÓN

[0001] En el presente documento se describen pequeñas moléculas heterobifuncionales, métodos para su elaboración, composiciones farmacéuticas y medicamentos que contienen dichas pequeñas moléculas heterobifuncionales, así como métodos para su uso en el tratamiento de enfermedades y afecciones como el cáncer, las enfermedades autoinmunes y las enfermedades inflamatorias.

ANTECEDENTES DE LA INVENCIÓN

[0002] La homeostasis celular, una característica clave de los organismos vivos, surge de las interacciones entre biomoléculas, como las interacciones entre proteínas (por ejemplo, enzimas) y sustratos, dentro y fuera de la célula. Tradicionalmente, la función de una proteína en particular en un estado patológico específico se ha investigado y controlado mediante el uso de moléculas monofuncionales (por ejemplo, un inhibidor), que ocupan el sitio activo de la proteína causante de la enfermedad, formando así complejos binarios que inhiben o reducen la actividad de dichas proteínas. Estas moléculas monofuncionales han proporcionado una vía conceptual hacia muchos fármacos aprobados por la FDA como medio para tratar la enfermedad.

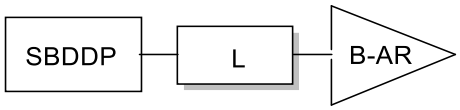
[0003] Sin embargo, muchas moléculas monofuncionales carecen de especificidad para las proteínas causantes de la enfermedad, lo que conlleva toxicidades indeseadas o falta de eficacia, o bien las proteínas causantes de la enfermedad se adaptan a las moléculas monofuncionales, lo que genera resistencia. Un enfoque alternativo con moléculas monofuncionales consiste en dirigirse a las proteínas correguladoras o coactivadoras de las proteínas causantes de la enfermedad. Sin embargo, este tipo de proteínas correguladoras o coactivadoras suelen estar presentes en todas las células, sanas o enfermas, y la inhibición de su actividad generalmente conlleva índices terapéuticos más estrechos.

[0004] En este documento se describen pequeñas moléculas heterobifuncionales que

interactúan con el receptor de andrógenos (AR) y una proteína dependiente de la enfermedad, formando así complejos ternarios únicamente en las células afectadas que expresan ambas proteínas, lo que conlleva la pérdida de función de la proteína dependiente de la enfermedad. Las pequeñas moléculas heterobifuncionales descritas en este documento comprenden al menos un ligando silencioso para la proteína dependiente de la enfermedad y al menos un ligando para AR. Estas pequeñas moléculas heterobifuncionales ofrecen un nuevo medio para el tratamiento de enfermedades o afecciones, con un índice terapéutico más amplio y ofrecen nuevas dianas terapéuticas frente a la expansión de las proteínas de la enfermedad, como el AR.

SINTESÍS DE LA INVENCIÓN

[0005] En algunas formas de realización, el compuesto de fórmula I es un compuesto de fórmula I', o una sal o solvato farmacéuticamente aceptable de este.



en donde:

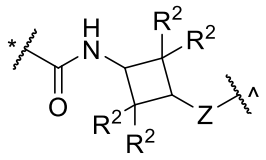
SBDDP es un ligando silencioso de una proteína dependiente de la enfermedad (DDP);

L es un ligador opcional; donde L está unido covalentemente en una posición de SBDDP que está expuesta al disolvente cuando SBDDP se une a DDP;

B-AR es un ligando del receptor de andrógenos (AR), en el que B-AR comprende:

1) un grupo principal que ocupa el dominio de unión al ligando (LBD) del AR y está unido covalentemente a una porción central; y

2) una porción de cola opcional unida covalentemente a la porción central; donde el núcleo comprende un ciclobutilo opcionalmente sustituido que tiene la estructura de Fórmula (C):



, Fórmula (C);

El grupo principal está unido covalentemente a Z en la posición (^);

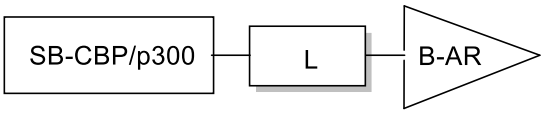
La porción de cola opcional comprende un anillo D que está unido covalentemente a la amida (*), donde el anillo D está opcionalmente sustituido con s R^3;

donde: Z es -O- o -NR^5-; y R^2 y R^3 se describen aquí;

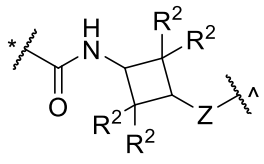
donde L está unido covalentemente a la porción central en la posición (*) si la porción de cola opcional está ausente, o L está unido covalentemente a la porción de cola si

está presente;
donde DDP y AR se expresan en una célula de interés (COI), y donde la abundancia relativa de AR en la COI es mayor que la abundancia relativa de DDP en la COI; o la COI es una célula enferma, y el AR está sobreexpresado, hiperactivo, o sobreexpresado e hiperactivo a la vez, o amplificado en la célula enferma en comparación con cuando la COI es una célula no enferma.

[0006] En algunas formas de realización, el compuesto de fórmula A es un compuesto de fórmula A-ii, o una sal o solvato farmacéuticamente aceptable de este.



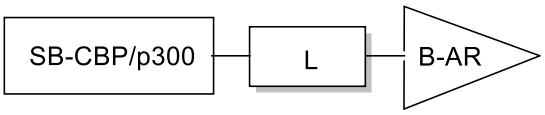
en donde:
SB-CBP/p300 es un ligando silencioso de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300);
L es un ligador opcional; donde L está unido covalentemente en una posición de SB-CBP/p300 que está expuesta al disolvente cuando SB se une a CBP/p300;
El B-AR es un ligando del receptor de andrógenos (AR), en el que el B-AR comprende:
1) un grupo principal que ocupa el dominio de unión al ligando (LBD) del AR y está unido covalentemente a una porción central; y
2) una porción de cola opcional unida covalentemente a la porción central; donde el núcleo comprende un ciclobutilo opcionalmente sustituido que tiene la estructura de Fórmula (C):



, Fórmula (C);

donde: el grupo cabeza está unido covalentemente a Z en la posición (^); la porción de cola opcional comprende un anillo D que está unido covalentemente a la amida (*), donde el anillo D está opcionalmente sustituido con s R^3;
donde: Z es -O- o -NR^5-; y R^2 y R^3 se describen aquí;
donde L está unido covalentemente a la porción central en la posición (*) si la porción de cola opcional está ausente, o L está unido covalentemente a la porción de cola si está presente.

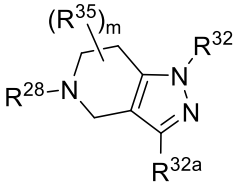
[0007] En algunas formas de realización, el compuesto de fórmula I es un compuesto de fórmula I', o una sal o solvato farmacéuticamente aceptable de este.



en donde:

SB-CBP/p300 es un ligando silencioso del bromodominio de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300), en el que el ligando de CBP/p300 comprende:

- una porción mimética de acetil-lisina que se une al sitio de unión de acetil-lisina (KAc) del bromodominio de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300) y tiene la siguiente estructura:



R^{28} es $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, $-C(=O)NH_2$, $-C(=O)NH(CH_3)$; o $-C(=O)NH(CH_2CH_3)$;

R^{32} es una porción que ocupa la región del bucle BC del bromodominio de CBP/p300;

R^{32a} es una porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300;

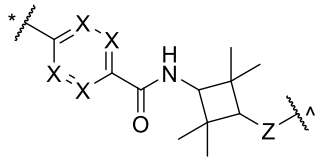
cada R^{35} es independientemente hidrógeno, C_1-C_4alquilo, o C_1-C_4fluoroalquilo;

m es 0, 1, 2, 3 o 4;

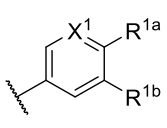
L es un ligador opcional; donde L está unido covalentemente al grupo R^{32}, o en la posición ocupada por R^{32}, o el grupo R^{32a};

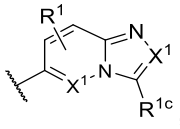
El B-AR es un ligando del receptor de andrógenos (AR), en el que el B-AR comprende:

- un grupo de cabeza que ocupa el dominio de unión al ligando (LBD) del AR y está unido covalentemente a un núcleo con una porción de cola unida covalentemente a la porción del núcleo; donde B-AR tiene la estructura de la fórmula (D):



, Fórmula (D);

donde el grupo de cabeza es 

o 

, y el grupo de cabeza está unido covalentemente a Z en la posición (^), y L está unido en la posición *;

Z es -O-, -NH- o $-N(C_1$-C_4alquilo)-; cada X^1 es independientemente $-CR^1-$ o -N-;

R^{1a} es -CN, $-NO_2$, $-C(=O)R^5$, $-C(=O)OR^5$, o $-C(=O)N(R^5)_2$;

R^{1b} es hidrógeno, halógeno, C_1-C_4alquilo sustituido o no sustituido, C_1-C_4fluoroalquilo, -CN, -OH o -OR^4;

R^{1c} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo o -CN;

cada R^1 es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH o -OR^4;

cada X es independientemente -CR^3- o -N-;

cada R^3 es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH, -OR^4 o -$N(R^5)_2$.

Cada R^4 es independientemente sustituido o no sustituido C_1-C_4alquilo, o C_1-C_4fluoroalquilo;

cada R^5 es independientemente hidrógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo; y

cada s es 1, 2 o 3.

[0008] En algunas formas de realización, se describe aquí un complejo ternario estable que comprende:

a. una o más proteínas dependientes de la enfermedad (PDE);

b. Receptor de andrógenos (AR); y

c. compuesto inhibidor condicional heterobifuncional como se describe en el presente documento;

donde DDP y AR están presentes en una célula de interés (COI) y la abundancia relativa de AR en la COI es mayor que la abundancia relativa de DDP en la COI.

[0009] En algunas formas de realización, el DDP es la proteína de unión a CREB (CBP)/p300.

[0010] En algunas formas de realización, se describe aquí un complejo ternario estable que comprende:

d. CBP/p300;

e. Receptor de andrógenos (AR); y

f. compuesto inhibidor condicional heterobifuncional como se describe en el presente documento;

donde CBP/p300 y DP están presentes en una célula de interés (COI) y la abundancia relativa de DP en la COI es mayor que la abundancia relativa de CBP/p300 en la COI.

[0011] En otro aspecto, se describe aquí un método para inhibir selectivamente la actividad de una proteína dependiente de la enfermedad (PDE) en una célula de interés (CI) de un mamífero que comprende la administración de un compuesto heterobifuncional como se describe aquí, o una sal o solvato farmacéuticamente aceptable de este, donde la CI expresa el receptor de andrógenos (RA). En algunas

formas de realización, el compuesto heterobifuncional descrito en el presente documento, o una sal o solvato farmacéuticamente aceptable de este, inhibe la actividad del DDP en el COI, pero no inhibe la actividad del DDP en las células que expresan el DDP y no expresan el AR. En algunas formas de realización, el AR está sobreexpresado, hiperactivo o ambas cosas a la vez en el COI. En algunas formas de realización, el DDP es la proteína de unión a CREB (CBP)/p300.

[0012] En otro aspecto, se describe aquí un método para tratar el cáncer en un mamífero que consiste en administrarle una cantidad terapéuticamente efectiva de un compuesto como el que se describe aquí, o una sal o solvato farmacéuticamente aceptable de este. En algunas formas de realización, el cáncer es un cáncer de uretra. En algunas formas de realización, el cáncer es cáncer de mama.

[0013] En otro aspecto, se describe aquí un método para tratar una enfermedad o afección dependiente del receptor de andrógenos o mediada por el receptor de andrógenos en mamíferos, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto como se describe aquí, o una sal o solvato farmacéuticamente aceptable de este. En algunas formas de realización, la enfermedad o afección dependiente del receptor de andrógenos o mediada por el receptor de andrógenos se selecciona entre la hiperplasia prostática benigna, el hirsutismo, los adenomas y las neoplasias de la próstata, las células tumorales benignas o malignas que contienen el receptor de andrógenos, el cáncer de próstata, el cáncer de mama, el cáncer de endometrio y el cáncer de útero.

[0014] También se divulga en la presente una composición farmacéutica que comprende un compuesto divulgado en la presente, o una sal, un solvato o estereoisómero farmacéuticamente aceptable de este y un excipiente farmacéuticamente aceptable. En algunas formas de realización, la composición farmacéutica está formulada para su administración a un mamífero por vía oral, intravenosa o subcutánea. En algunas formas de realización, la composición farmacéutica es para la administración en la conjuntiva. En algunas formas de realización, la composición farmacéutica se presenta en forma de comprimido, píldora, cápsula, líquido o suspensión.

[0015] En cierto modo, los compuestos heterobifuncionales descritos en este documento, o una sal farmacéuticamente aceptable, o un solvato de los mismos, se utilizan en el tratamiento de enfermedades o afecciones, como el cáncer, las enfermedades autoinmunes y las enfermedades inflamatorias. En algunas formas de realización, la enfermedad o trastorno es cáncer. En algunas formas de realización, el

cáncer comprende niveles alterados de expresión de AR. En algunas formas de realización, el cáncer comprende niveles alterados de expresión del receptor de andrógenos. En algunas formas de realización, los niveles de expresión DP alterados comprenden AR sobreexpresado, AR hiperactivo, AR amplificado o combinaciones de los mismos.

[0016] En cualquiera de las formas de realización descritas en el presente documento, el mamífero es un ser humano. En algunas formas de realización, los compuestos aquí descritos se administran por vía oral a un ser humano.

[0017] Otros objetos, características y ventajas de los compuestos, métodos y composiciones que se describen en el presente documento se harán evidentes a partir de la siguiente descripción detallada. Sin embargo, debe entenderse que la descripción detallada y los ejemplos específicos, si bien indican formas de realización específicas, se dan a modo de ilustración únicamente, ya que diversos cambios y modificaciones dentro del espíritu y el alcance de la presente divulgación resultarán evidentes para los expertos en la materia a partir de esta descripción detallada.

BREVE DESCRIPCIÓN DE LAS FIGURAS

[0018] **FIG.1** muestra el ensayo de formación del complejo ternario para **Compuesto 109** y **Compuesto 106**.

[0019] **La figura 2** muestra la respuesta normalizada de transferencia de energía de resonancia de bioluminiscencia (BRET) en función de la concentración del compuesto para **el compuesto 109** y el control GNE-781.

[0020] **La figura 3** muestra la respuesta normalizada de transferencia de energía de resonancia de bioluminiscencia (BRET) en función de la concentración del compuesto para GNE-781.

[0021] **FIG.4** muestra el ensayo de formación del complejo ternario para **Compuesto 424** y **Compuesto 360**.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0022] Normalmente, las células humanas crecen y se multiplican mediante la división celular para formar nuevas células según las necesidades del organismo. Cada célula humana contiene un conjunto de genes y proteínas, muchos de los cuales son necesarios para la supervivencia y la proliferación, y la alteración de estos genes y proteínas conlleva la pérdida de capacidad de respuesta o la muerte celular.

[0023] Cuando las células envejecen o se dañan, mueren y otras células nuevas ocupan su lugar. En ocasiones, este proceso ordenado se interrumpe y las células anormales o dañadas crecen y se multiplican indebidamente. En el contexto de

enfermedades como el cáncer, las enfermedades autoinmunes o las afecciones inflamatorias, ciertas proteínas impulsan el crecimiento y la multiplicación desordenados de células anormales o dañadas.

[0024] Las moléculas monofuncionales convencionales (por ejemplo, activadores, inhibidores) forman complejos binarios con una proteína diana. En estos complejos binarios, los activadores o inhibidores actúan sobre un sitio funcional, ya sea de forma ortostérica o alostérica, para modular la proteína diana.

[0025] Muchos de los cambios celulares deseados no pueden lograrse únicamente mediante la inhibición. Se ha desarrollado otra clase de moléculas, es decir, moléculas bifuncionales, que actúan induciendo la proximidad entre las proteínas objetivo para formar complejos ternarios, lo que desencadena una serie de funciones más allá de la inhibición.

[0026] Las moléculas bifuncionales se han utilizado principalmente por su potencial para interactuar simultáneamente con dos objetivos macromoleculares y formar complejos ternarios que, a su vez, dan lugar a actividades biológicas y celulares nuevas y únicas. Las moléculas bifuncionales se han mostrado prometedoras en aplicaciones como la dimerización inducida químicamente, la inhibición de las interacciones proteína-proteína (PPI), la degradación de proteínas objetivo, la catálisis simultánea de dos o más procesos enzimáticos y la promoción o inhibición de la agregación de proteínas. Sin embargo, las moléculas bifuncionales no se limitan a la interacción simultánea con diferentes objetivos. Estas moléculas pueden diseñarse racionalmente a partir de dos grupos químicos funcionales para diversas funciones duales, como la inhibición dual de proteínas sinérgicas en enfermedades, la administración dirigida de fármacos y la elaboración de perfiles basados en la actividad. Se han propuesto este tipo de aplicaciones para sustituir las terapias combinadas.

[0027] En los complejos ternarios, las moléculas bifuncionales pueden unirse a diversos sitios, incluidos los sitios activos o alostéricos. Mientras que los inhibidores convencionales se basan en la ocupación, las moléculas bifuncionales suelen basarse en eventos específicos. Como resultado, los inhibidores convencionales son estequiométricos, mientras que las moléculas bifuncionales pueden ser subestequiométricas y catalíticas. Además, los inhibidores convencionales requieren una fuerte afinidad de unión, mientras que las moléculas bifuncionales pueden presentar afinidades de unión bajas o moderadas a las proteínas objetivo, ya que algunos complejos ternarios dependen de la cooperatividad. En comparación con los inhibidores de proteínas, que pueden afectar globalmente a las proteínas diana, estas moléculas

bifuncionales pueden utilizarse para localizar la actividad enzimática en una diana determinada. Además, los complejos binarios presentan un efecto de unión por saturación, donde a altas concentraciones, el sitio de unión se encuentra ocupado. Por el contrario, los complejos ternarios pueden presentar un efecto de gancho, donde las altas concentraciones de la molécula pequeña pueden saturar los dos socios de unión en complejos binarios individuales, lo que resulta en una pérdida de eficacia a una dosis más alta. Se han desarrollado marcos matemáticos para describir los equilibrios de tres cuerpos para respaldar los hallazgos experimentales y teóricos de estos complejos ternarios (EF Douglass Jr., et al., Un modelo matemático integral para equilibrios de unión de tres cuerpos, *J. Am. Chem. Soc.*, 135 (2013), pp. 6092-6099).

[0028] Las células cancerosas muestran alteraciones extensas en los niveles de expresión de proteínas, que son impulsoras de su transformación maligna. Las proteínas con niveles de expresión alterados en el cáncer participan en la síntesis de proteínas y degradación, vías de señalización y metabólicas, reparación del ADN, apoptosis y otros procesos celulares, cuyas alteraciones causan el desarrollo y la progresión del tumor.

[0029] Un componente clave del desarrollo exitoso de fármacos es la evaluación del índice terapéutico (IT), la relación entre la dosis o exposición de un fármaco necesaria para obtener el efecto terapéutico deseado y la dosis o exposición a partir de la cual la toxicidad se vuelve limitante. Si bien los fármacos con un TI alto eliminan eficazmente las células cancerosas con toxicidades manejables, los fármacos con un TI bajo causan efectos secundarios significativos a dosis eficaces o inferiores. Las quimioterapias citotóxicas, que normalmente se dirigen a las células en proliferación, generalmente tienen índices terapéuticos bajos.

[0030] La modulación de los niveles de proteínas causantes de la enfermedad es un objetivo anticancerígeno eficaz, que se logra mediante la focalización en proteínas sobreexpresadas en el cáncer, tales como, entre otras, el receptor de andrógenos, el receptor de estrógenos, el receptor 2 del factor de crecimiento epidérmico (HER2) y el factor de crecimiento endotelial vascular (VEGF). El desarrollo de terapias dirigidas, típicamente moléculas monofuncionales, ha proporcionado vías alternativas para lograr altos índices de inhibición terapéutica (TI) ya sea mediante la focalización en genes desregulados del cáncer con requisitos limitados para la homeostasis en adultos (por ejemplo, ABL, KIT, TRK, ALK), o mediante el desarrollo de inhibidores sesgados por mutaciones (por ejemplo, $KRAS^{G12C}$).

[0031] Sin embargo, la inhibición de proteínas que son necesarias para la supervivencia y proliferación de las células cancerosas (es decir, proteínas

dependientes de la enfermedad), como los reguladores del ciclo celular, las quinasas mitóticas y los reguladores epigenéticos, da como resultado una pérdida de aptitud celular o la muerte celular de las células cancerosas, pero las mismas proteínas también son el objetivo en células sanas. El resultado es un fármaco con baja eficacia terapéutica que o bien no obtiene la aprobación de los organismos reguladores o tiene un uso limitado en el tratamiento.

[0032] En el presente documento se describe una nueva modalidad de tratamiento para el cáncer y otras enfermedades. Los nuevos compuestos heterobifuncionales que se describen en este documento comprenden al menos dos compuestos monofuncionales diferentes: uno que actúa sobre una proteína causante de una enfermedad y otro que actúa sobre una proteína dependiente de la enfermedad, con un enlace opcional que los conecta entre sí. La focalización de la proteína dependiente de la enfermedad se logra mediante un ligando silencioso, de modo que la unión del ligando silencioso a la proteína dependiente de la enfermedad en la célula enferma (es decir, la célula cancerosa) o en las células sanas produce una inhibición mínima o nula de la proteína dependiente de la enfermedad. Cuando el ligando de la proteína causante de la enfermedad se une a su objetivo y el ligando silencioso se une al suyo, el resultado es la inhibición de la proteína dependiente de la enfermedad. Los nuevos compuestos heterobifuncionales descritos en este documento son agentes terapéuticos con un alto índice terapéutico (IT).

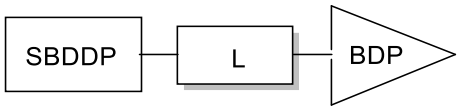
[0033] Los pares de proteínas para los compuestos heterobifuncionales descritos en este documento se pueden elegir de recursos como, entre otros: The Cancer Genome Atlas (TCGA), el proyecto TCGA Pan-Cancer, el consorcio The Cancer Cell Line Encyclopedia (CCLE), el Genomics of Drug Sensitivity in Cancer (GDSC), el Clinical Proteomic Tumour Analysis Consortium (CPTAC), la plataforma Protein Interaction Network Analysis (PINA), la red de interacción proteína-proteína (PPI) basada en métodos computacionales se han utilizado para identificar genes específicos de la enfermedad, módulos y subredes de subtipos de cáncer (Kann MG. Interacciones proteicas y enfermedades: enfoques computacionales para descubrir la etiología de las enfermedades. *Breve información biográfica*. 2007;8:333–46), Base de datos de proteómica (PD), Mapa de dependencias (DepMap) y Base de datos de abundancia de proteínas (PAXdb).

Inhibidores heterobifuncionales

[0034] En algunas de las formas de realización aquí descritas se encuentra un inhibidor heterobifuncional. En algunas formas de realización, el inhibidor de PDE es un

inhibidor de PDE-4.

[0035] En algunas formas de realización, la molécula heterobifuncional es un compuesto de fórmula (II):



en donde:

SB es un ligando silencioso de una proteína dependiente de la enfermedad (DDP);

L es un ligador opcional; y

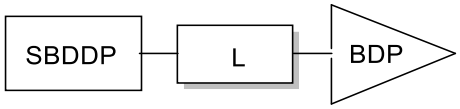
BDP es un ligando de una proteína causante de enfermedad (DP), donde la DP es el receptor de andrógenos.

[0036] En algunas formas de realización descritas en el presente documento, se trata de un complejo ternario estable que comprende:

a. una o más proteínas dependientes de la enfermedad (PDE);

b. una proteína de enfermedad (PD), donde la PD es el receptor de andrógenos; y

c. Compuesto inhibidor condicional heterobifuncional de fórmula (I):



en donde:

SBDDP es un ligando silencioso de una proteína dependiente de la enfermedad (DDP);

L es un ligador opcional; y

BDP es un ligando de una proteína de enfermedad (DP), donde la DP es el receptor de andrógenos;

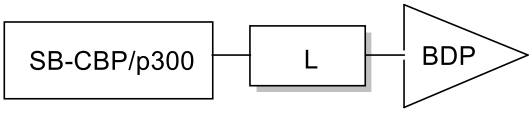
donde DDP y DP están presentes en una célula de interés (COI) y la abundancia relativa de DP en la COI es mayor que la abundancia relativa de DDP en la COI.

[0037] En algunas formas de realización descritas en el presente documento, se trata de un complejo ternario estable que comprende:

a. CBP/p300;

b. una proteína de enfermedad (PD), donde la PD es el receptor de andrógenos; y

c. Compuesto inhibidor condicional heterobifuncional de fórmula (II):



en donde:

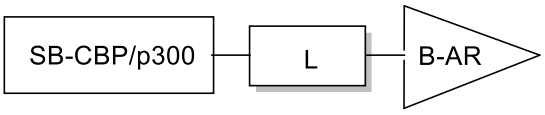
SB-CBP/p300 es un ligando silencioso de CBP/p300;

L es un ligador opcional; y

BDP es un ligando de una proteína de enfermedad (DP), donde la DP es el receptor de andrógenos;

donde CBP/p300 y DP están presentes en una célula de interés (COI) y la abundancia relativa de DP en la COI es mayor que la abundancia relativa de CBP/p300 en la COI.

[0038] En algunas formas de realización, en la presente se proporciona un compuesto de fórmula (I)



en donde:

SB-CBP/p300 es un ligando silencioso de CBP/p300;

L es un ligador opcional; y

El receptor B-AR es un ligando del receptor de andrógenos (AR).

[0039] En algunas formas de realización, en la presente se proporciona un compuesto de fórmula (I)

a. un ligando de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300);

b. un ligando de una proteína de enfermedad (DP); y

c. un ligador opcional que conecta covalentemente a) con b);

donde el ligador opcional se une covalentemente en una posición de a) que está expuesta al disolvente cuando a) se une a CBP/p300.

[0040] En algunas formas de realización, en las que el SBDDP se une al DDP e inhibe la actividad del DDP en el COI si el BDP se une simultáneamente al AR y la abundancia relativa del DP en el COI es mayor que la del DDP en el COI.

[0041] En algunas formas de realización, BDP es un ligando no silencioso o un ligando silencioso de una proteína de enfermedad (DP). En algunas formas de realización, BDP es un encuadernador no silencioso de un AR. En algunas formas de realización, el BDP actúa como un ligando silencioso de la proteína AR, implicada en la enfermedad.

[0042] En algunas formas de realización, tanto DDP como AR se expresan en una célula de interés (COI). En algunas formas de realización, tanto CBP/p300 como DP se expresan en una célula de interés (COI). En algunas formas de realización, tanto CBP/p300 como AR se expresan en una célula de interés (COI).

[0043] En algunas formas de realización, la abundancia relativa del AR en el COI es

mayor que la abundancia relativa del DDP en el COI. En algunas formas de realización, la abundancia relativa del DP en el COI es mayor que la abundancia relativa del DDP en el COI por un factor de al menos aproximadamente 2, al menos aproximadamente 5, al menos aproximadamente 10, al menos aproximadamente 50, al menos aproximadamente 100 o al menos aproximadamente 250. En algunas formas de realización, la abundancia relativa del DP en el COI es mayor que la abundancia relativa del DDP en el COI por un factor de al menos aproximadamente 100. En algunas formas de realización, la abundancia relativa del DP en el COI es mayor que la abundancia relativa de CBP/p300 en el COI. En algunas formas de realización, la abundancia relativa del DP en el COI es mayor que la abundancia relativa de CBP/p300 en el COI por un factor de al menos aproximadamente 2, al menos aproximadamente 5, al menos aproximadamente 10, al menos aproximadamente 50, al menos aproximadamente 100 o al menos aproximadamente 250. En algunas formas de realización, la abundancia relativa del DP en el COI es mayor que la abundancia relativa de CBP/p300 en el COI por un factor de al menos aproximadamente 100. En algunas formas de realización, la abundancia relativa de AR en el COI es mayor que la abundancia relativa de CBP/p300 en el COI. En algunas formas de realización, la abundancia relativa de AR en el COI es mayor que la abundancia relativa de CBP/p300 en el COI por un factor de al menos aproximadamente 2, al menos aproximadamente 5, al menos aproximadamente 10, al menos aproximadamente 50, al menos aproximadamente 100 o al menos aproximadamente 250. En algunas formas de realización, la abundancia relativa de AR en el COI es mayor que la abundancia relativa de CBP/p300 en el COI por un factor de al menos aproximadamente 100.

[0044] En algunas formas de realización, la célula de interés (COI) es una célula enferma, y la proteína de difusión (DP) se sobreexpresa, se hiperactiva, o ambas cosas a la vez, o se amplifica en la célula enferma en comparación con cuando la célula de interés es una célula sana. En algunas formas de realización, la célula de interés (COI) es una célula enferma, y la proteína DP se sobreexpresa en la célula enferma en comparación con cuando la célula de interés es una célula sana. En algunas formas de realización, la célula de interés (COI) es una célula enferma, y la proteína DP está hiperactiva en la célula enferma en comparación con cuando la célula de interés es una célula sana. En algunas formas de realización, la célula de interés (COI) es una célula enferma, y la proteína DP se sobreexpresa y se vuelve hiperactiva en la célula enferma en comparación con cuando la célula de interés es una célula sana. En algunas formas de realización, la célula de interés (COI) es una célula enferma, y el DP se amplifica en

la célula enferma en comparación con cuando la COI es una célula no enferma. En algunas formas de realización, COI es una célula enferma, y AR está sobreexpresado, hiperactivo, o ambas cosas a la vez, o amplificado en la célula enferma en comparación con cuando COI es una célula no enferma.

[0045] En algunas formas de realización, la actividad del DDP se reduce o inhibe por el compuesto de fórmula (I), (II) o (III) cuando el DDP y el DP se expresan en el mismo COI y la abundancia relativa del DP en el COI es mayor que la abundancia relativa del DDP en el COI. En algunas formas de realización, la actividad del DDP se reduce por el compuesto de fórmula (I), (II) o (III) cuando el DDP y el DP se expresan en el mismo COI y la abundancia relativa del DP en el COI es mayor que la abundancia relativa del DDP en el COI. En algunas formas de realización, la actividad del DDP es inhibida por el compuesto de fórmula (I), (II) o (III) cuando el DDP y el DP se expresan en el mismo COI y la abundancia relativa del DP en el COI es mayor que la abundancia relativa del DDP en el COI.

[0046] En algunas formas de realización, la actividad de la CBP/p300 se reduce o inhibe por el compuesto de Fórmula (Ia) cuando la CBP/p300 y la DP se expresan en el mismo COI y la abundancia relativa de la DP en el COI es mayor que la abundancia relativa de la CBP/p300 en el COI.

[0047] En algunas formas de realización, la actividad de CBP/p300 se reduce o inhibe por el compuesto de la Fórmula (III) cuando CBP/p300 y AR se expresan en el mismo COI y la abundancia relativa de AR en el COI es mayor que la abundancia relativa de CBP/p300 en el COI.

[0048] En algunas formas de realización, la actividad del DDP no se ve alterada por el compuesto de fórmula (I), (II) o (III) cuando el DDP y el DP no se expresan ambos en el mismo COI y/o la abundancia relativa del DP en el COI no es mayor que la abundancia relativa del DDP en el COI.

[0049] En algunas formas de realización, la actividad del CBP/p300 no se ve alterada por el compuesto de fórmula (Ia) cuando el CBP/p300 y el DP no se expresan ambos en el mismo COI y/o la abundancia relativa del DP en el COI no es mayor que la abundancia relativa del CBP/p300 en el COI.

[0050] En algunas formas de realización, la actividad de CBP/p300 no se ve alterada por el compuesto de la Fórmula (III) cuando CBP/p300 y AR no se expresan ambos en el mismo COI y/o la abundancia relativa de AR en el COI no es mayor que la abundancia relativa de CBP/p300 en el COI.

[0051] En algunas formas de realización, el DP es el receptor de andrógenos (AR) y

el BDP es un ligando del AR. En algunas formas de realización, el DP es el receptor de andrógenos (AR) y el BDP es un antagonista o agonista del AR. En algunas formas de realización, el DP es el receptor de andrógenos (AR) y el BDP es un antagonista del AR que comprende una N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida o una N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida. En algunas formas de realización, el DP es el receptor de andrógenos (AR) y el BDP es un antagonista del AR que es flutamida, hidroxiflutamida, nilutamida, bicalutamida, enzalutamida, apalutamida, ODM201, AZD3514, BMS641988 o N-[trans-3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-1-(2-hidroxietil)-1H-pirazol-4-carboxamida.

Célula de Interés (COI)

[0052] En algunas formas de realización, la célula de interés (COI) es una célula enferma en la que se desea la inhibición de la proteína dependiente de la enfermedad (DDP). En algunas formas de realización, la célula es una célula de mamífero. En algunas formas de realización, la célula es una célula de mamífero. En algunos casos, la célula cancerosa está asociada a un carcinoma, sarcoma, leucemia, linfoma, mieloma o al sistema nervioso central. En algunos casos, la célula cancerosa está asociada a un carcinoma, por ejemplo, carcinoma de células escamosas, adenocarcinoma, carcinoma de células transicionales o carcinoma de células basales. En algunos casos, la célula cancerosa es una célula epitelial, por ejemplo, una célula escamosa, una célula adenomatosa, una célula de transición o una célula basal. En algunos casos, la célula cancerosa está asociada a un sarcoma, por ejemplo, un sarcoma óseo o un sarcoma de tejidos blandos. En algunas formas de realización, la célula cancerosa es una célula ósea, una célula cartilaginosa o una célula muscular. En algunas formas de realización, la célula cancerosa está asociada a una leucemia. En algunas formas de realización, la célula huésped es una célula CHO-K1. En algunas formas de realización, la célula cancerosa está asociada a un linfoma o mieloma. En algunas formas de realización, la célula cancerosa es un glóbulo blanco o una célula plasmática. En algunas formas de realización, la célula cancerosa está asociada al sistema nervioso central, por ejemplo, al cerebro o a la médula espinal. En algunas formas de realización, la célula huésped es una célula CHO-K1.

[0053] En algunas formas de realización, el COI es una célula asociada con cáncer de cabeza y cuello, cáncer de laringe e hipofaringe, cáncer de cavidad nasal y senos paranasales, cáncer nasofaríngeo, cáncer de cavidad oral (boca) y orofaringe (garganta), o cáncer de glándulas salivales. En algunas formas de realización, el COI

es una célula asociada con cáncer anal, cáncer de las vías biliares, cáncer colorrectal, cáncer de esófago, cáncer de vesícula biliar, tumores neuroendocrinos gastrointestinales, tumores del estroma gastrointestinal, cáncer de hígado, cáncer de páncreas, tumores neuroendocrinos pancreáticos, cáncer de intestino delgado o cáncer de estómago. En algunas formas de realización, el COI es una célula asociada con el cáncer de vejiga, el cáncer de riñón o el tumor de Wilms. En algunas formas de realización, la célula de interés (COI) es una célula asociada con cáncer de pulmón, tumor carcinoide de pulmón o mesotelioma maligno. En algunas formas de realización, el COI es una célula asociada al cáncer de mama. En algunas formas de realización, el COI es una célula asociada con cáncer de cuello uterino, cáncer de endometrio, cáncer de ovario, cáncer de pene, cáncer de próstata, cáncer de testículo, sarcoma uterino, cáncer vaginal o cáncer de vulva. En algunas formas de realización, el COI es una célula asociada con cáncer de glándulas suprarrenales, tumores neuroendocrinos gastrointestinales, tumores carcinoides de pulmón, tumores neuroendocrinos de páncreas, tumores de la hipófisis o cáncer de tiroides. En algunas formas de realización, el COI es una célula asociada con cáncer de piel, cáncer de piel de células basales y escamosas, sarcoma de Kaposi, linfoma de la piel, melanoma o cáncer de piel de células de Merkel. En algunas formas de realización, el COI es una célula asociada con cáncer de hueso, tumores de la familia de Ewing, osteosarcoma, rabdomiosarcoma o sarcoma de tejidos blandos. En algunas formas de realización, el COI es una célula asociada con el cáncer de ojo o el retinoblastoma. En algunas formas de realización, el COI es una célula asociada con tumores cerebrales y de la médula espinal o neuroblastoma. En algunas formas de realización, el COI es una célula asociada con leucemia, leucemia linfocítica aguda, leucemia mieloide aguda, leucemia linfocítica crónica, leucemia mieloide crónica, leucemia mielomonocítica crónica, linfoma, linfoma no Hodgkin, linfoma de Hodgkin, mieloma múltiple, síndromes mielodisplásicos, cáncer de timo o macroglobulinemia de Waldenström.

[0054] En algunas formas de realización, el COI es una célula asociada con el cáncer de próstata o el cáncer de mama. En algunas formas de realización, el COI es una célula asociada con el cáncer de próstata, el cáncer de mama luminal y el cáncer de mama triple negativo con receptor de andrógenos luminal.

Proteína dependiente de la enfermedad (DDP)

[0055] “Proteína dependiente de la enfermedad” o “DDP” se refiere a cualquiera de las proteínas expresadas en la célula de interés que son necesarias para el funcionamiento, el mantenimiento o la supervivencia celular en una enfermedad

particular. Es decir, la enfermedad indicada depende de la proteína específica para sobrevivir. En algunas formas de realización, una celda de interés incluye un tipo de DDP. En algunas formas de realización, una celda de interés expresa más de un tipo de DDP, y cada tipo de DDP realiza funciones distintas de cualquier otro tipo de DDP en la celda de interés. En algunas formas de realización, una celda de interés expresa más de un tipo de DDP, y cada tipo de DDP realiza funciones sustancialmente iguales o superpuestas con al menos otro tipo de DDP en la celda de interés.

[0056] En algunas formas de realización, la proteína dependiente de la enfermedad (DDP) es el factor de transcripción 1 que contiene AT-Hook (AHCTF1), la subunidad 1 del complejo promotor de la anafase (ANAPC1), ANAPC4, ANAPC5, la proteína ATM (ataxia-telangiectasia mutada), la proteína ATR (ataxia telangiectasia y relacionada con Rad3), la quinasa Aurora A (AurkA), la quinasa Aurora B (AurkB), la proteína 4 que contiene bromodominio (BRD4), el factor de transcripción con dedo PHD de bromodominio (BPTF), la quinasa B de serina/treonina del punto de control mitótico BUB1 (BUB1B), la proteína de unión a CREB (CBP)/p300, la proteína quinasa relacionada con el ciclo de división celular 7 (CDC7), CDC16, CDC23, CDC27, CDC45, la proteína W del centrómero (CENPW), la subunidad b del factor de ensamblaje de la cromatina 1 (CHAF1B) y la proteína 4 de unión al ADN de la helicasa del cromodominio (CHD4), quinasa de punto de control 1 (CHK1), CHK2, subunidad 1 de la quinasa de polirribonucleótidos del factor de escisión (CLP1), CWC22, quinasa dependiente de ciclina 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, CDK11a, proteína 5 asociada al citoesqueleto (CKAP5), factor 1 asociado a DDB1 y CUL4 (DCAF1), helicasa DEAD-box 1 (DBR1), DDX10, DDX41, DDX47, DDX54, DDX56, subunidad de la sintasa de dehidrodolicil difosfato (DHDDS), sintasa de desoxihipusina (DHPS), helicasa DEAH-box 8 (DHX8), DONSON, metiltransferasa de ADN 1 (DNMT1), homólogo de la ligasa de proteína ubiquitina E3 sin dentículos (DTL), histona acetiltransferasa P300 (EP300), proteína de unión E1A P400 (EP400), cuerpos polares extra huso como 1, separasa (ESPL1)/separina, proteína F-Box 5 (FBXO5), proteína asociada al orgánulo nuclear Gem 5 (GEMIN5), GINS2, GTPasa GPN-Loop 3 (GPN3), subunidad 1 del complejo similar a HAUS augmin (HAUS1), HAUS6, factor de célula huésped C1 (HCFC1), histona desacetilasa 1 (HDAC1), HDAC2, HDAC3, proteína 1 que contiene repeticiones HEAT (HEATR1), subunidad 11 del complejo integrador (INTS11), lisina acetiltransferasa 8 (KAT8)/MYST1, miembro 11 de la familia de la kinesina (KIF11), KIF18A, KIF23, proteína 1 similar a la deficiente en arresto mitótico 2 (MAD2A/MAD2L1), MAK16, quinasa de serina/treonina asociada a microtúbulos similar (MASTL), ATPasa

AAA Midasina 1 (MDN1), subunidad 14 del complejo mediador (MED14), MED11, MED28, quinasa de proteína activada por mitógeno 1 (MEK1), MEK2, MIS18A, proteína 22 similar a la proteína sensible al metil metanosulfonato (MMS22L), Myc, diana de rapamicina en mamíferos (MTOR), proteína 8 regulada negativamente durante el desarrollo y expresada en células precursoras neuronales (NEDD8), NIP7, homólogo 4 asociado al complejo nucleolar (NOC4L), proteína nucleolar 6 (NOL6), homólogo 1 de Notchless (NLE1), NUF2, nucleoporina 205 (NUP205), NUS1, proteína 5 que interactúa con Opa (OIP5), muerte celular programada 11 (PDCD11), Fosfatidilinositol-3 quinasa (PI3K), quinasa tipo Polo 1 (PLK1), ADN polimerasa alfa 1, subunidad catalítica (POLA1), ADN polimerasa delta 1, subunidad catalítica (POLD1), ADN polimerasa épsilon, subunidad catalítica (POLE), ADN polimerasa épsilon, subunidad 2 (POLE2), dominio de peptidilprolil isomerasa y repetición WD que contiene 1 (PPWD1), proteína reguladora de la citocinesis 1 (PRC1), ADN primasa subunidad 1 (PRIM1)/ADN PRIMASA, proteína arginina metiltransferasa 5 (PRMT5), subunidades del proteasoma 20S, RAD51, proteína activadora de GTPasa Rac 1 (RACGAP1), ribonucleósido-difosfato reductasa subunidad M1 (RRM1), exportación de ácido ribonucleico 1 (RAE1), ARN polimerasa I subunidad B (POLR1B), ARN polimerasa II subunidad J (POLR2J), proteína 1 asociada a la ARN polimerasa II (RPAP1), ARN guanililtransferasa y 5'-fosfatasa (RNGTT), factor de empalme 3b subunidad 1 (SF3B1), regulador de la cromatina dependiente de actina, asociado a la matriz y relacionado con SWI/SNF, subfamilia A, miembro 2/4 (SMARCA2/4), polipéptido 5 del complejo activador del ARN nuclear pequeño (SNAPC5), mantenimiento estructural de los cromosomas 4 (SMC4), SMG1, SGO1, coactivador 1 del receptor de esteroides (SRC1), SRC2, SRC3, SLU7, SPC24, SPT6H, SPT5H, proteína andamiaje Symplekin (SYMPK), TIMELESS, tiorredoxina similar a 4a (TXNL4A), proteína de reparación del ADN similar a Tonsoku (TONSL), topoisomerasa II alfa (TOP2A), TPX2, proteína asociada al dominio de transformación/transcripción (TRRAP), subunidad 8 del complejo de partículas de proteína de tráfico (TRAPPC8), TSR2, proteína de transcripción expresada ubicuamente (UXT), URB1, UTP15, UTP20, peptidasa específica de ubiquitina similar a 1 (USPL1), proteína 25 asociada a la clasificación de proteínas vacuolares (VPS25), proteína 3 que contiene repeticiones WD (WDR3), WDR5, WDR12, WDR43, WDR46, WDR70, WD74, WEE1, proteína 11 de unión al dominio WW (WBP11), proteína 2 de unión al grupo A de xeroderma pigmentoso (XAB2) o Exportina 1 (XPO1).

[0057] En algunas formas de realización, la proteína dependiente de la enfermedad (DDP) es Ataxia-telangiectasia mutada (ATM), Ataxia telangiectasia y proteína

relacionada con Rad3 (ATR), Aurora quinasa A (AurkA), AurkB, proteína quinasa relacionada con el ciclo de división celular 7 (CDC7), quinasa de punto de control 1 (CHK1), CHK2, quinasa dependiente de ciclina 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, ADN metiltransferasa 1 (DNMT1), Exportina 1 (XPO1), histona deacetilasa 1 (HDAC1), HDAC2, HDAC3, miembro 11 de la familia de la kinesina (KIF11), proteína quinasa activada por mitógeno quinasa 1 (MEK1), MEK2, Myc, proteína 8 regulada negativamente durante el desarrollo expresada en células precursoras neuronales (NEDD8), SMARCA2, SMARCA4, Proteína de unión a CREB (CBP)/p300, proteína 5 que contiene repeticiones WD (WDR5), factor 1 asociado a DDB1 y CUL4 (DCAF1), fosfatidilinositol-3 quinasa (PI3K), proteína arginina metiltransferasa 5 (PRMT5), subunidad 1 del factor de empalme 3b (SF3B1), WEE1, subunidades del proteasoma 20S, coactivador 1 del receptor de esteroides (SRC1), SRC2 o SRC3. En algunas formas de realización, DDP es Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2, SMARCA4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphodilinositol-3 kinase (PI3K) o WEE1. En algunas formas de realización, DDP es Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2, SMARCA4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphodilinositol-3 kinase (PI3K) o WEE1. En algunas formas de realización, la mutación es una mutación de p300 o SMARCA2. En algunas formas de realización, DDP es CBP/p300. En algunas formas de realización, el poloxámero es poloxámero 2 o 4.

[0058] En algunas formas de realización, cuando la proteína causante de la enfermedad es el receptor de andrógenos (AR), entonces el DDP es un coactivador o corregulador del AR. Los andrógenos, que actúan a través del receptor de andrógenos (AR), son esenciales para el desarrollo y mantenimiento normales de la próstata. El receptor de andrógenos (AR) unido a andrógenos funciona como un factor de transcripción que regula genes implicados en diversos procesos fisiológicos. La actividad transcripcional del receptor de andrógenos (AR) se ve afectada por correguladores que influyen en diversas propiedades funcionales del AR, incluyendo la selectividad del ligando y la capacidad de unión al ADN. Como promotores de los genes diana, los correguladores participan en la modificación del ADN, ya sea directamente mediante la modificación de las histonas o indirectamente mediante el reclutamiento de complejos modificadores de la cromatina, además de funcionar en el reclutamiento de la maquinaria transcripcional basal. La actividad anómala de los correguladores, debida

a mutaciones o a niveles de expresión alterados, puede ser un factor que contribuya a la progresión de enfermedades relacionadas con la actividad del receptor de andrógenos (AR), como el cáncer de próstata.

[0059] La progresión del cáncer de próstata también es sensible a los andrógenos. La ablación androgénica quirúrgica y/o farmacológica sigue siendo la forma predominante de tratamiento para el cáncer de próstata avanzado. La terapia de ablación de andrógenos a menudo se combina con el tratamiento con antiandrógenos no esteroideos, como la hidroxiflutamida, para bloquear la acción residual de los andrógenos suprarrenales. Si bien entre el 70 % y el 80 % de los pacientes responden inicialmente a la terapia de ablación de andrógenos, los tumores finalmente se vuelven resistentes y, de hecho, pueden proliferar en respuesta a los antiandrógenos. Dado que el receptor de andrógenos (AR) se expresa generalmente en los tumores de próstata y sus metástasis, la regulación aberrante de la actividad del AR por parte de los correguladores puede contribuir a la progresión del cáncer de próstata o al efecto agonista adquirido de los antiandrógenos.

[0060] Además, la activación del AR independiente de andrógenos es un fenómeno bien conocido y puede ocurrir a través de varios mecanismos diferentes, incluida la activación por interleucinas. Por ejemplo, se ha demostrado que la interleucina-6 (IL-6) activa la expresión génica dependiente del receptor de andrógenos en ausencia de andrógenos. La activación del receptor de andrógenos (AR) y la expresión de los genes diana del AR por la IL-6 requiere de la proteína p300 y su actividad HAT. De forma similar a la IL-6, la interleucina-4 (IL-4) activa el AR, aumenta la expresión de la proteína CBP/p300 y mejora la interacción de CBP/p300 con el AR en el promotor KLK3. Por lo tanto, CBP/p300 parece ser crucial para la actividad transcripcional del AR tanto en presencia como en ausencia de andrógenos.

[0061] En algunas formas de realización, los coactivadores o coactivadores o correguladores de AR son AKT1, AurkA, regulador 1 de chaperona molecular de la familia BAG (BAG1), beta-catenina, proteína de susceptibilidad al cáncer de mama tipo 1 (BRCA1), BRD4, C-jun, calmodulina 1, caveolina 1, CDK4/6, CDK9, subunidad 5b de la citocromo C oxidasa (COX5B), CBP/p300, CD1, CDK7, factor de transcripción 1 de la familia Dachshund (DACH1), proteína asociada al dominio de muerte (Daxx), DCAF1, L-3,4-dihidroxifenilalanina (L-DOPA), proteína 6 que contiene el dominio de unión al calcio EF-hand (EFCAB6), receptor del factor de crecimiento epidérmico (EGFR), Forkhead Box O1 (FOXO1), gliceraldehído-3-fosfato deshidrogenasa (GAPDH), gelsolina, subunidad de la proteína de unión a nucleótidos de guanina beta-2-like 1

(GNB2L1), glucógeno sintasa quinasa 3 beta (GSK3B), HDAC1, proteína de choque térmico 90 alfa, miembro 1 de la clase a (HSP90AA1), HTATIP, MAGEA11, MED1, Myc, MYST2, coactivador del receptor nuclear 1 (NCOA1), NCOA2, NCOA3, NCOA4, NCOA6, correpresor del receptor nuclear 2 (NCOR2), proteína de unión a octámeros que no contiene dominio POU (NONO), proteína 2G4 asociada a la proliferación (PA2G4), P21 (RAC1), quinasa activada 6 (PAK6), POZ/BTB y dedo de zinc que contiene gancho 1 (PATZ1), inhibidor de proteína de STAT 2 activado (PIAS2), factor de procesamiento de pre-ARNm 6 (PRPF6), homólogo de fosfatasa y tensina (PTEN), RAD9A, proteína de unión a RAN 9 (RANBP9), Ring finger and CHY zinc finger domain containing 1 (RCHY1), proteína del retinoblastoma, proteína de dedo anular 4 (RNF4), RNF14, factor 3 asociado al espliceosoma, proteína de reciclaje U4/U6 (SART3), sirtuina 1 (SIRT1), SMAD3, SMARCA2/4, pequeño socio heterodimérico, Src, región determinante del sexo Y (SRY), STAT3, supervilina (SVIL), receptor testicular 2, receptor testicular 4, transcripto 1 inducido por el factor de crecimiento transformante beta 1 (TGFB1I1), factor modulador del elemento TATA 1 (TMF1), motivo tripartito que contiene 68 (TRIM68), enzima conjugadora de ubiquitina E2 I (UBE2I), chaperona similar a la prefoldina expresada ubicuamente (UXT), WEE1 y proteína 1 que contiene dedo de zinc tipo MIZ (ZMIZ1).

Proteína de unión silenciosa dependiente de la enfermedad (SBDDP)

[0062] La expresión "ligando silencioso" se refiere a un compuesto (o fragmento de un compuesto heterobifuncional) que se une a una proteína objetivo sin alterar sustancialmente su función. En algunos casos, un ligando silencioso no produce activación ni inhibición funcional de la proteína diana.

[0063] Se entiende que algunos ligandos silenciosos pueden, al unirse a una proteína objetivo, provocar o inducir algún efecto medible o detectable en la función de la proteína. Sin embargo, en tales casos, la alteración medible de la función proteica no resulta perjudicial para el funcionamiento normal de la proteína diana en concentraciones relevantes para inducir la inhibición de dicha proteína.

[0064] También se entiende que el ligando silencioso a una proteína objetivo no altera sustancialmente la función de la proteína cuando se incorpora a los compuestos inhibidores condicionales heterobifuncionales aquí descritos, a menos que el componente ligando no silencioso (NSB) del compuesto inhibidor condicional heterobifuncional también se una simultáneamente a la proteína de la enfermedad (DP) en la misma célula.

[0065] En algunos casos, un ligando silencioso puede ser silencioso porque se une a

un dominio de una proteína diana que no es un dominio relevante para la actividad de dicha proteína. En otras formas de realización, un ligando silencioso puede ser silencioso porque es un ligando alostérico de la proteína objetivo. En otras formas de realización, un aglutinante silencioso puede ser silencioso porque su incorporación a un compuesto heterobifuncional reduce la actividad del aglutinante en comparación con cuando no está incorporado a un compuesto heterobifuncional. Por ejemplo, un compuesto puede ser un modulador de una proteína objetivo cuando no es un componente de un compuesto heterobifuncional, sino que se convierte en un ligando silencioso de la proteína objetivo en virtud de su incorporación a un compuesto heterobifuncional descrito en el presente documento.

[0066] “Aglutinante de una proteína de enfermedad” o “BDP” se refiere a un compuesto (o fragmento de un compuesto heterobifuncional) que se une a una proteína diana de la enfermedad y: 1) no altera sustancialmente la función de la proteína; o 2) altera sustancialmente la función de la proteína. En algunas formas de realización, un ligando de una proteína causante de enfermedad, cuando se incorpora a los compuestos heterobifuncionales aquí descritos, no altera sustancialmente la función de la proteína causante de la enfermedad. En algunas formas de realización, un ligando de una proteína causante de enfermedad, cuando se incorpora a los compuestos heterobifuncionales aquí descritos, no altera sustancialmente la función de la proteína causante de la enfermedad, a menos que el componente ligando silencioso del compuesto condicional heterobifuncional también se una simultáneamente a una proteína dependiente de la enfermedad en la misma célula.

[0067] La expresión "ligando no silencioso" o "NSB" se refiere a un compuesto (o fragmento de un compuesto heterobifuncional) que se une a una proteína diana causante de una enfermedad y altera sustancialmente su función. Los NSB incluyen, entre otros, agonistas, agonistas inversos, antagonistas, antagonistas neutros, antagonistas silenciosos, antagonistas competitivos, antagonistas irreversibles, antagonistas reversibles, inhibidores, inhibidores irreversibles, inhibidores reversibles, moduladores alostéricos, moduladores alostéricos negativos y moduladores alostéricos positivos.

[0068] Silent Antagonist es un fármaco que atenúa los efectos de los agonistas o agonistas inversos, produciendo una reducción funcional en la transducción de señales. Afecta únicamente a la activación del receptor dependiente del ligando y no presenta actividad intrínseca por sí misma. También conocido como antagonista neutral.

[0069] Un agonista es un fármaco que se une a un receptor y lo activa. Puede ser

total, parcial o inverso. Un agonista completo tiene una alta eficacia, produciendo una respuesta completa al tiempo que ocupa una proporción relativamente baja de receptores. Un agonista parcial tiene menor eficacia que un agonista completo. Produce una activación subóptima incluso cuando ocupa la totalidad de la población de receptores, por lo que no puede producir la respuesta máxima, independientemente de la concentración aplicada. Un agonista inverso produce un efecto opuesto al de un agonista, pero se une al mismo sitio de unión del receptor que un agonista.

[0070] Un modulador alostérico es un fármaco que se une a un receptor en un sitio distinto del sitio activo. Induce un cambio conformacional en el receptor, lo que altera la afinidad del receptor por el ligando endógeno. Los moduladores alostéricos positivos aumentan la afinidad, mientras que los moduladores alostéricos negativos la disminuyen.

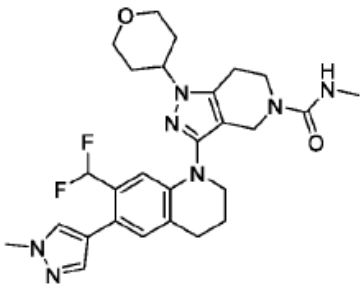
[0071] Un antagonista es un fármaco que atenúa el efecto de un agonista. Pueden ser competitivos o no competitivos, y ambos tipos pueden ser reversibles o irreversibles. Un antagonista competitivo se une al mismo sitio que el agonista, pero no lo activa, bloqueando así la acción del agonista. Un antagonista no competitivo se une a un sitio alostérico (no agonista) del receptor para impedir su activación. Un antagonista reversible se une al receptor de forma no covalente, por lo que puede ser "eliminado". Un antagonista irreversible se une covalentemente al receptor y no puede ser desplazado ni por ligandos competidores ni por lavados.

[0072] La eficacia describe la forma en que los agonistas varían en la respuesta que producen cuando ocupan el mismo número de receptores. Los agonistas de alta eficacia producen su respuesta máxima ocupando una proporción relativamente baja de la población total de receptores. Los agonistas de menor eficacia no activan los receptores en la misma medida y es posible que no puedan producir la respuesta máxima (véase Agonista parcial).

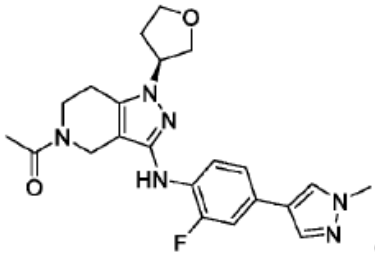
[0073] En algunas formas de realización, SBDDP es un ligando CBP/p300. En algunas formas de realización, SBDDP es un ligando del bromodominio CBP/p300. En algunas formas de realización, SBDDP es un ligando del dominio de la histona acetiltransferasa (HAT) CBP/p300. En algunas formas de realización, SBDDP es un ligando de bromodominio CBP/p300 que comprende un benzimidazol, piperidina, benzodiazepinona, indol, oxazolidinediona, esqueleto barbitúrico, esqueleto tiobarbitúrico o alcaloide. En algunas formas de realización, SBDDP es un ligando de CBP/p300 como se describe en Zhang-Xu He, *et al., European Journal of Medicinal Chemistry*, Volumen 209, 2021, 112861, que se incorpora por referencia para dicho

ligando de CBP/p300. En algunas formas de realización, SBDDP es un ligando de CBP/p300 como cualquiera de los compuestos 1 a 75, tal como se describe en Zhang-Xu He, *et al., European Journal of Medicinal Chemistry*, Volumen 209, 2021, 112861, que se incorpora por referencia para dichos ligandos de CBP/p300.

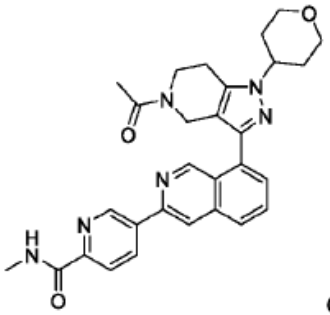
[0074] En algunas formas de realización, SBDDP tiene una de las siguientes estructuras:



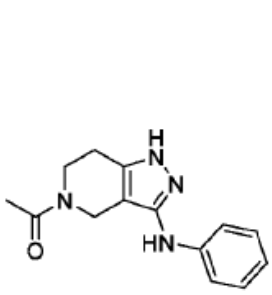
GNE-781,



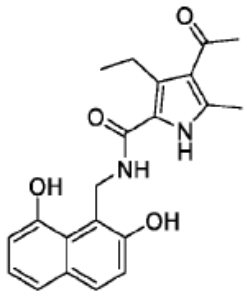
GNE-272,



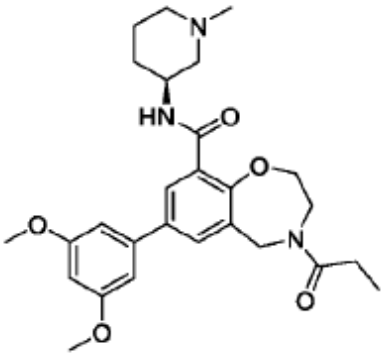
GNE-207,



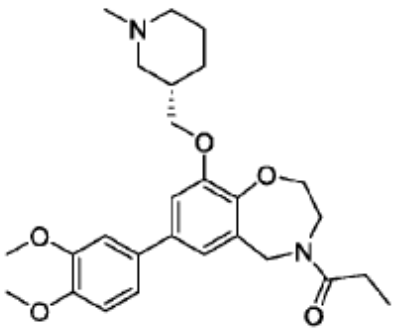
,



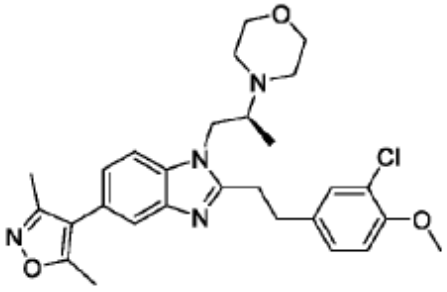
XDM-CBP,



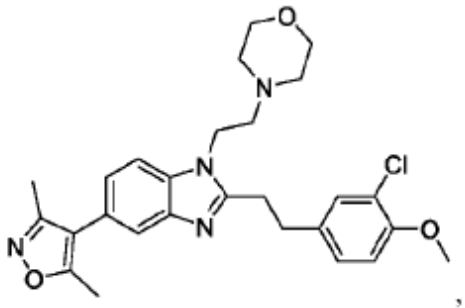
TPOP146,



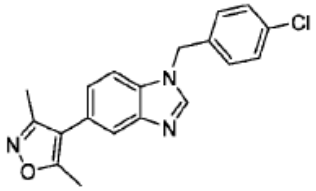
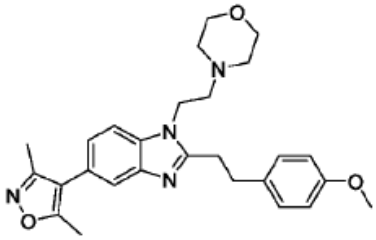
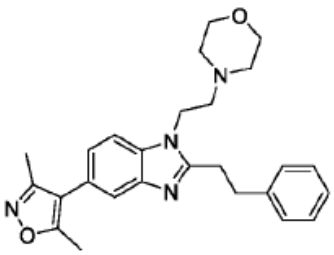
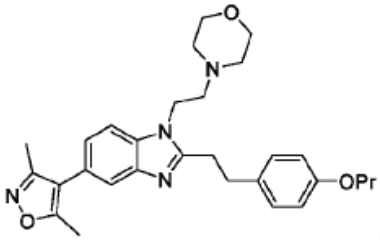
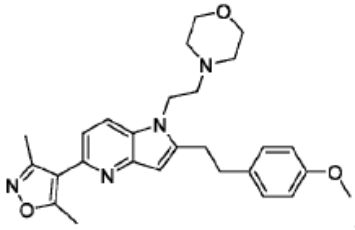
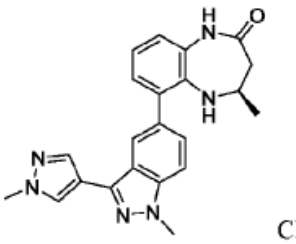
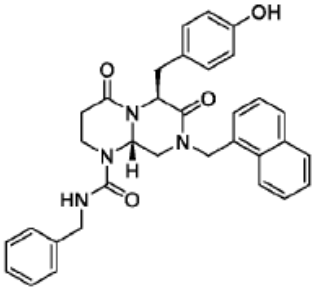
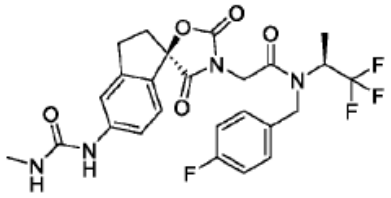
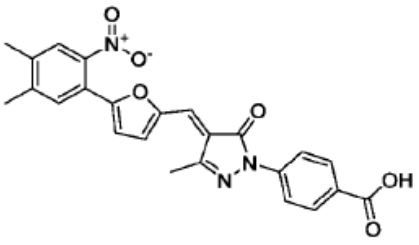
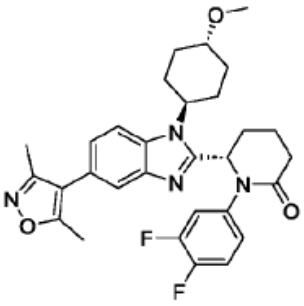
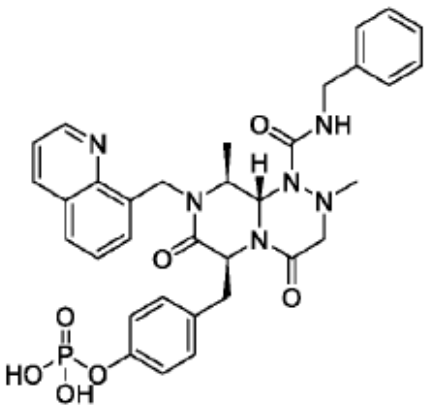
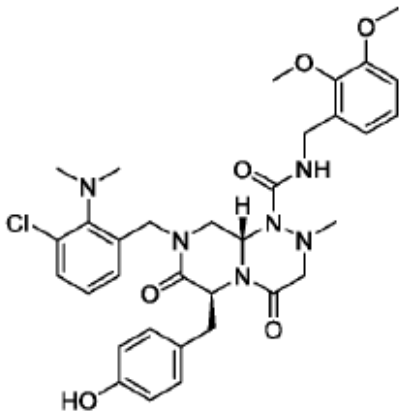
I-CBP112,

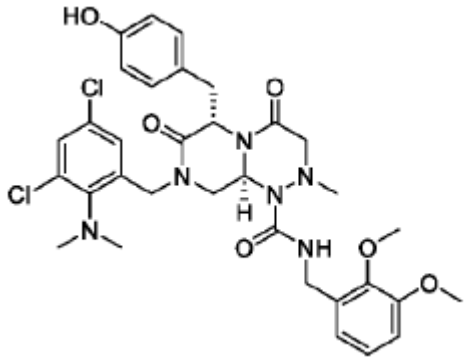


SGC-CBP30,



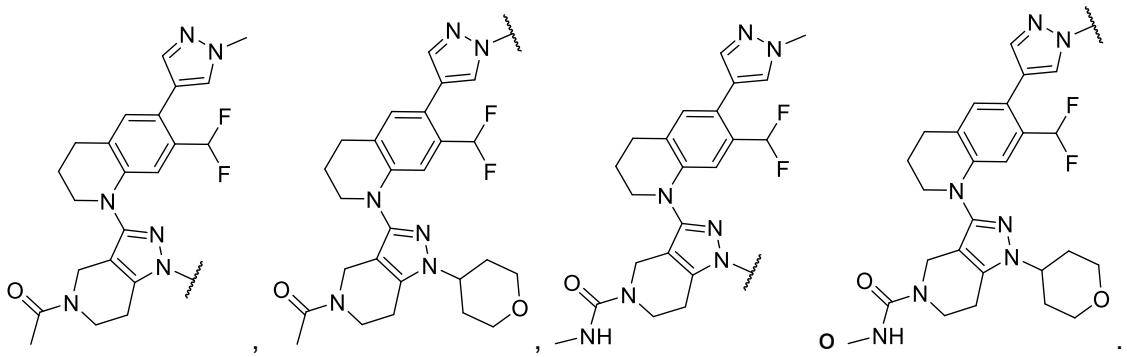
,







CPI-63

ICG-001,

A-485,

C646,

inobrodib (CCS1477),

PRI-724,

YH249, o



YH250.

[0075] En algunas formas de realización, SBDDP tiene una de las siguientes estructuras:



Proteína de la enfermedad (DP)

[0076] En algunas formas de realización, la DP es una proteína que se expresa selectivamente en un cáncer o COI.

[0077] En algunas formas de realización, el DP es un receptor hormonal nuclear. En algunas formas de realización, el DP es un receptor hormonal, por ejemplo, el receptor de andrógenos (AR), el receptor de estrógenos (ER), el receptor de ácido retinoico (RAR), el receptor de vitamina D (VDR), el receptor de glucocorticoides (GR), el receptor de mineralocorticoides (MR) o el receptor de progesterona (PR). En algunas formas de realización, el DP es AR o ER. En algunas formas de realización, el DP es AR.

[0078] En algunas formas de realización, el DP es AR.

Proteína ligada a una proteína causante de enfermedad (BDP)

[0079] En algunas formas de realización, el BDP es un encuadernador no silencioso de un AR. En algunas implementaciones, el BDP es un encuadernador silencioso de un AR.

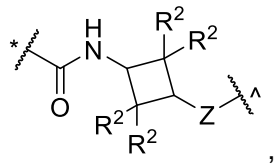
[0080] En algunas formas de realización, el AR es un ligando del receptor de andrógenos (AR), donde B-AR comprende:

1) un grupo principal que ocupa el dominio de unión al ligando (LBD) del AR y está unido

covalentemente a una porción central, donde la porción central comprende un ciclobutilo opcionalmente sustituido; y

2) una porción de cola opcional unida covalentemente a la porción central.

[0081] En algunas formas de realización, el núcleo comprende un ciclobutilo opcionalmente sustituido que tiene la estructura de Fórmula (C):



, Fórmula (C);

donde: el grupo cabeza está unido covalentemente a Z en la posición (^); la porción de cola opcional comprende un anillo D que está unido covalentemente a la amida (*), cada R^2 es $-CH_3$; donde el anillo D es un arilo de 5, 6, 8, 9 o 10 miembros o un heteroarilo de 5, 6, 8, 9 o 10 miembros que está opcionalmente sustituido con s R^3; Z es -O- o -NH- o -N(alquilo)-.

[0082] En algunas formas de realización, la porción de cabeza del antagonista de AR forma enlaces de hidrógeno con las cadenas laterales de Gln 711 y Arg752 del LBD de AR.

[0083] En algunas formas de realización, el grupo principal de B-AR comprende 4-cianofenilo; 3-fluoro-4-cianofenilo; 3-cloro-4-cianofenilo; 3-metoxi-4-cianofenilo; 3-metil-4-cianofenilo; 3-trifluorometil-4-cianofenilo; 3-trifluorometoxi-4-cianofenilo; 5-fluoro-6-cianopiridin-3-ilo; 5-cloro-6-cianopiridin-3-ilo; 5-metoxi-6-cianopiridin-3-ilo; 5-metil-6-cianopiridin-3-ilo; 5-trifluorometil-6-cianopiridin-3-ilo; 5-trifluorometoxi-6-cianopiridin-3-ilo; [1,2,4]triazolo[4,3-b]piridazin-6-ilo; o 3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-ilo.

[0084] En algunas formas de realización, el patógeno es un patógeno intracelular. En algunas formas de realización, el BDP es un antagonista AR que comprende una N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida o una N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida. En algunas formas de realización, el BDP es un antagonista de AR que es N-[trans-3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-1-(2-hidroxietil)-1H-pirazol-4-carboxamida.

[0085] En algunas formas de realización, el grupo principal y el núcleo de B-AR son:

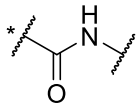
N-(3-(3-fluoro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-metoxi-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

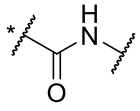
N-(3-(3-metil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-(3-trifluorometoxi-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-((5-fluoro-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-((5-cloro-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-((5-metoxi-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-((5-metil -6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-((5-trifluorometil-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*; o
N-(3-((5-trifluorometoxi-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

donde la acetamida-* es 

.

[0086] En algunas formas de realización, el grupo principal y el núcleo de B-AR son:
N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-(3-metoxi-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-(3-metil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*; o
N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

donde la acetamida-* es 

.

[0087] En algunas formas de realización, B-AR comprende además una porción de cola que está unida covalentemente a la posición (*), donde la porción de cola es un anillo D que es fenilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, triazolilo, pirrolilo, imidazolilo, pirazolilo, piridilo, indolilo, isoindolilo, indolizinilo, bencimidazolilo, naftilo, quinolilo, isoquinolilo, quinoxalinilo, quinazolinilo, indazolilo o benzotriazolilo; donde el anillo D está opcionalmente sustituido con s R^3; s es 1, 2 o 3; cada R^3 es independientemente hidrógeno, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, o $-C(=O)NH(CH_3)$.

Enfoques representativos para el diseño de compuestos heterobifuncionales

[0088] Los compuestos heterobifuncionales que se describen en este documento incluyen tres componentes: el ligando que se une a la proteína diana (es decir, la proteína causante de la enfermedad), el ligando que se une a la proteína dependiente de la enfermedad (PDE) y el ligador. Se conocen las estructuras cristalinas de muchas de estas proteínas y las interacciones de unión de cada componente dentro de su sitio de unión respectivo se pueden visualizar con un software de modelado adecuado. Además, también se puede realizar un modelado por computadora para determinar la

ubicación relativa de las dos proteínas.

[0089] El Protein Data Bank (PDB) es una base de datos para los datos estructurales tridimensionales de grandes moléculas biológicas, como proteínas y ácidos nucleicos (*Nucleic Acids Res*. 2019 Jan 8;47(D1):D520-D528. doi: 10,1093/nar/gky949). Los datos son enviados por biólogos y bioquímicos de todo el mundo y son de libre acceso en Internet a través de los sitios web de sus organizaciones miembros (por ejemplo, PDBe - www.pdbe.org, PDBj - www.pdbj.org, RCSB - www.rcsb.org/pdb y BMRB - www.bmrb.wisc.edu). El PDB está supervisado por una organización llamada Banco Mundial de Datos de Proteínas - wwPDB - www.wwpdb.org.

[0090] En algunas implementaciones, la búsqueda en la base de datos PDB y la manipulación de modelos 3D de proteínas se realizan con PyMOL. PyMOL es un sistema de visualización molecular patrocinado por los usuarios, basado en código abierto, mantenido y distribuido por Schrödinger. Se contemplan otros motores de búsqueda de bases de datos PDB y sistemas de visualización molecular.

[0091] El modelo de acoplamiento de ligandos en proteínas candidatas y el modelado de complejos ternarios se pueden construir en el paquete de software Rosetta (Leaver-Fay A, et al., ROSETTA3: un paquete de software orientado a objetos para la simulación y el diseño de macromoléculas. Methods Enzymol 2011; 487:545-74.

[0092] Se pueden identificar nuevos ligandos silenciosos para DDP utilizando métodos conocidos en el arte, como el descubrimiento de compuestos líderes basado en fragmentos (FBLD) (Kirsch P.; *et al.,* Conceptos y principios básicos del diseño de fármacos basado en fragmentos. Molecules 2019, 24 (23), 4309; Lamoree B.; et al. Perspectivas actuales en el descubrimiento de compuestos líderes basado en fragmentos (FBLD). *Essays Biochem*. 2017, 61 (5), 453–464; Erlanson DA; *et al*. Descubrimiento de fármacos basado en fragmentos. *J. Med. Chem.* 2004, 47 (14), 3463–3482; Shuker SB; et al. Descubrimiento de ligandos de alta afinidad para proteínas: SAR por RMN. Science 1996, 274 (5292), 1531–1534), enfoques de bibliotecas codificadas por ADN (DEL) y métodos tradicionales de cribado de alto rendimiento (HTS).

[0093] Las bibliotecas de cribado utilizadas en FBLD están compuestas de pequeñas moléculas llamadas fragmentos que cumplen ampliamente con lo que ahora se reconoce ampliamente como la regla de tres (Ro3) (Congreve M.; et al., 'Regla de tres' para el descubrimiento de compuestos líderes basado en fragmentos?. *Drug Discovery Today* 2003, 8 (19), 876–877; Jhoti H.; et al., La 'regla de tres' para el descubrimiento de fármacos basado en fragmentos: ¿dónde estamos ahora?. Nat. Rev. Drug Discovery

2013, 12 (8), 644–644). El pequeño tamaño y la simplicidad de los fragmentos permiten un enfoque minimalista para el descubrimiento de fármacos, mediante el cual se puede cubrir de manera eficiente un vasto espacio químico utilizando bibliotecas de tan solo unos pocos cientos de moléculas. Esto hace que el cribado de fragmentos resulte atractivo tanto para la industria como para los investigadores académicos, y representa un enfoque muy accesible, rentable y sostenible para el descubrimiento de compuestos activos. Además, a diferencia de las bibliotecas convencionales utilizadas para el cribado de alto rendimiento (HTS), las bibliotecas de fragmentos no están sesgadas hacia objetivos explorados previamente. Esto convierte a FBLD en un método indispensable para evaluar la capacidad de unión a ligandos de los sitios de unión de proteínas novedosas, incluidos los sitios de interacción proteína-proteína (PPI).

[0094] En algunos casos, el pequeño tamaño de los fragmentos da como resultado que tengan una baja afinidad de unión con las proteínas. Por este motivo, los fragmentos suelen analizarse a altas concentraciones utilizando técnicas biofísicas como la resonancia magnética nuclear (RMN), la resonancia de plasmones superficiales (RPS), la fluorimetría diferencial de barrido (DSF; también conocida como ensayo de desplazamiento térmico (TSA)) y la cristalografía de rayos X. Los ligandos débiles pueden optimizarse hábilmente para convertirse en ligandos potentes y personalizados para proteínas mediante metodologías de crecimiento, fusión e hibridación de fragmentos. Sin embargo, la búsqueda exitosa de tales enfoques a menudo depende de la determinación del modo de unión de los fragmentos a la proteína objetivo, típicamente utilizando métodos cristalográficos de rayos X y/o ^{15}N experimentos de RMN 2D y/o microscopía electrónica criogénica (crio-EM) (Saur M.; *et al*., Fragment-based drug discovery using cryo-EM. Drug Discovery Today 2020: 25-3 (490).

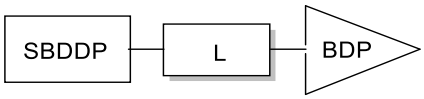
[0095] La técnica DEL se logra mediante química combinatoria y técnicas de codificación de ADN. Gracias a la modularidad de las bibliotecas, los DEL se pueden construir de una manera que ahorra tiempo y mano de obra. Esta tecnología puede construir y examinar bibliotecas de compuestos combinatorios a una escala sin precedentes (de cientos de miles de millones) y descubrir numerosos ligandos de alta afinidad con alta eficiencia y bajo costo a través del cribado de afinidad de objetivos proteicos y la secuenciación y decodificación de alto rendimiento (Buller *et al*., (2010). Descubrimiento de fármacos mediante bibliotecas químicas codificadas por ADN. *Bioconjugado. Química.* 21 (9), 1571–15802010; Kalliokoski T. (2015). Análisis centrado en el precio de los componentes básicos disponibles comercialmente para la síntesis de bibliotecas combinatorias. *Combinación ACS. Ciencia*. 17 (10), 600–607; Goodnow y

otros, (2017). Química codificada por ADN: permitiendo un muestreo más profundo del espacio químico. Nat. Rev. Drug Discov. 16 14(2): 131-147. DEL puede utilizarse para crear bibliotecas de compuestos con mayor peso molecular. Empíricamente, estas bibliotecas DEL parecen muy adecuadas para descubrir ligandos para dianas de interacción proteína-proteína (PPI), que son cada vez más necesarias para obtener resultados positivos.

[0096] Los ligadores también pueden diseñarse y evaluarse. Capturar la amplitud de las conformaciones viables del ligador es muy similar a modelar la flexibilidad de las moléculas similares a fármacos cuando se acoplan a proteínas. Para este propósito, el software OMEGA (Hawkins PC, et al., Comparación de la coincidencia de formas y el acoplamiento como herramientas de cribado virtual. *J Med Chem*. 2007; 50:74-82; Hawkins PC, Nicholls A. Generación de conformaciones con OMEGA: aprendizaje a partir del conjunto de datos y análisis de fallos. *Modelo de información química J.* 2012; 52:2919-36).

Compuestos

[0097] En algunas formas de realización, la molécula heterobifuncional es un compuesto de fórmula (II):



en donde:

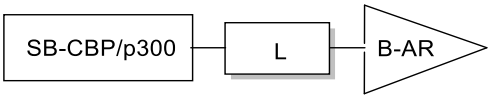
SB es un ligando silencioso de una proteína dependiente de la enfermedad (DDP);

L es un ligador opcional; y

BDP es un ligando de una proteína causante de enfermedad (DP).

[0098] En algunas formas de realización, la EM es EMR. En algunas formas de realización, el BDP es un antagonista AR que comprende una N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida o una N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida. En algunas formas de realización, el BDP es un antagonista de AR que es N-[trans-3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-1-(2-hidroxietil)-1H-pirazol-4-carboxamida.

[0099] En algunas formas de realización descritas en el presente documento se encuentran compuestos inhibidores condicionales heterobifuncionales de fórmula (III):



en donde:

SB-CBP/p300 es un ligando silencioso de CBP/p300;

L es un ligador opcional; y

El receptor B-AR es un ligando del receptor de andrógenos (AR).

[00100] En algunas formas de realización, en la presente se proporciona un compuesto de fórmula (I)

a. un ligando de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300);

b. un ligando de una proteína de enfermedad (DP); y

c. un ligador opcional que conecta covalentemente a) con b);

donde el ligador opcional se une covalentemente en una posición de a) que está expuesta al disolvente cuando a) se une a CBP/p300.

[00101] En algunas formas de realización, el ligando de CBP/p300 se une al sitio de unión de acetil-lisina (Kac) del bromodominio CBP/p300. En algunas formas de realización, el ligando de CBP/p300 comprende una porción mimética de acetil-lisina que se une al sitio de unión de acetil-lisina (KAc) del bromodominio de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300).

[00102] En algunas formas de realización, el ligador opcional se une covalentemente en una posición de a) que está expuesta al disolvente cuando a) se une al sitio de unión de KAc del bromodominio de CBP/p300.

[00103] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina establece o imita una interacción de enlace de hidrógeno con Asn1168 en el bolsillo de unión de Asn del bromodominio de CBP, o establece o imita una interacción de enlace de hidrógeno con Asn1132 en el bolsillo de unión de Asn del bromodominio de p300.

[00104] En algunas formas de realización, a) comprende además una porción que interactúa con Arg1173 en el bromodominio de CBP o Asn1137 en el bromodominio de p300.

[00105] En algunas formas de realización, en las que a) comprende además:

1) una porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300; o

2) una porción que ocupa la región del bucle BC del bromodominio de CBP/p300; o

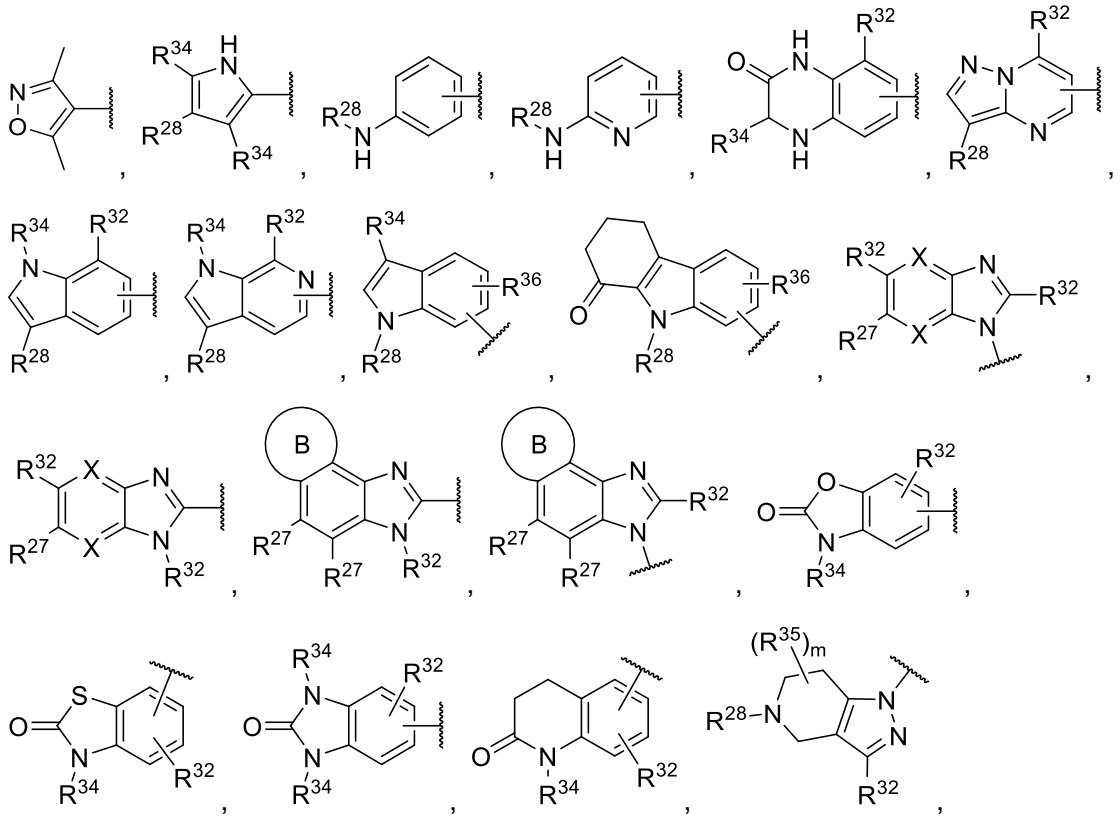
3) tanto 1) como 2).

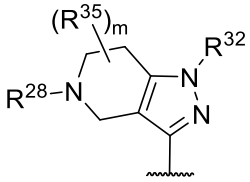
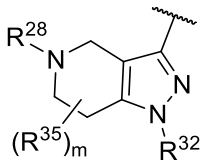
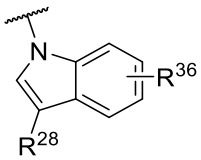
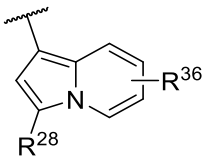
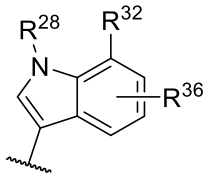
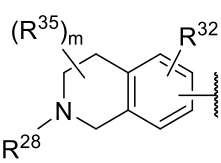
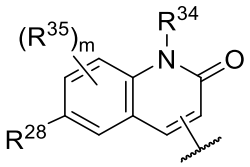
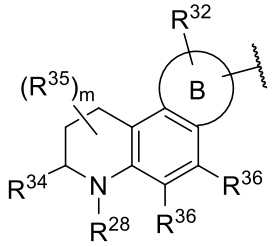
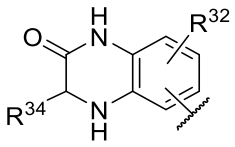
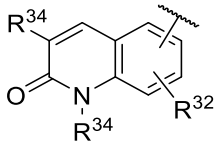
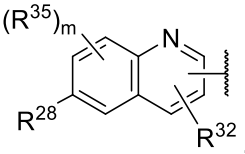
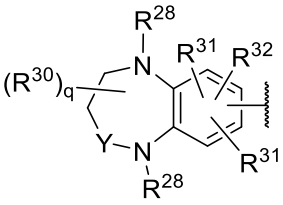
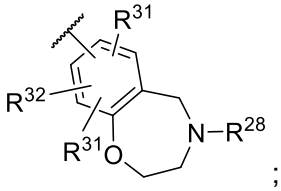
[00106] En algunas formas de realización, en las que la porción que comprende un mimético de acetil-lisina comprende una porción seleccionada de pirrolidonilo, fenilo,

piridinilo, piridinilo, triazolilo, pirrolilo, isoxazolilo, pirazolilo, quinolinilo, tetrahidroquinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, quinazolonilo, quinazolinilo, dihidroquinazolinonilo, imidazo[4,5-c]quinolinilo fusionado a un dimetilisoxazolilo, triazoloftalazinilo, indolizinilo, benzoimidazolilo, isoxazol-indolizinilo, tienodiazepina-indolizinilo, benzodiazepina-indolizinilo, 5-isoxazolilbenzimidazolilo, 6-isoxazolilbenzimidazolilo, 7-isoxazolo-quinolinilo, diazobencilo, triazoloftalazinilo, isoxazoloquinolinilo, 2-tiazolidinonilo, triazolopirimidinilo, tienodiazepinilo, benzodiazepinilo, benzotriazepinilo, triazolobenzodiazepinilo, triazolotienodiazepinilo, triazolotienodiazepinilo e isoxazol-azepinilo.

[00107] En algunas formas de realización, el ligador opcional de c) está unido covalentemente a a) en: la porción mimética de acetil-lisina; o la porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300, si está presente; o la porción que ocupa la región del bucle BC del bromodominio de CBP/p300, si está presente; donde el ligador opcional de c) está unido covalentemente a a) en una posición que no interfiere con la unión de la porción mimética de acetil-lisina en el sitio de unión de lisina acetilada (KAc) de CBP/p300.

[00108] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende una porción seleccionada de entre:




,

,

,

,

,

,

,

,

,

,

,

, o

;

Cada R^{32} es independientemente una porción opcional que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300;

o cada R^{32} es independientemente una porción opcional que ocupa la región del bucle BC del bromodominio de CBP/p300;

 es el punto de unión al ligador opcional que conecta covalentemente a) con b);

o es R^{32} y el ligador opcional que conecta covalentemente a) con b) está unido a R^{32};

cada R^{28} es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -C(=O)R^b, o -C(=O)N(R^b)$_2$;

cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

cada R^{35} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -OH, -OR^a o -N(R^b)$_2$;

m es 0, 1, 2, 3 o 4;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

Y es -$C(R^{30})_2$- o C(=O);cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

q es 1, 2, 3 o 4;

cada R^{31} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

cada R^{36} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^a o -$N(R^b)_2$;

El anillo B es un heterocicloalquilo fusionado, sustituido o no sustituido, de 5 o 6 miembros;

cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_8cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

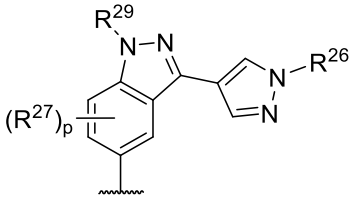
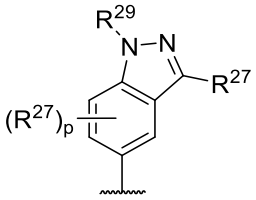
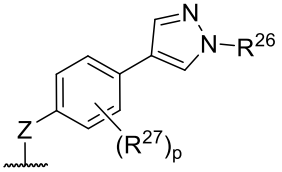
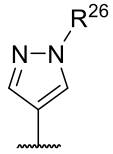
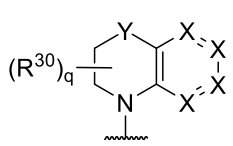
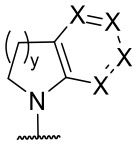
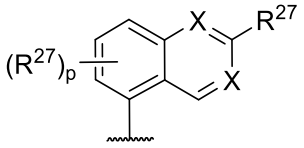
cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo

monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00109] En algunas formas de realización, la porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300 es R^{32}, donde:

R^{32} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_2-C_6alquenilo sustituido o no sustituido, C_2-C_6alquinilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_{12}cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 12 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido;

o R^{32} es  ,  ,  ,  ,  ,  , o  ;

es 1 o 2.

Z es -NR^c-, -O- o -S-;

R^9 es hidrógeno o alquilo C_{1-6} no sustituido;

R^{26} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada X es independientemente -CR^{27}- o -N-;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -OC(=O)N(R^b)$_2$, -SR^b, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2OR^b$, -S(=O)$_2$N(R^b)$_2$, -N(R^b)$_2$, -NR^bC(=O)N(R^b)$_2$, -NR^bC(=O)R^a, -NR^bC(=O)OR^a, -NR^bS(=O)$_2R^a$, -C(=O)R^b, -C(=O)OR^b, o -C(=O)N(R^b)$_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno o alquilo C_{1-6} no sustituido;

R^{29} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

Y es -CH^{30}-, -O- o -$N(R_{28})$-,

cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

q es 1, 2, 3 o 4;

o R^{32} es -LC;

L es un alquilo C_1-C_6 sustituido o no sustituido, o un heteroalquilo C_1-C_6 sustituido o no sustituido;

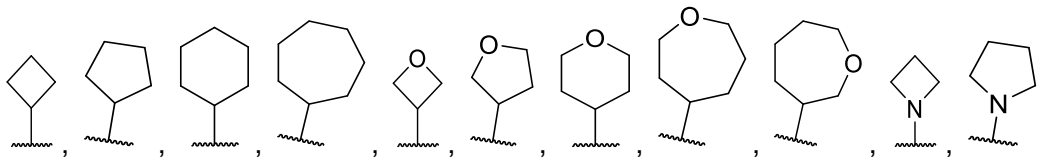
C es C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido;

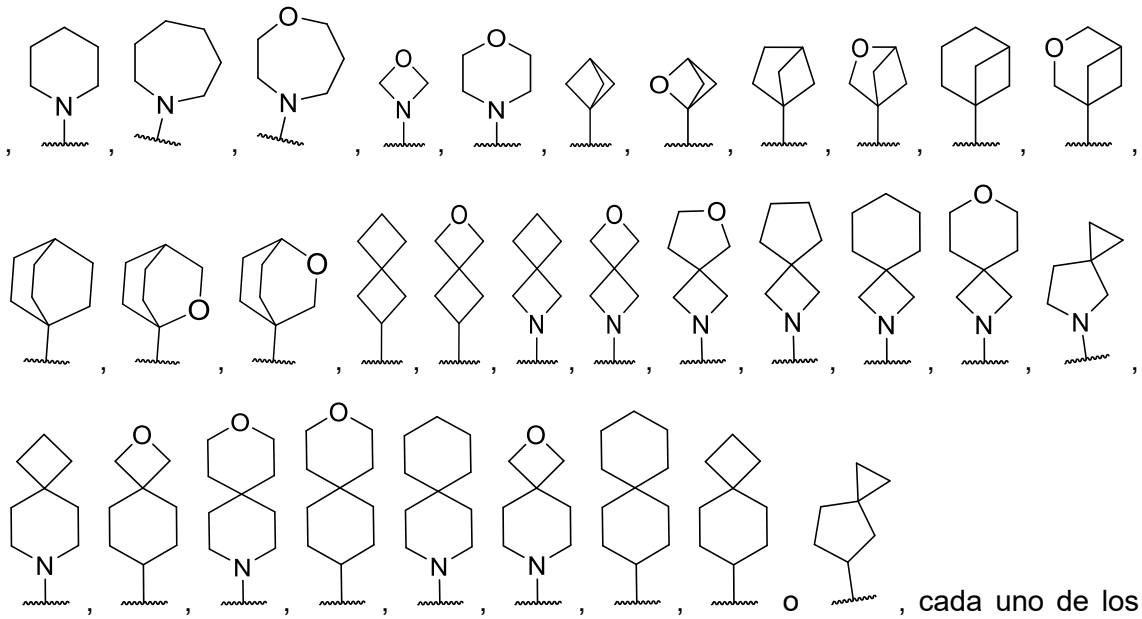
Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_8cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

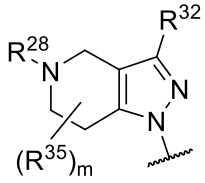
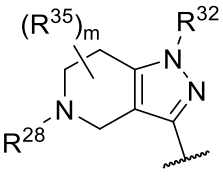
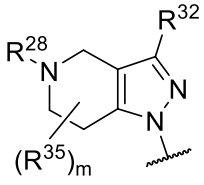
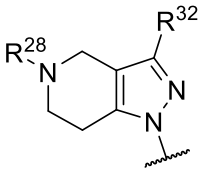
cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

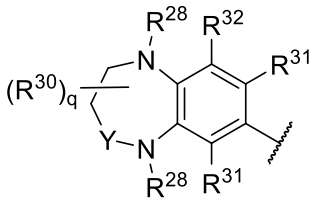
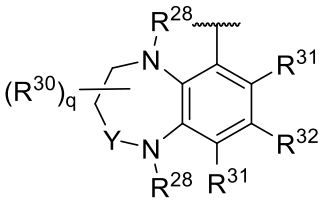
o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

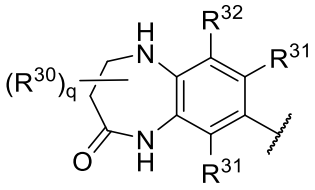
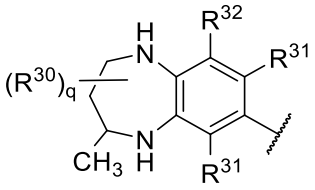
[00110] En algunas formas de realización, la porción que ocupa la región del bucle BC del bromodominio de CBP/p300 es R^{32}, donde:

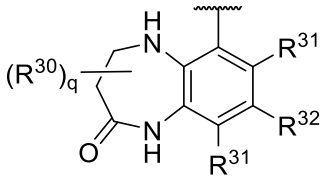
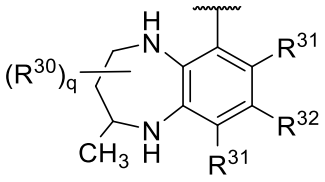
R^{32} es 

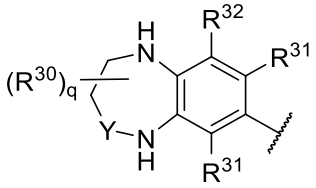

o , cada uno de los cuales está sustituido o no sustituido.

[00111] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  o  . En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  . En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  .

[00112] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  o  . En algunas formas de realización, la porción que comprende un mimético de acetil-lisina

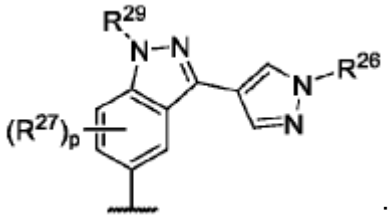
comprende  ,  ,

 o  .

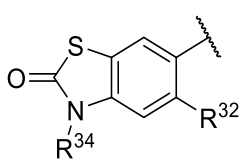
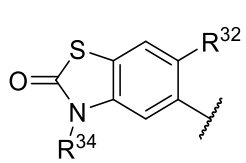
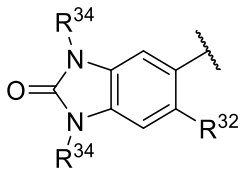
[00113] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  ;

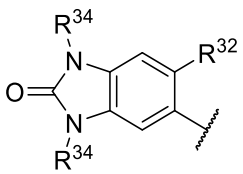
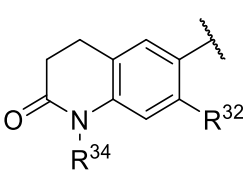
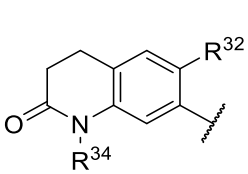
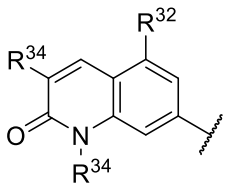
en donde:

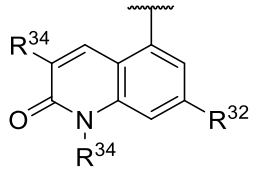
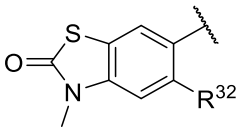
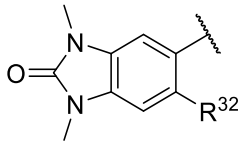
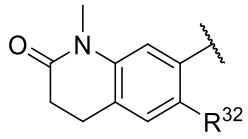
cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

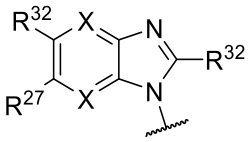
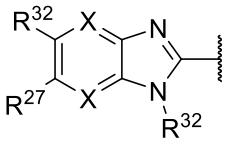
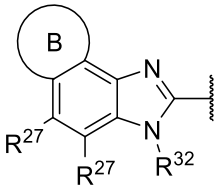
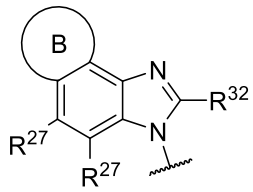
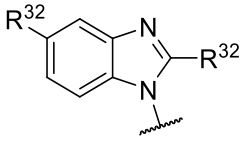
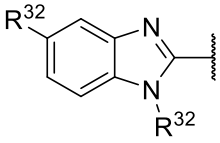
R^{32} es  ; y

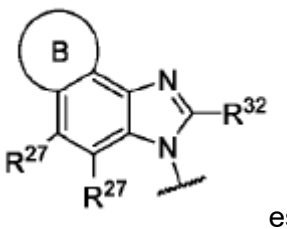
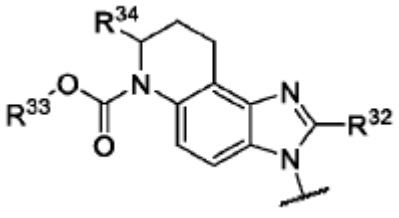
cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -SR^b, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2$OR^b, -S(=O)$_2$N(R^b)$_2$, -N(R^b)$_2$, -NR^bC(=O)N(R^b)$_2$, -NR^bC(=O)R^a, -NR^bC(=O)OR^a, -NR^bS(=O)$_2R^a$, -C(=O)R^b, -C(=O)OR^b, o -C(=O)N(R^b)$_2$.

[00114] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  ,  ,  ,

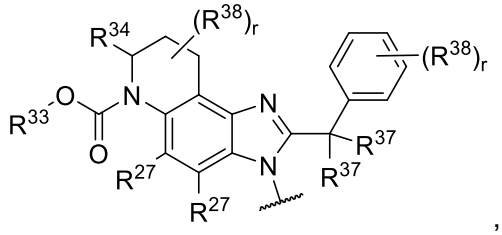
 ,  ,  ,  o


. En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  ,  o  .

[00115] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende  ,  ,  o  . En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende la porción que comprende un mimético de acetil-lisina comprende  o  . En algunas formas de realización,



es .

[00116] En algunas formas de realización, la porción que comprende un mimético de acetil-lisina comprende



,

en donde:

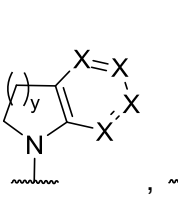
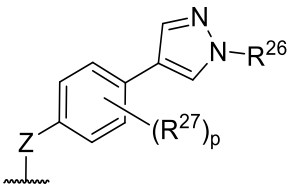
cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^a o -$N(R^b)_2$;

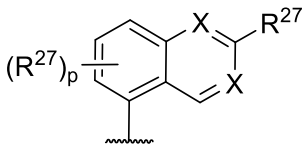
R^{33} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, o C_1-C_6heteroalquilo sustituido o no sustituido;

R^{34} es hidrógeno o alquilo C_{1-6} no sustituido;

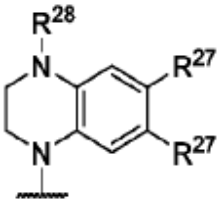
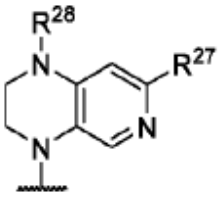
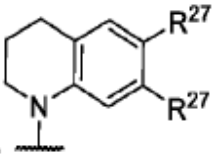
cada R^{38} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

m es 0, 1, 2, 3 o 4;

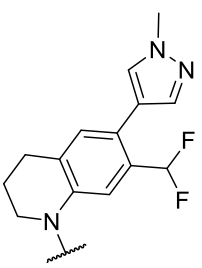
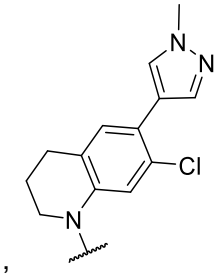
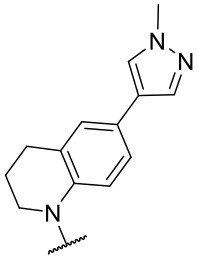
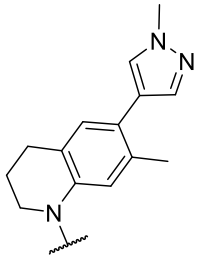
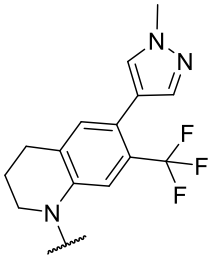
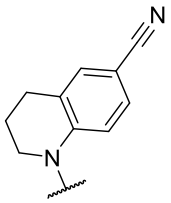
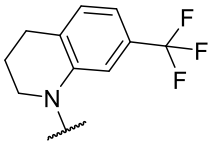
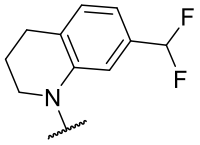
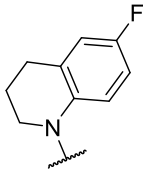
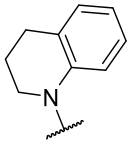
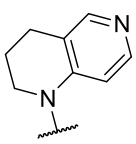
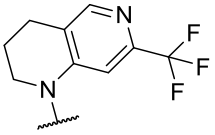
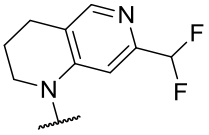
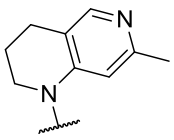
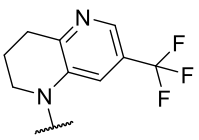
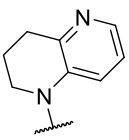
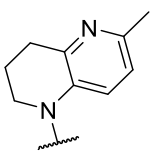
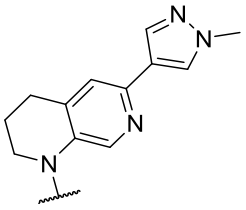
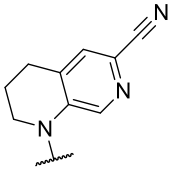
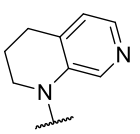
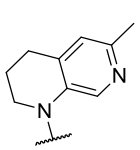
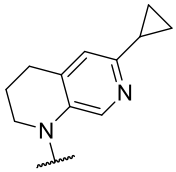
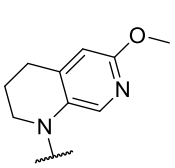
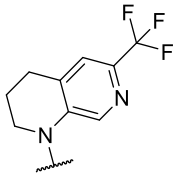
[00117] En algunas formas de realización, R^{32} es  , 

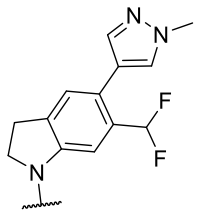
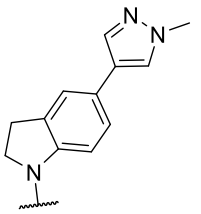
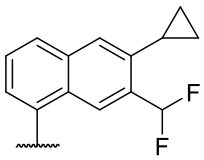
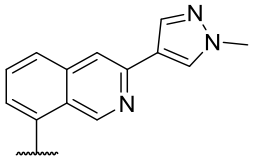
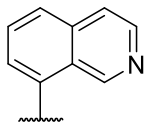
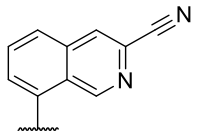
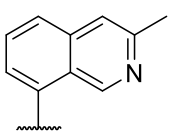
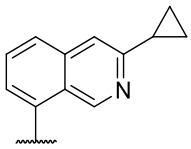
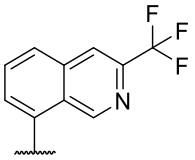
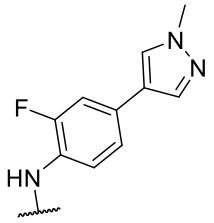
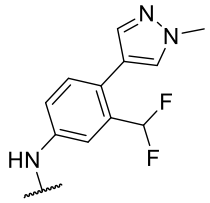
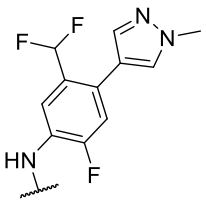
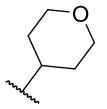
o  ; cada R^{27} es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -OH o -OR^a; y cada R^a es independientemente C_1-C_6alquilo sustituido o no sustituido.

[00118] En algunas formas de realización, R^{32} es

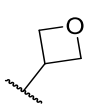
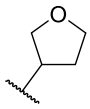
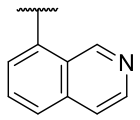
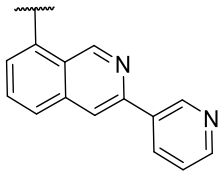
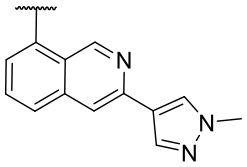
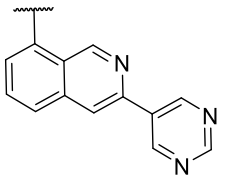
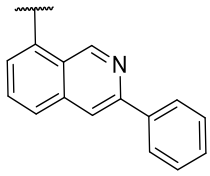
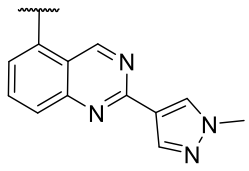
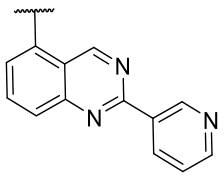




[00119] En algunas formas de realización, cada R^{27} es independientemente hidrógeno, $-CH_3$, $-CH_2CH_3$, -F, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, ciclopropilo, ciclobutilo, oxetanilo, tetrahidrofurano, tetrahidropiranilo, fenilo, pirazolilo, 1-metilpirazolilo, piridinilo o pirimidinilo.

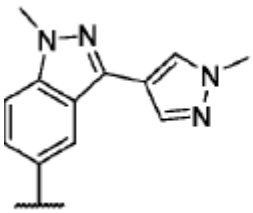
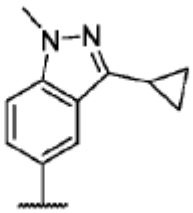
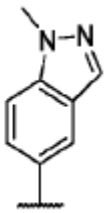
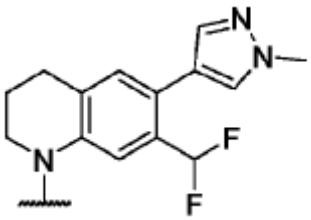
[00120] En algunas formas de realización, R^{32} es 
























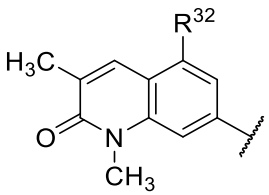


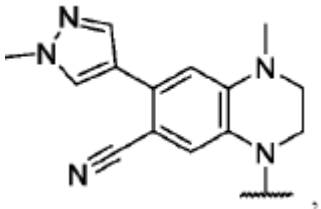









o .

[00121] En algunas formas de realización, R^{32} es

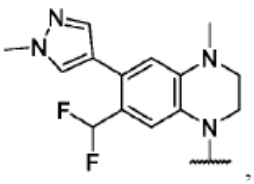
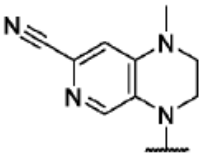
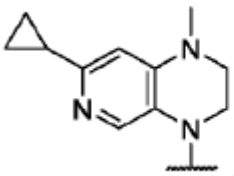
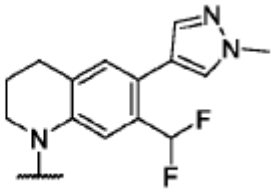
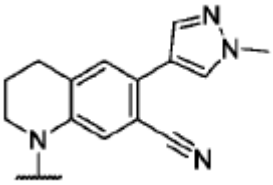



o

.

[00122] En algunas formas de realización, R^{32} es

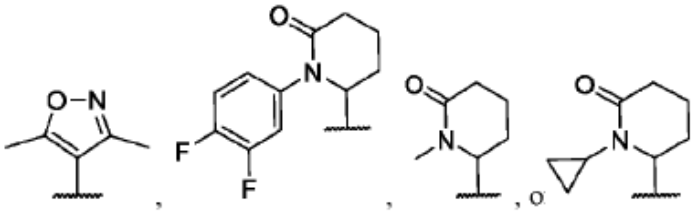

.



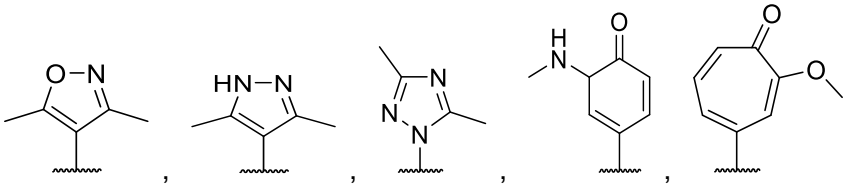
[00123] En algunas formas de realización, R^{32} es

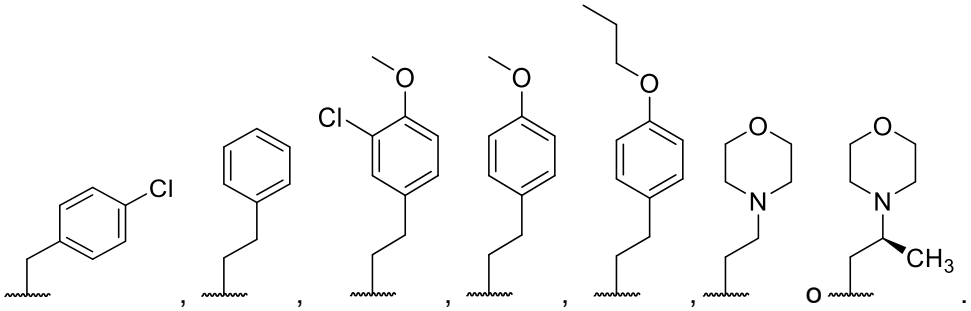






[00124] En algunas formas de realización, R^{32} es



. En algunas formas de realización, R^{32} es





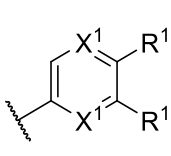
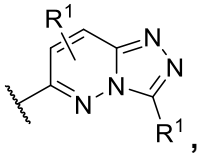
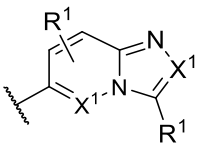
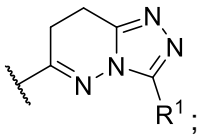
[00125] En algunas formas de realización, B-AR es un ligando AR no esteroideo o un ligando AR esteroideo.

[00126] En algunas formas de realización, B-AR es *N*-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida o *N*-(3-(3-trifluorometil-4-cianofenoxi)-

2,2,4,4-tetrametilciclobutil)-aril-carboxamida.

[00127] En algunas formas de realización, B-AR es flutamida, hidroxiflutamida, nilutamida, bicalutamida, enzalutamida, apalutamida, ODM201, AZD3514, BMS641988 o N-[trans-3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-1-(2-hidroxietil)-1H-pirazol-4-carboxamida.

[00128] En algunas formas de realización, B-AR comprende un grupo de cabezal y un núcleo opcional, donde el grupo de cabezal se selecciona de:


,

,

, y

;

X^1 es CR^1 o N;

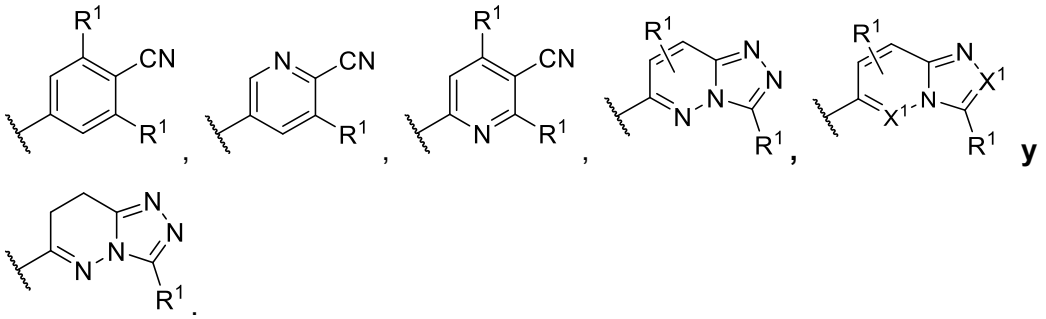
cada R^1 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$OC(=O)N(R^5)_2$, -$OC(=O)OR^5$, -$OC(=O)NR^5$, -SH, -SR^4, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2OR^4$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$NR^5C(=O)OR^5$, -$NR^5S(=O)_2R^5$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$.

cada R^4 es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^5 es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^5 en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

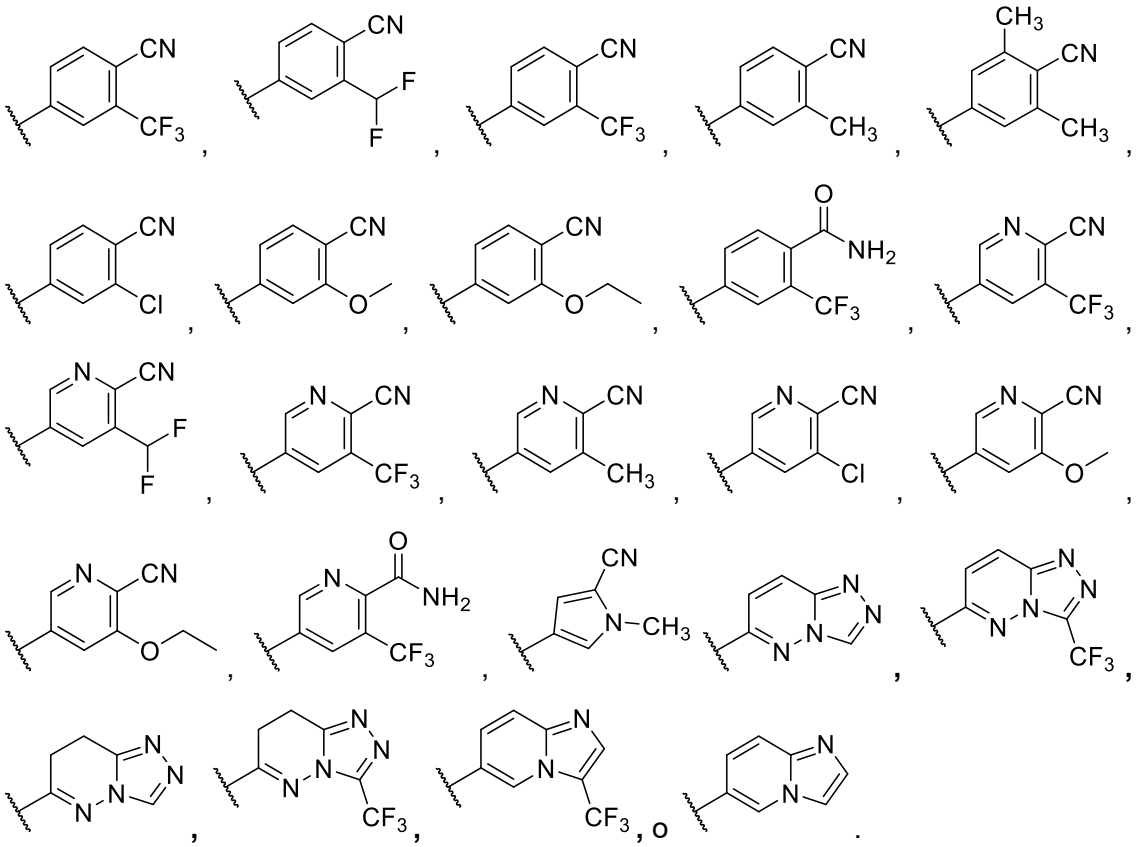
[00129] En algunas formas de realización, la quimioterapia basada en platino se selecciona de:



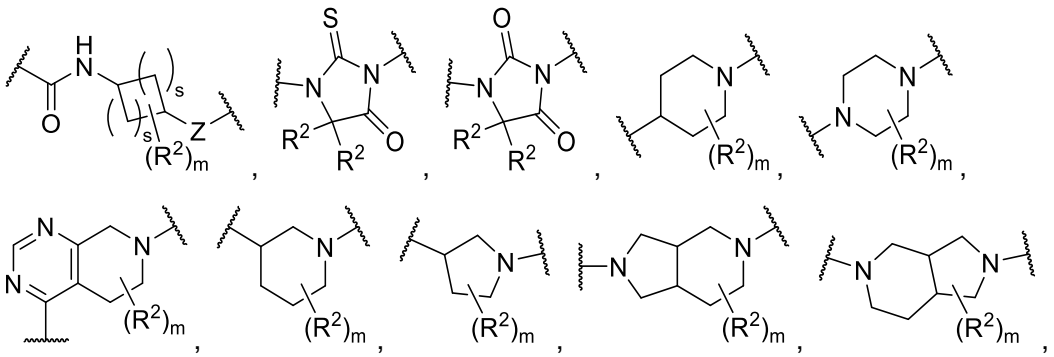
y

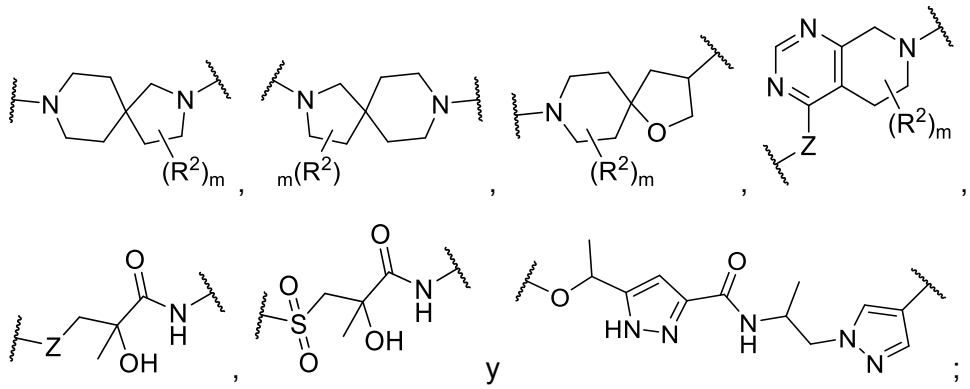
.

[00130] En algunas formas de realización, el grupo principal se selecciona de:



[00131] En algunas formas de realización, el núcleo opcional comprende un grupo seleccionado de entre:





X es O o NR^5;

cada R^2 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$; o

dos R^2 en el mismo átomo de carbono se toman junto con el átomo de carbono al que están unidos para formar un cicloalquilo C_3-C_8 sustituido o no sustituido o un heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido;

m es 0, 1, 2, 3 o 4;

cada n es independientemente 1, 2 o 3;

cada R^4 es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

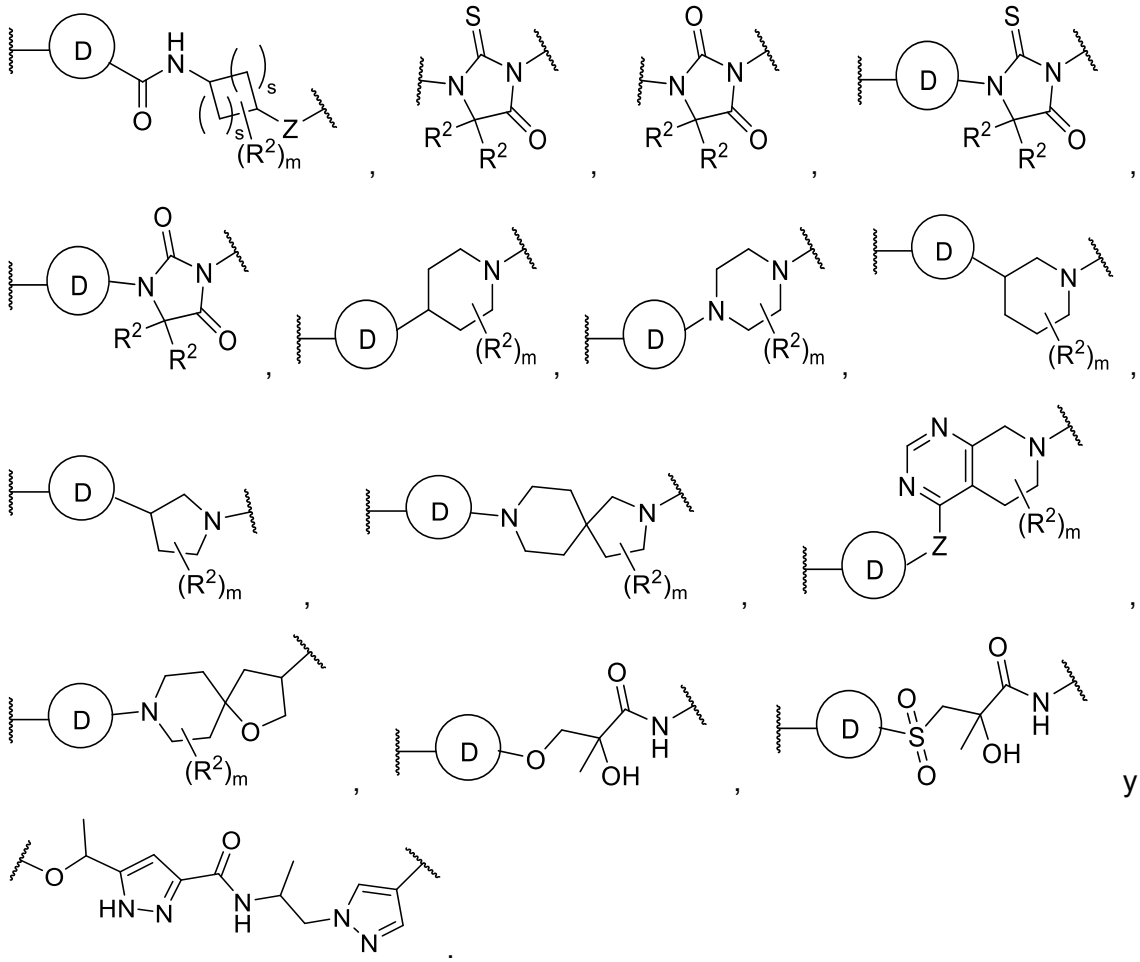
cada R^5 es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^5 en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

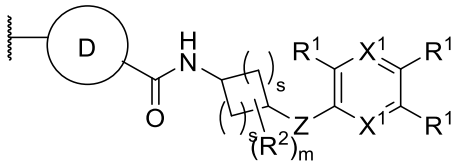
[00132] En algunas formas de realización, el núcleo opcional comprende además un anillo D que es un arilo de 5, 6, 8, 9 o 10 miembros o un heteroarilo de 5, 6, 8, 9 o 10 miembros que está opcionalmente sustituido con s R^3; cada R^3 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^4

o -$N(R^5)_2$.

[00133] En algunas formas de realización, el núcleo opcional comprende un grupo seleccionado de entre:



[00134] En algunas formas de realización, B-AR tiene la estructura de la fórmula (IIIa), o una sal o solvato farmacéuticamente aceptable de esta:



Fórmula (IIIa)

en donde:

cada X es independientemente $-CR^3-$ o -N-;

X^1 es CR^1 o N;

X es O o NR^5;

cada R^1 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o

no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$OC(=O)N(R^5)_2$, -$OC(=O)OR^5$, -$OC(=O)NR^5$, -SH, -SR^4, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2OR^4$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$NR^5C(=O)OR^5$, -$NR^5S(=O)_2R^5$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$;

cada R^2 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$;

anillo D que es un arilo de 5, 6, 8, 9 o 10 miembros o un heteroarilo de 5, 6, 8, 9 o 10 miembros que opcionalmente está sustituido con s R^3;

R^3 es hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^4 o -$N(R^5)_2$;

n es 0, 1, 2, 3 o 5;

m es 0, 1, 2, 3 o 4;

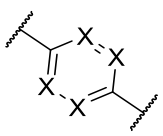
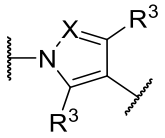
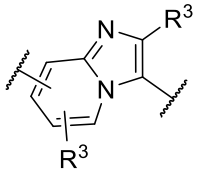
cada n es independientemente 1, 2 o 3;

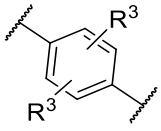
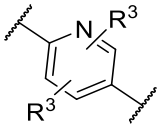
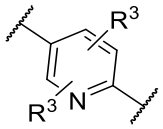
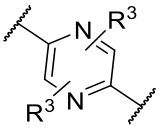
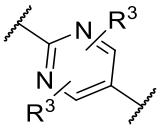
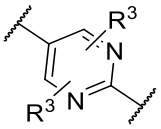
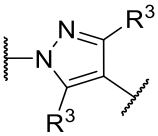
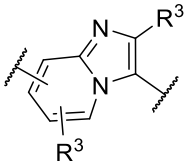
cada R^4 es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^5 es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

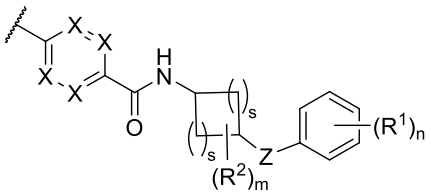
o dos R^5 en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00135] En algunas formas de realización, el anillo D es fenilo, naftilo, piridinilo, pirimidinilo, piridazinilo, pirazinilo, triazinilo, pirrolilo, tiazolilo, oxazolilo, isoxazolilo, oxadiazolilo, imidazolilo, pirazolilo, isotiazolilo, triazolilo y tetrazolilo, donde cada anillo D está opcionalmente sustituido con s R^3.

[00136] En algunas formas de realización, el anillo D es  ,  o  ; cada X es independientemente -CR^3- o -N-.

[00137] En algunas formas de realización, el anillo D es  ,  ,  ,  ,  ,  ,  o  .

[00138] En algunas formas de realización, B-AR tiene la estructura de la fórmula (IIIa), o una sal o solvato farmacéuticamente aceptable de esta:



Fórmula (IIIa)

en donde:

cada X es independientemente -CR^3- o -N-;

X es O o NR^5;

cada R^1 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$OC(=O)N(R^5)_2$, -$OC(=O)OR^5$, -$OC(=O)NR^5$, -SH, -SR^4, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2OR^4$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$NR^5C(=O)OR^5$, -$NR^5S(=O)_2R^5$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$;

cada R^2 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -

$N(R^5)_2$, $-NR^5C(=O)NR^5$, $-NR^5C(=O)R^4$, $-C(=O)R^5$, $-C(=O)OR^5$, o $-C(=O)N(R^5)_2$;

R^3 es hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, $-OR^4$ o $-N(R^5)_2$;

n es 0, 1, 2, 3 o 5;

m es 0, 1, 2, 3 o 4;

cada n es independientemente 1, 2 o 3;

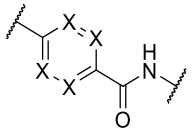
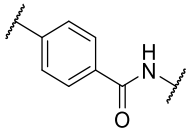
cada R^4 es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

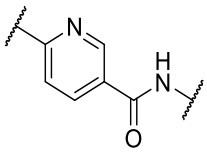
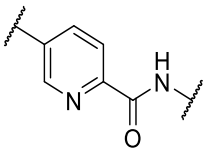
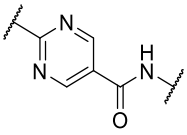
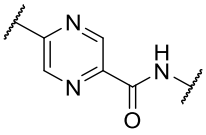
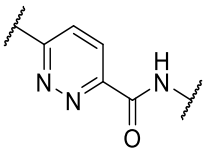
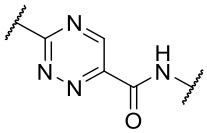
cada R^5 es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

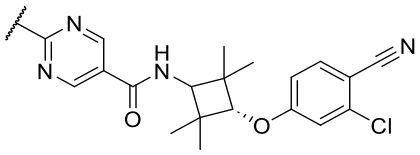
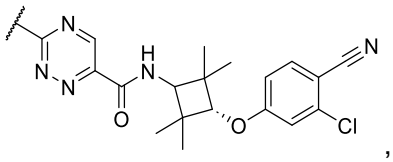
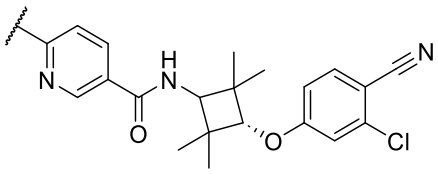
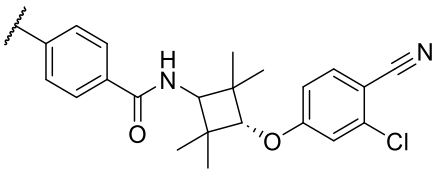
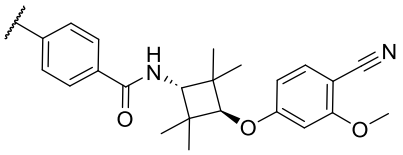
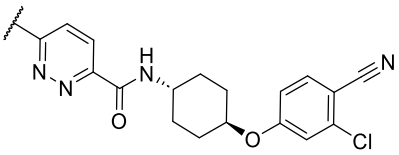
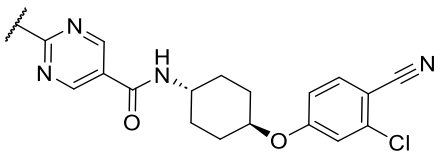
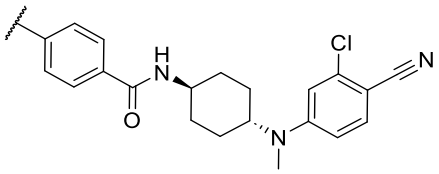
o dos R^5 en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

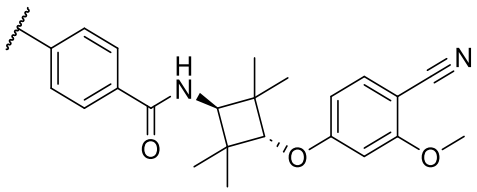
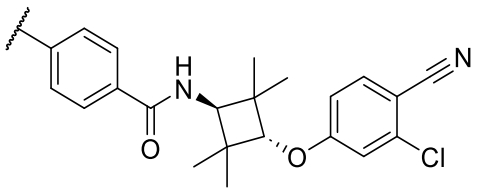
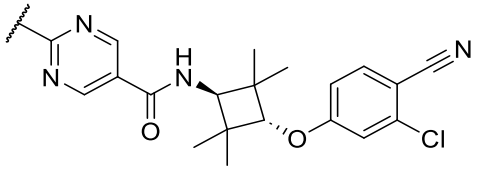
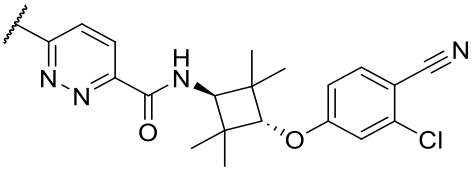
[00139] En otra forma de realización, p es 1 y R^2 es oxo o alquil $C_{1\text{-}6}$ no sustituido. En algunas formas de realización, m es 4 y cada R^2 es $-CH_3$. En algunas formas de realización, dos R^2 en el mismo átomo de carbono se toman junto con el átomo de carbono al que están unidos para formar un ciclobutilo sustituido o no sustituido, ciclopentilo sustituido o no sustituido, ciclohexilo sustituido o no sustituido, oxetanilo sustituido o no sustituido, tetrahidrofurano sustituido o no sustituido, tetrahidropiranilo sustituido o no sustituido, azetidina sustituida o no sustituida, pirrolidinilo sustituido o no sustituido, o un piperidinilo sustituido o no sustituido. En algunas formas de realización, dos R^2 en el mismo átomo de carbono se toman junto con el átomo de carbono al que están unidos para formar un ciclobutilo sustituido o no sustituido.

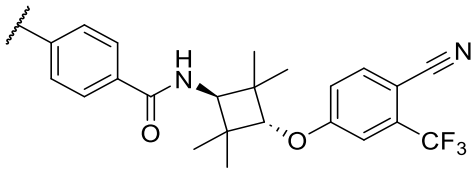
[00140] En algunas formas de realización, n es 2 y un R^1 es halógeno y el otro R^1 es -CN. En algunas formas de realización, n es 2 y un R^1 es -Cl y el otro R^1 es -CN.

[00141] En algunas formas de realización,  es  ,

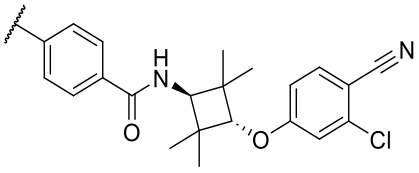
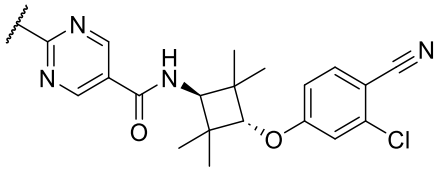
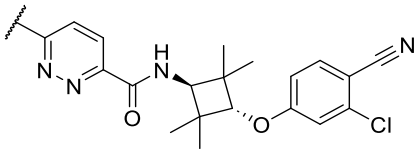
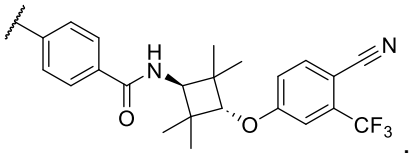

,

,

,

,

o

.

[00142] En algunas formas de realización, B-AR tiene una de las siguientes estructuras:

,

,

,

,

,

,

o

, o una sal o solvato farmacéuticamente aceptable de este.

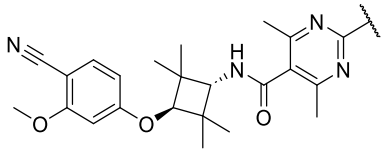
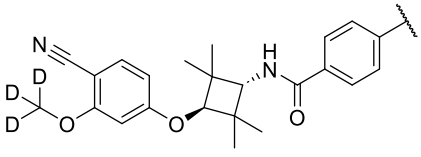
[00143] En algunas formas de realización, B-Ar tiene una de las siguientes estructuras:

,

,

,

o

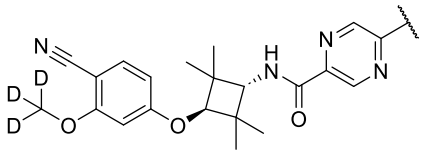
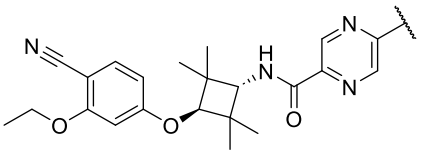

, o una sal o solvato farmacéuticamente aceptable de este.

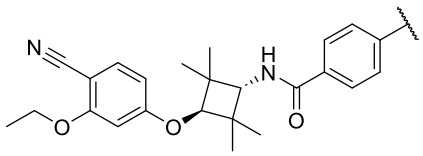
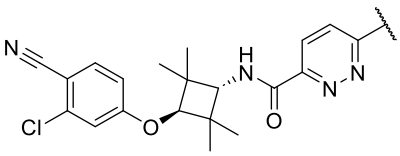
[00144] En algunas formas de realización, la EM es EMR. En algunas formas de realización, el BDP es un antagonista AR que comprende una N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida o una N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)-aril-carboxamida. En algunas formas de realización, el BDP es un antagonista AR que es flutamida, hidroxiflutamida, nilutamida, bicalutamida, enzalutamida, apalutamida, ODM201, AZD3514, BMS641988 o N-[trans-3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-1-(2-hidroxietil)-1H-pirazol-4-carboxamida.

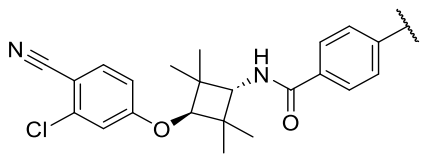
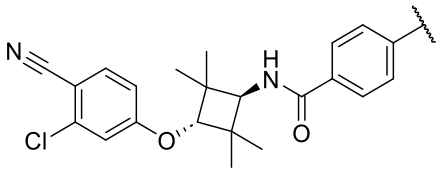
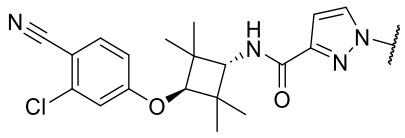
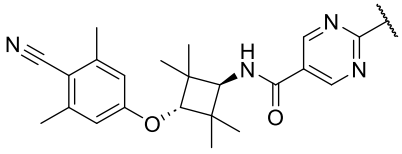
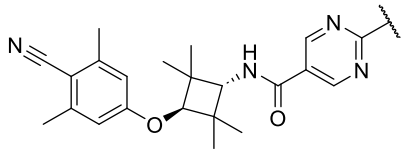
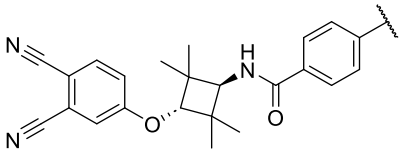
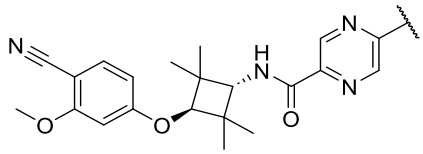
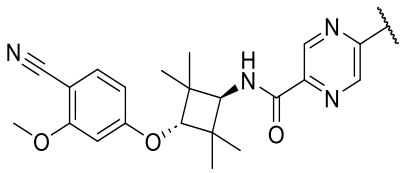
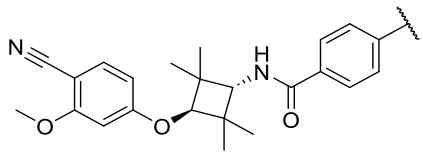
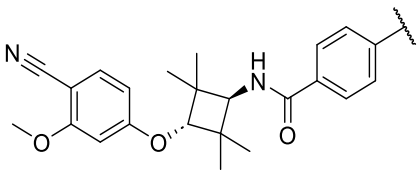
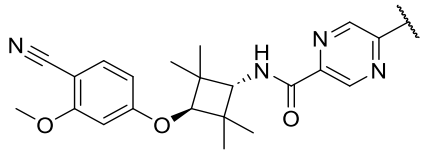
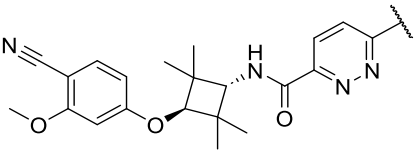
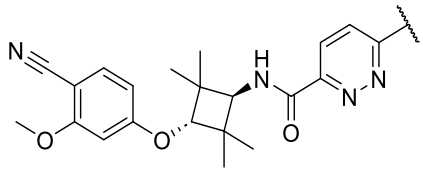
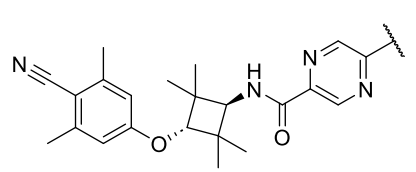
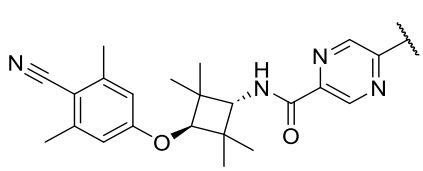
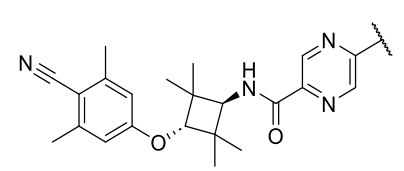
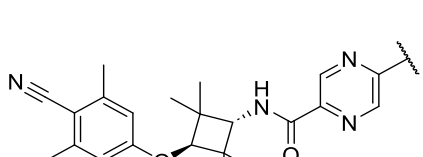
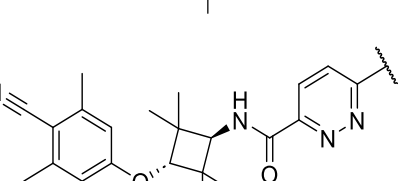
[00145] En algunas formas de realización, el BDP tiene una de las siguientes estructuras:  ,  ,  o  .

[00146] En algunas formas de realización, la formulación tiene una o más de las siguientes propiedades:

 ,  ,

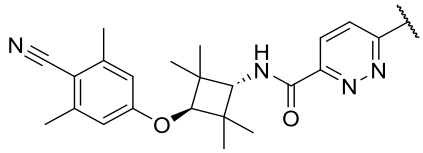
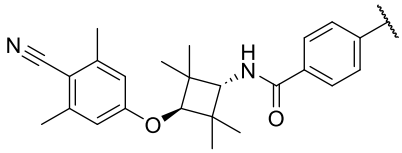
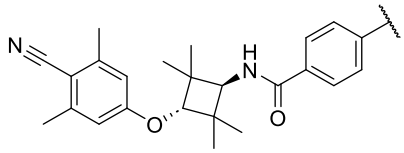
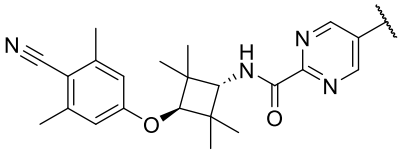
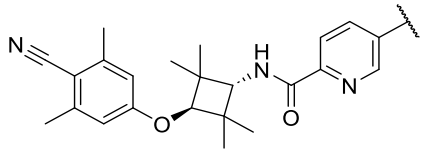
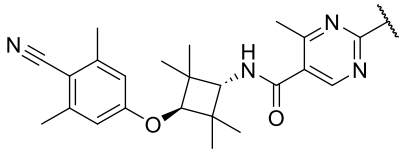
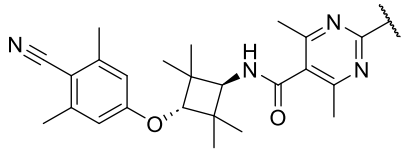
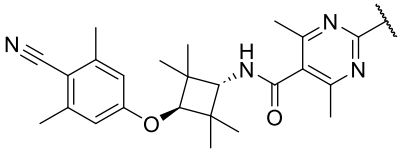
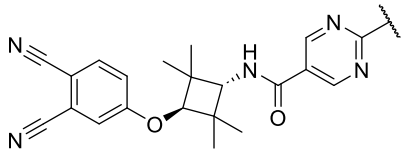
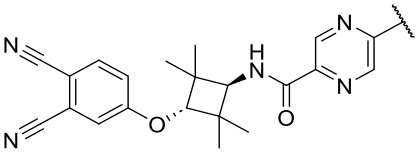
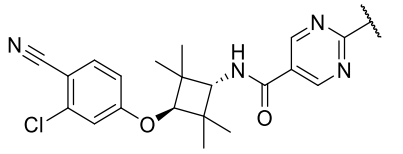
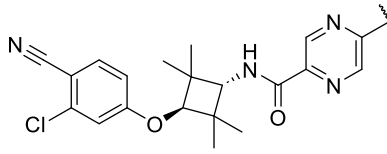
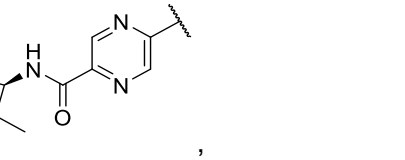
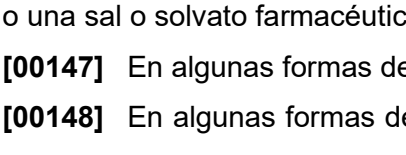
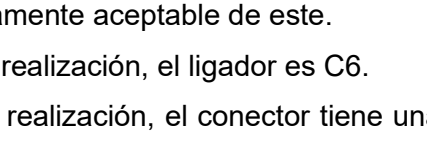
 ,  ,

 ,  ,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,
o

,

,

,

o una sal o solvato farmacéuticamente aceptable de este.

[00147] En algunas formas de realización, el ligador es C6.

[00148] En algunas formas de realización, el conector tiene una longitud predefinida, uniendo así el SBDDP y el BDP y permitiendo una distancia adecuada entre ellos.

[00149] En algunas formas de realización, el ligador es flexible. En algunas formas de realización, el ligador es TEG.

[00150] En algunas formas de realización, el ligador es un dinucléotido. En algunas formas de realización, el antígeno comprende un antígeno no polipeptídico. En algunas formas de realización, el ligador es un dinucléotido. En algunas formas de realización, el ligador es un dinucléotido.

[00151] En algunas formas de realización, el uso de ligadores trivalentes permite la

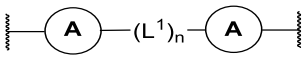
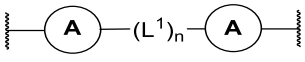
preparación de compuestos heterotrifuncionales que comprenden un ligando silencioso a un DDP y dos ligandos a una proteína de la enfermedad, o dos ligandos silenciosos a un DDP y un ligando a una proteína de la enfermedad, uniendo así simultáneamente una proteína de la enfermedad y un DDP y formando un complejo ternario productivo. En algunos casos, estos compuestos heterotrifuncionales darían como resultado una actividad anticancerígena más sostenida y más potente.

[00152] En algunas formas de realización, el ligador comprende una o más estructuras lineales, una o más estructuras no lineales, una o más estructuras ramificadas, una o más estructuras cíclicas, una o más fracciones flexibles, una o más fracciones rígidas o combinaciones de las mismas.

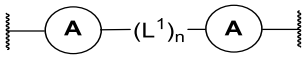
[00153] En algunas formas de realización, el ligador comprende uno o más componentes ligadores. En algunas formas de realización, el ligador comprende de 1 a 3, de 1 a 5, de 1 a 10, de 5 a 10 o de 5 a 20 residuos de aminoácidos. En algunas formas de realización, uno o más aminoácidos del ligador son aminoácidos no naturales. En algunas formas de realización, el ligador es un dinucléotido. El enlace peptídico está compuesto por L-aminoácidos y/o D-aminoácidos.

[00154] En algunas formas de realización, el ligador tiene una longitud de 1 a 100 átomos, de 1 a 50 átomos, de 1 a 30 átomos, de 1 a 20 átomos, de 1 a 15 átomos, de 1 a 10 átomos o de 1 a 5 átomos. En algunas formas de realización, el ligador tiene una longitud de 1 a 10 átomos. En algunas formas de realización, el ligador tiene una longitud de entre 1 y 20 átomos.

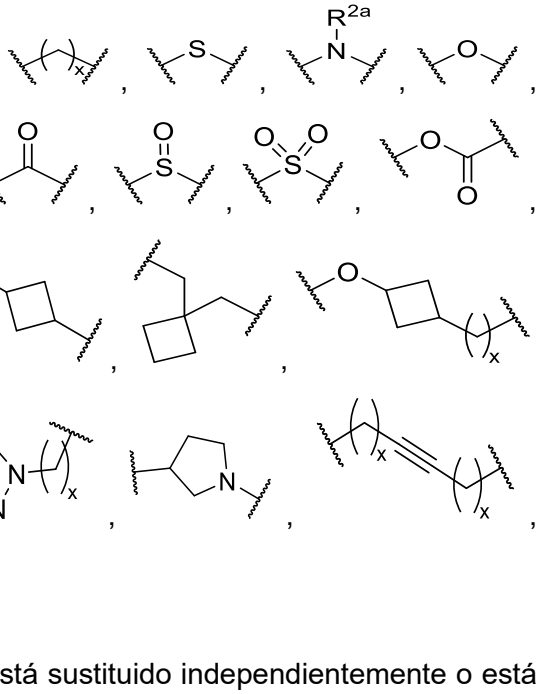
[00155] En algunas formas de realización, el conector comprende regiones flexibles y/o rígidas.

[00156] En algunas formas de realización, el ligador es L, donde L está ausente o es  . En ciertas formas de realización, L está ausente. En algunas formas de realización, L es  .

[00157] En algunas formas de realización, L comprende C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_{10}cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 10 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, o combinaciones de los mismos.

[00158] En algunas formas de realización, L está ausente o  , en cuyo caso:

cada A está ausente independientemente, cicloalquilo monocíclico sustituido o no sustituido C_3-C_{10}, cicloalquilo bicíclico puenteado sustituido o no sustituido C_3-C_{10}, cicloalquilo bicíclico fusionado sustituido o no sustituido C_3-C_{10}, cicloalquilo espiro bicíclico sustituido o no sustituido C_3-C_{10}, cicloalquilo monocíclico sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo, bicíclico puenteado sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo, bicíclico fusionado sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo, bicíclico espiro sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo,arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido, donde cada A está independientemente no sustituido o sustituido con x R^{2b};

cada L^1 está ausente independientemente,  , donde cada L^1 no está sustituido independientemente o está sustituido con x R^{2b};

n es 2, 3, 4, 5 o 6;

Cada n es independientemente 0, 1, 3, 4, 5, 6 o 7 (preferentemente, 0 o 1);

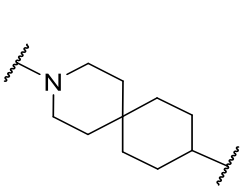
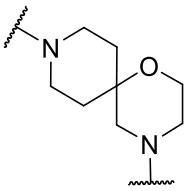
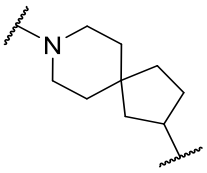
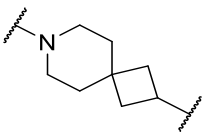
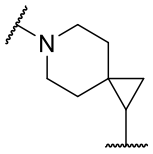
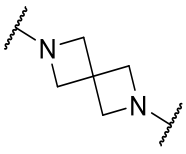
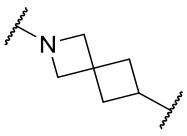
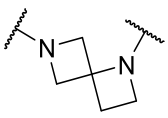
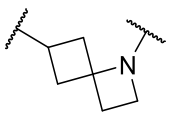
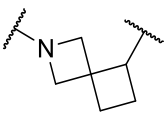
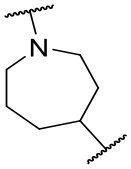
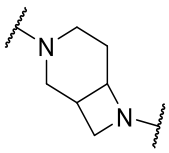
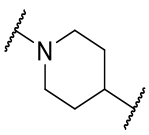
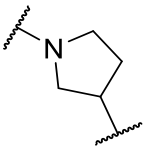
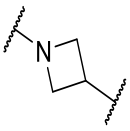
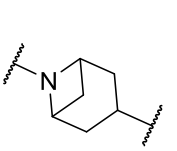
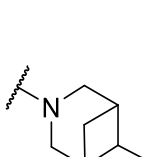
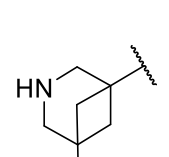
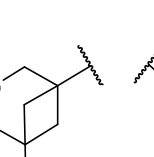
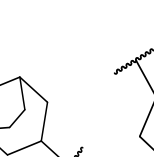
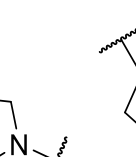
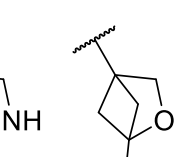
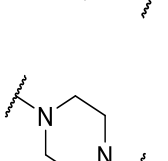
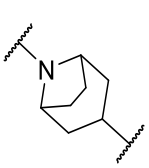
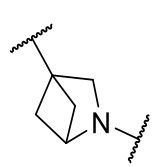
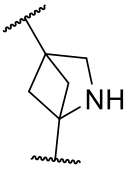
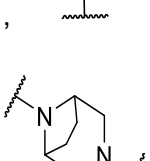
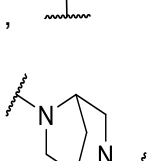
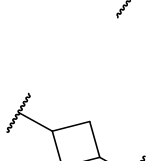
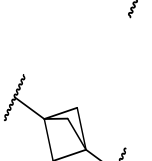
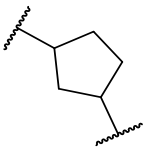
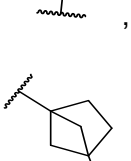
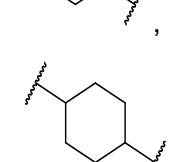
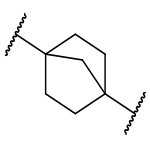
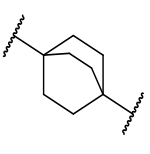
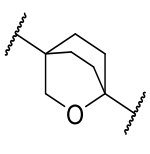
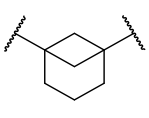
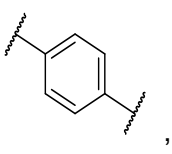
cada R^{2a} es independientemente hidrógeno o alquilo C_1-C_6sustituido o no sustituido; y

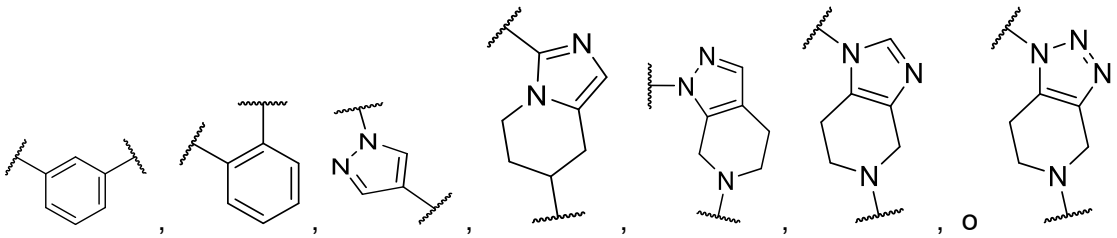
cada R^{2b} es independientemente hidrógeno, halógeno, alquil C_1-C_6 sustituido o no sustituido, fluoroalquilo C_1-C_6 sustituido o no sustituido, heteroalquilo C_1-C_6 sustituido o no sustituido, cicloalquilo C_3-C_8 sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)$;

Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_8cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

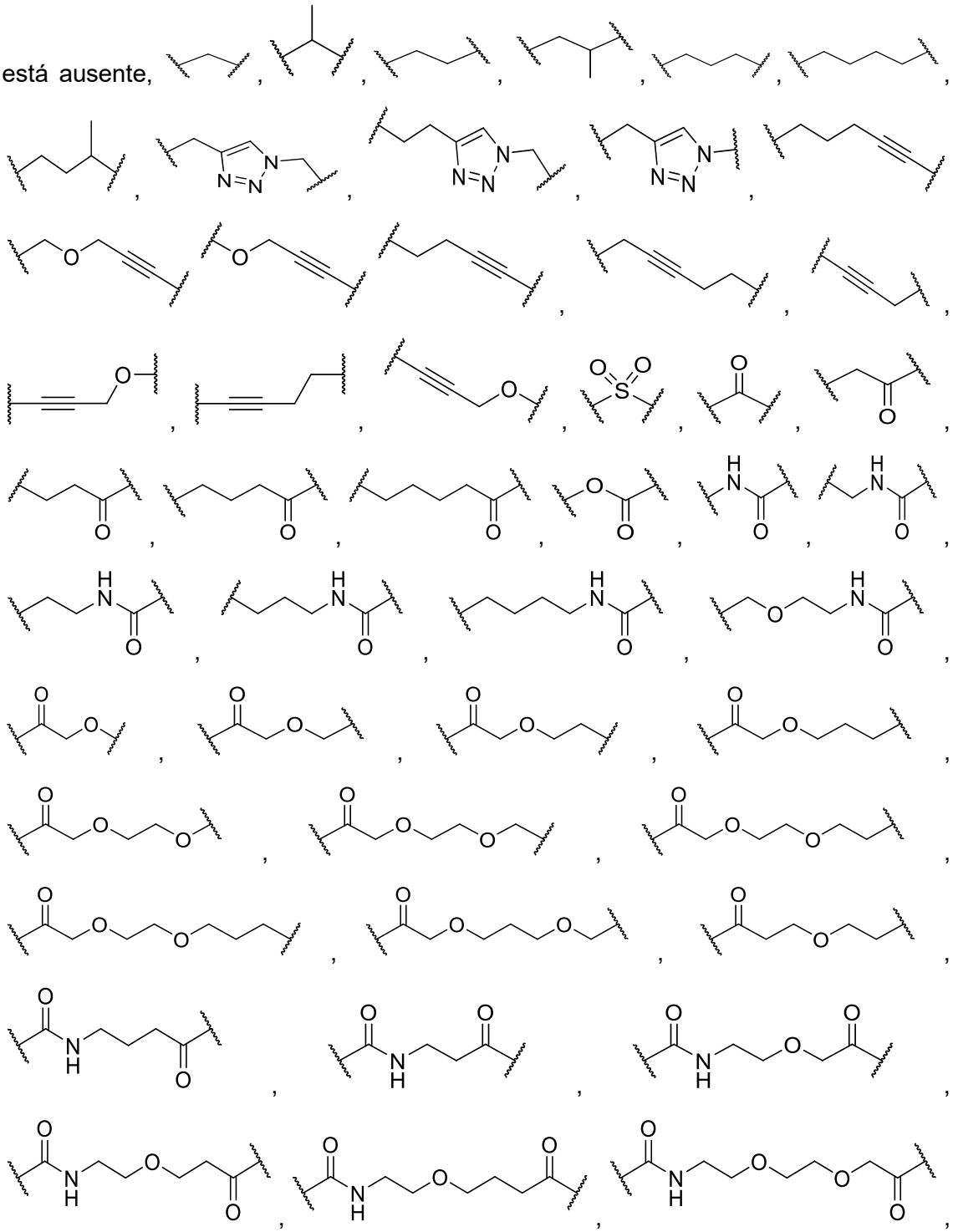
cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

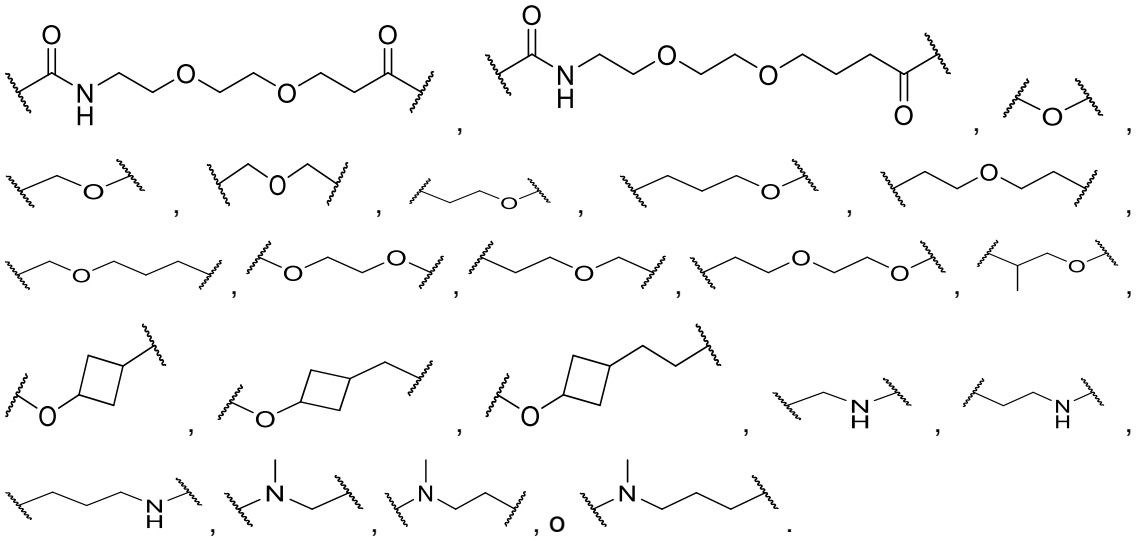
o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

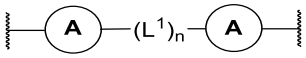
[00159] En algunas formas de realización, cada A está ausente de forma independiente,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  ,  ,  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

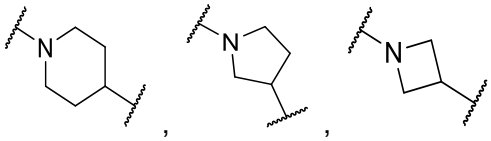


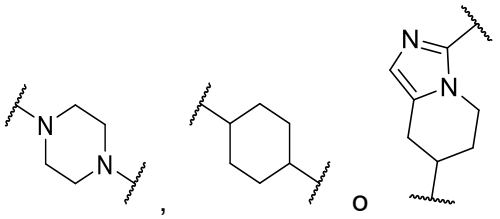
donde cada A no está sustituido de forma independiente o está sustituido con x R^{2b}; $(L^1)_n$ está ausente,



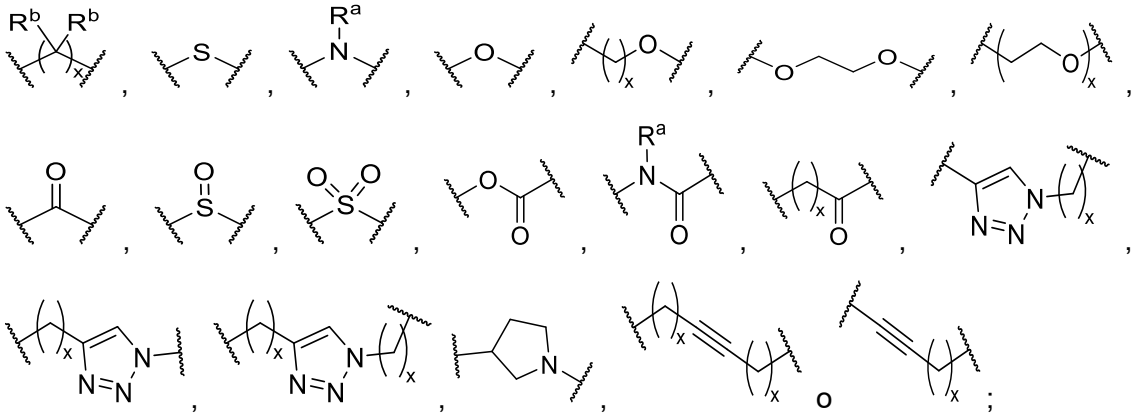


[00160] En algunas formas de realización, L está ausente o  , en cuyo caso:

cada A está independientemente ausente, 



; cada L^1 está independientemente ausente,

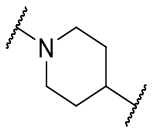
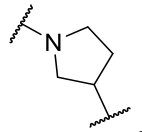
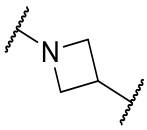
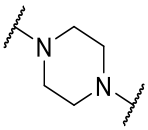
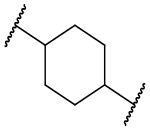
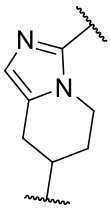
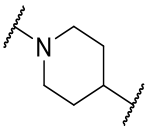
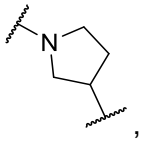
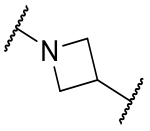
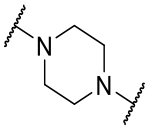
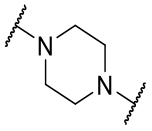
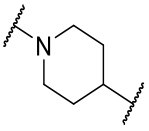


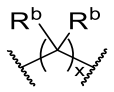
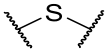
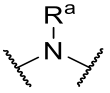
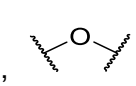
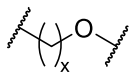
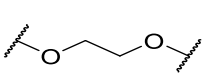
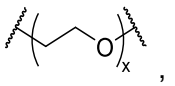
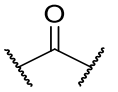
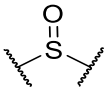
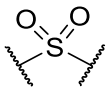
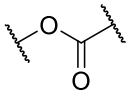
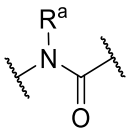
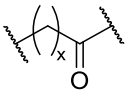
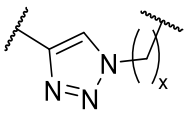
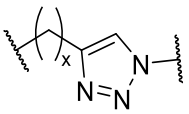
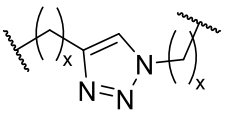
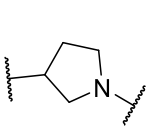
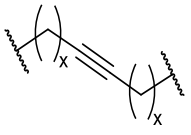
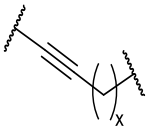
n es 1, 2 o 3;

Cada n es independientemente 0, 1, 2, 3, 4, 5 o 6 (preferentemente, 0 o 1);

cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

Cada R^b es independientemente hidrógeno, halógeno o alquilo C_1-C_6 sustituido o no sustituido.

[00161] En algunas formas de realización, cada A está ausente, ausente,  ,  ,  ,  ,  , o  de forma independiente. En algunas formas de realización, cada A es independientemente  ,  ,  , o  . En algunas formas de realización, cada A está ausente de forma independiente,  , o  .

[00162] En algunas formas de realización, cada ausente,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o  ;

n es 1, 2 o 3;

Cada n es independientemente 0, 1, 2, 3, 4, 5 o 6 (preferentemente, 0 o 1);

cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

Cada R^b es independientemente hidrógeno, halógeno o alquilo C_1-C_6 sustituido o no sustituido.

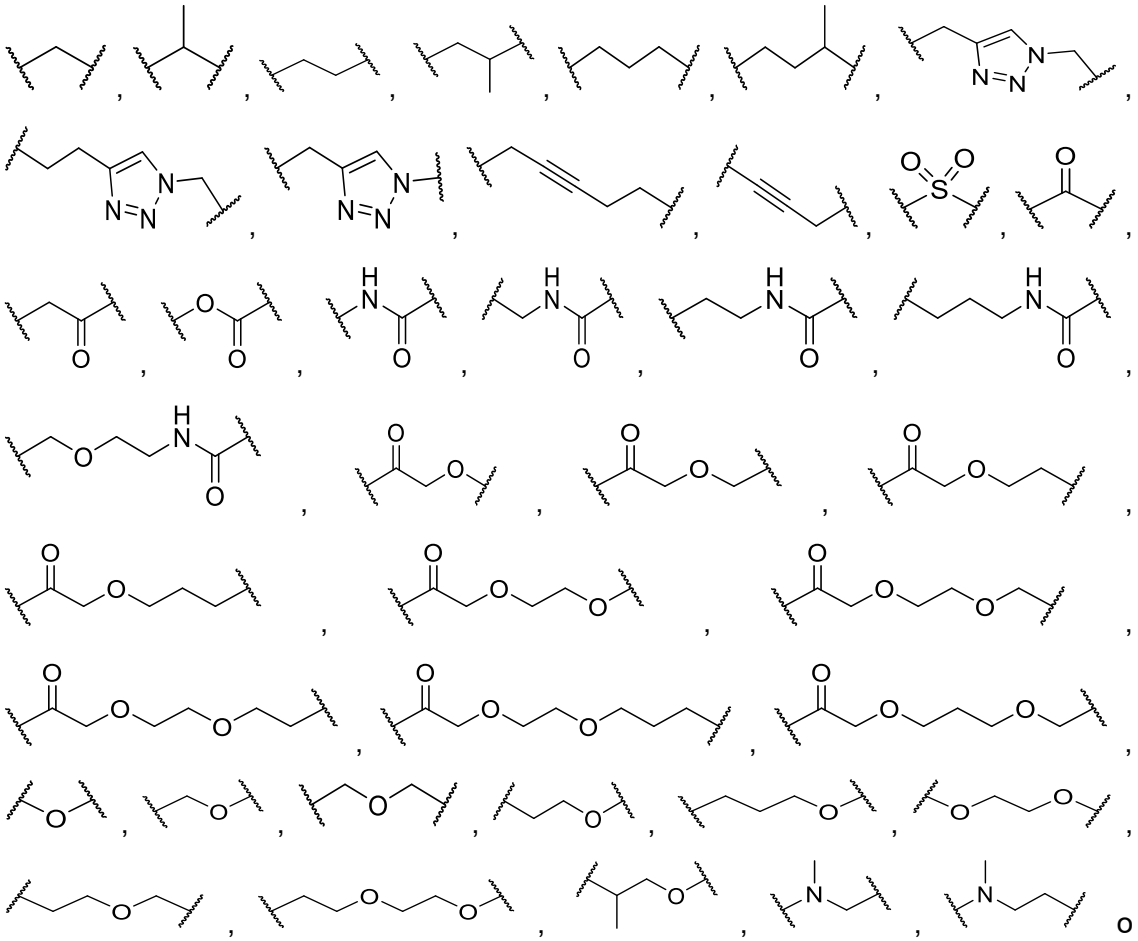
[00163] En algunas formas de realización, n es 1. En algunas formas de realización, n es 2. En algunas formas de realización, n es 3.

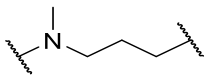
[00164] En algunas formas de realización, y es 1. En algunas formas de realización, X es cloruro. En algunas formas de realización, X es cloruro. En algunas formas de realización, X es cloruro. En algunas formas de realización, X es cloruro. En algunas formas de realización, X es cloruro.

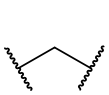
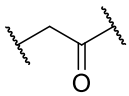
[00165] En algunas formas de realización, R^{11} es hidrógeno. En algunas formas de realización, cada R^a es un alquilo C_1-C_6 sustituido o no sustituido de forma independiente. En algunas formas de realización, cada R^a es independientemente hidrógeno, metilo, etilo, propilo, isopropilo, n-butilo, isobutilo o ter-butilo. En algunas formas de realización, cada R' es metilo. En algunas formas de realización, R^3 es metilo.

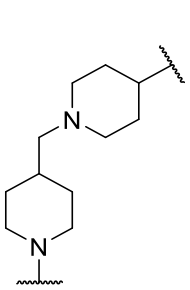
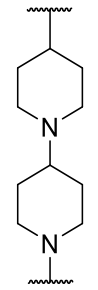
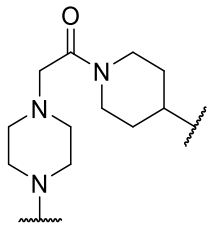
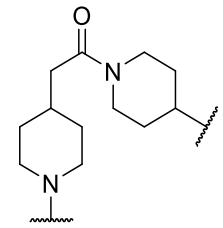
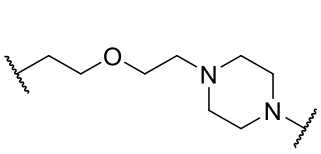
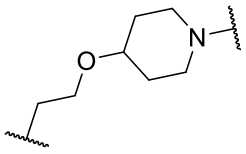
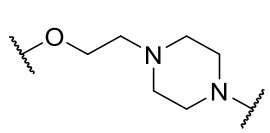
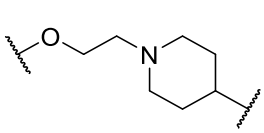
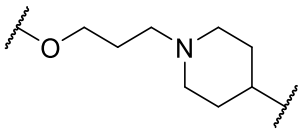
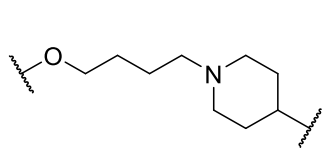
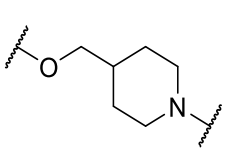
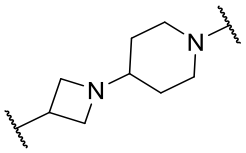
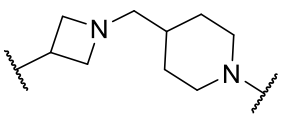
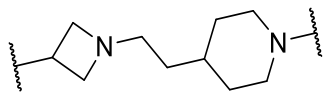
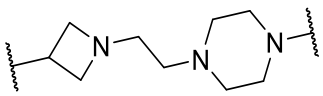
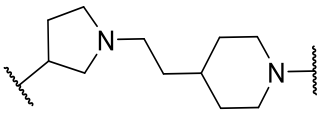
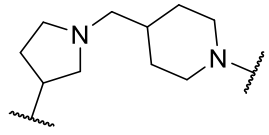
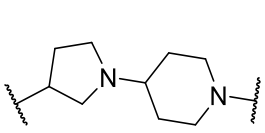
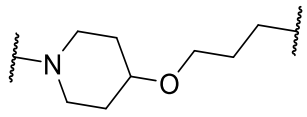
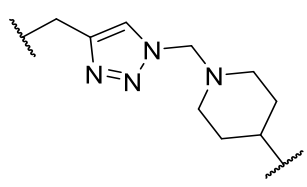
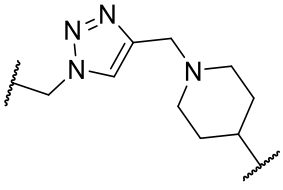
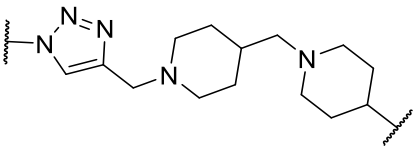
[00166] En algunas formas de realización, R^{11} es hidrógeno. En algunas formas de realización, cada R^b es un alquilo C_1-C_6 sustituido o no sustituido de forma independiente. En algunas formas de realización, cada R^b es independientemente hidrógeno, metilo, etilo, propilo, isopropilo, n-butilo, isobutilo o ter-butilo. En algunas formas de realización, cada R' es metilo. En algunas formas de realización, R^3 es metilo.

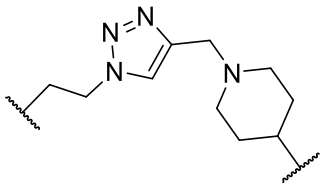
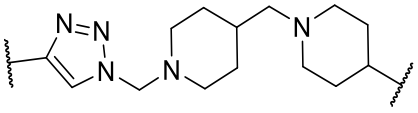
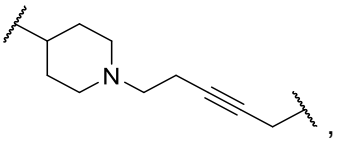
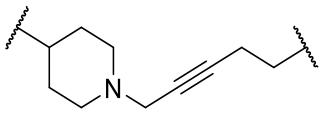
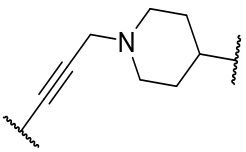
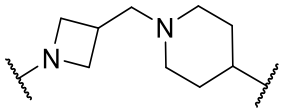
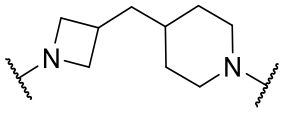
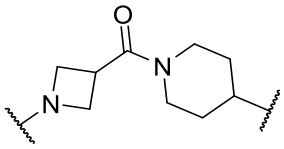
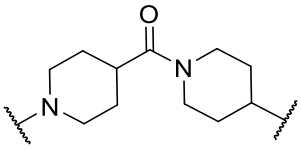
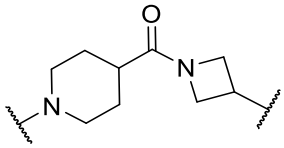
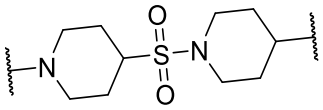
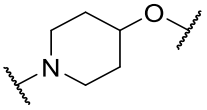
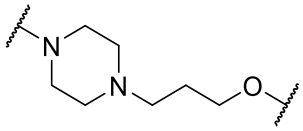
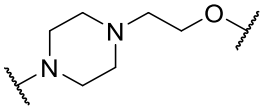
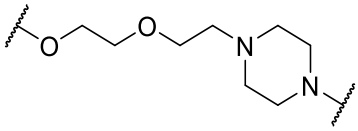
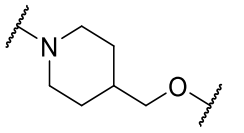
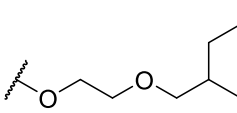
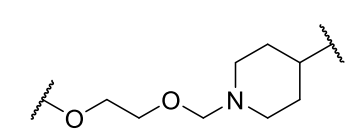
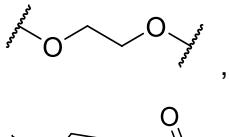
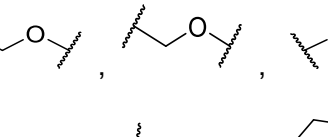
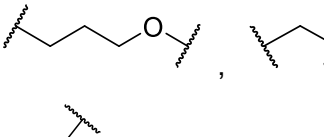
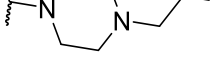
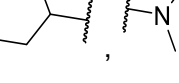
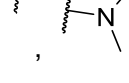
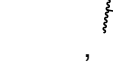
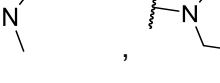
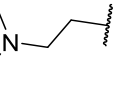
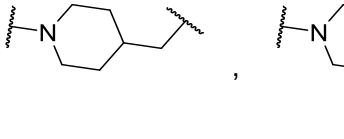
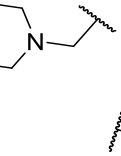
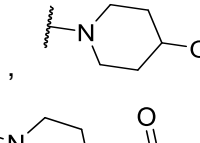
[00167] En algunas formas de realización, $(L^1)_n$ está ausente, $(L^1)_n$ está ausente,

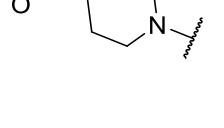
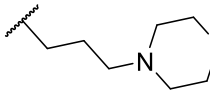
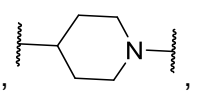
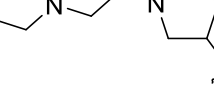
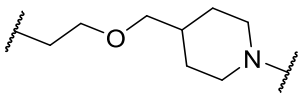
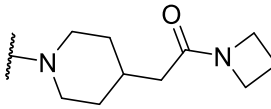
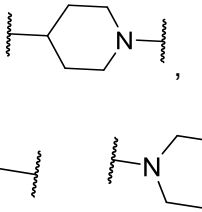
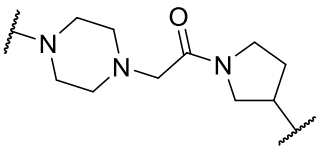
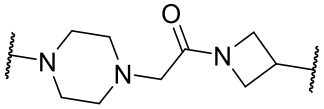


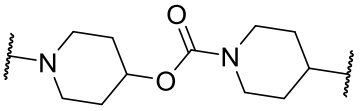
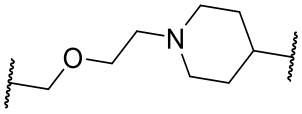

.

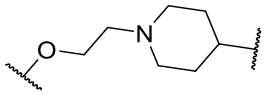
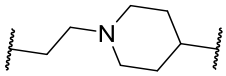
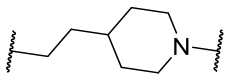
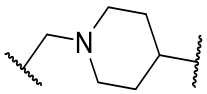
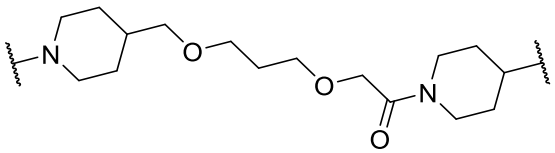
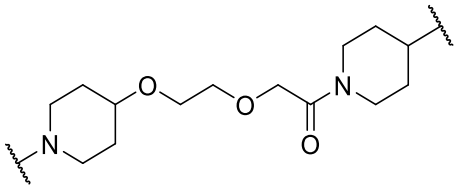
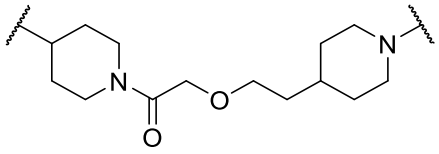
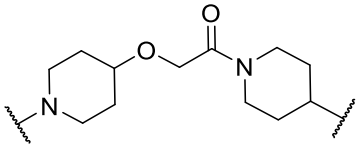
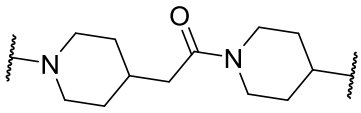
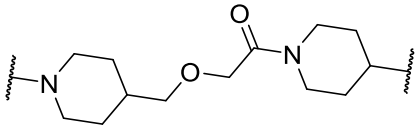
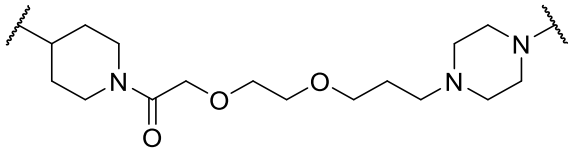
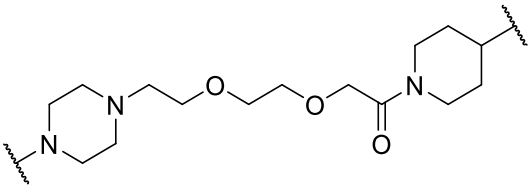
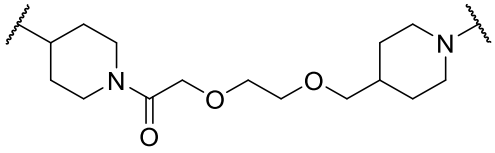
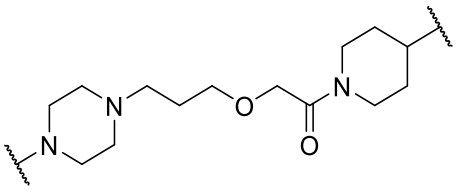
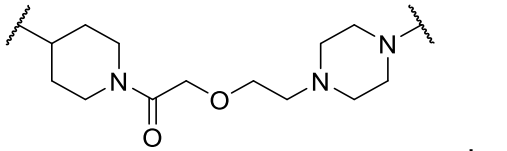
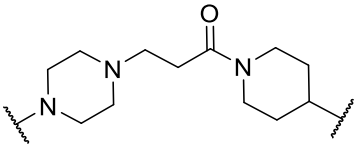
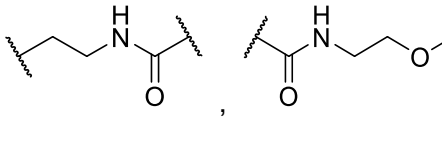
[00168] . En algunas formas de realización, $(L^1)_n$ está ausente,  o  .

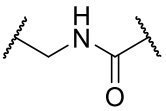
[00169] En algunas formas de realización, L es  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

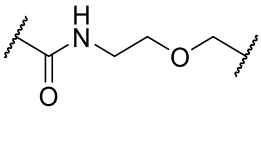
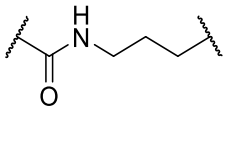
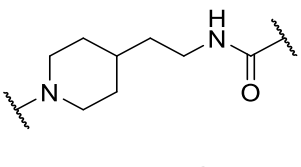
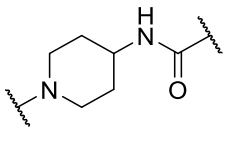
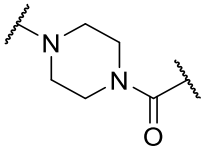
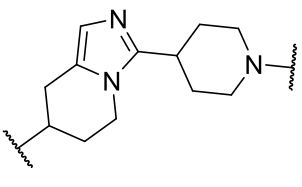
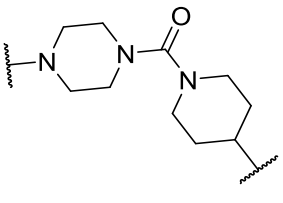

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

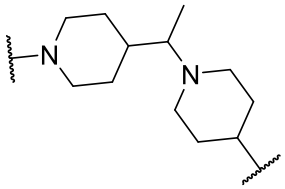
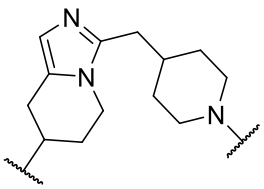
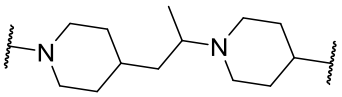
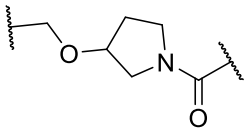
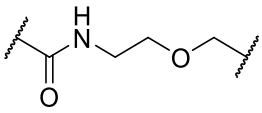
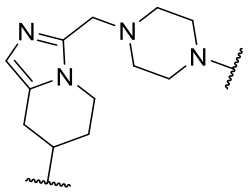
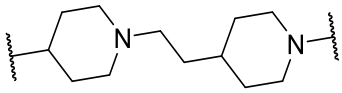
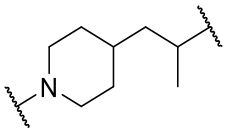
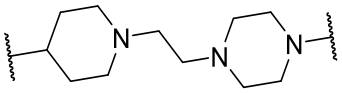
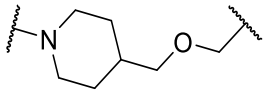
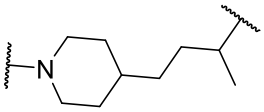
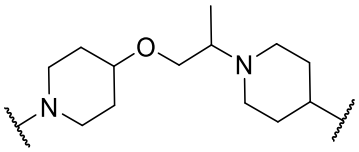
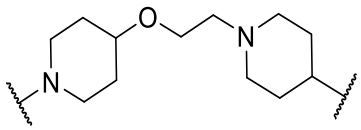
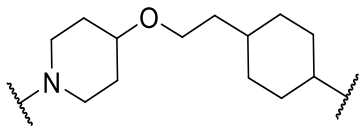
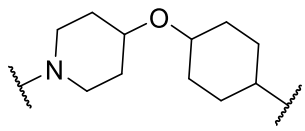
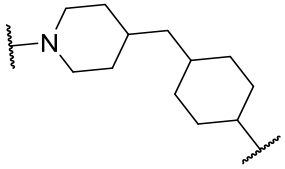
,

,

,

,

,

,

,

,

,

,

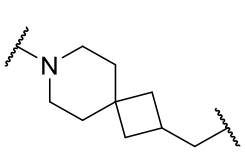
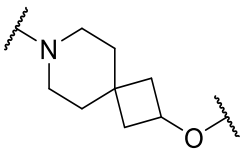
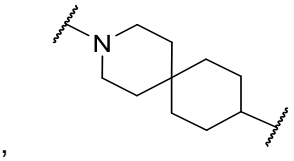
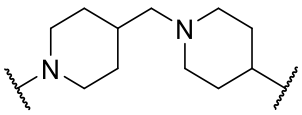
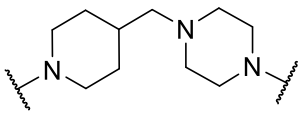
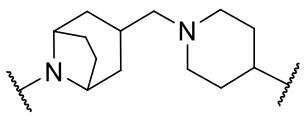
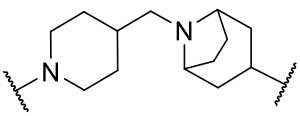
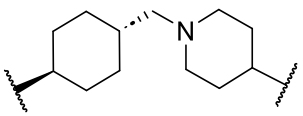
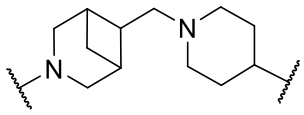
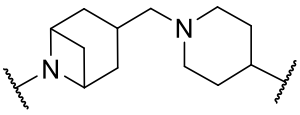
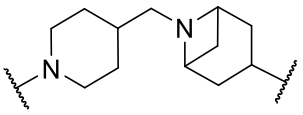
,

,

,

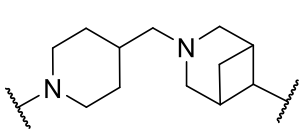
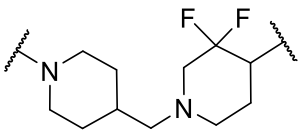
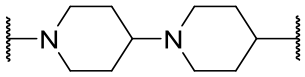
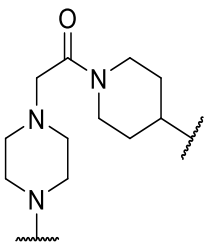
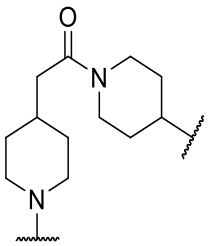
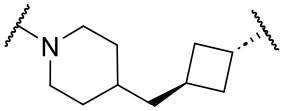
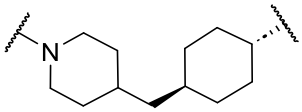
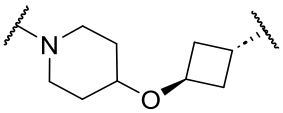
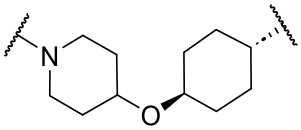
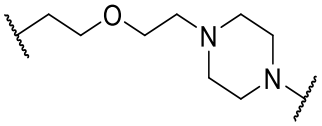
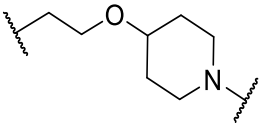
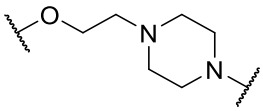
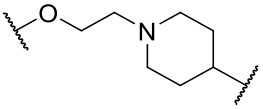
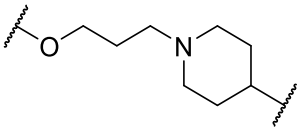
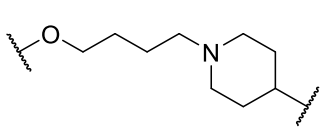
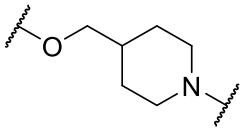
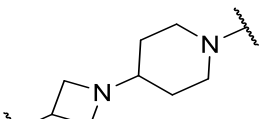
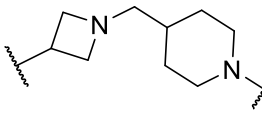
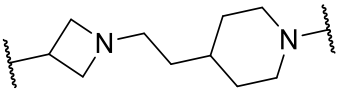
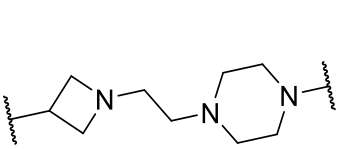
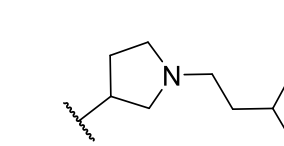
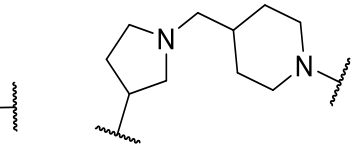

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

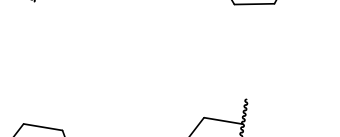
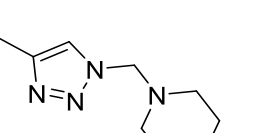
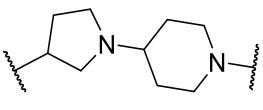
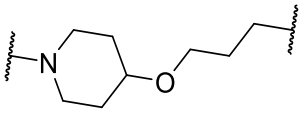
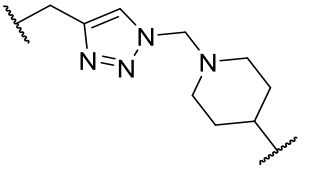
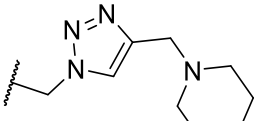
,

,

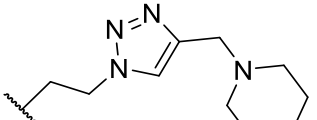
,

,

,

,

,

,

,

,

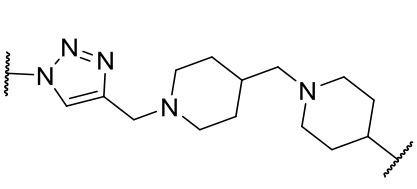

,

,

,

,

,

,

,

,

,

,

,

,

,

,

o

, o una sal o solvato farmacéuticamente aceptable de este.

[00170] En algunas formas de realización, L es

,

,

,

,

,

,

,

,

,

,

,

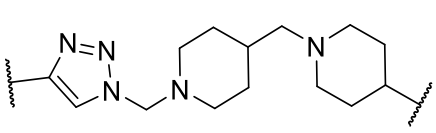
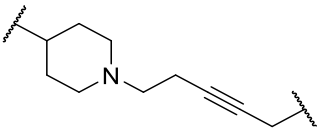
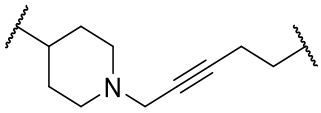
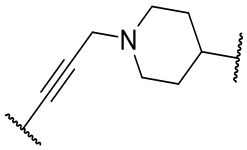
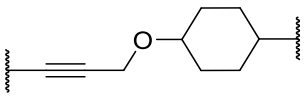
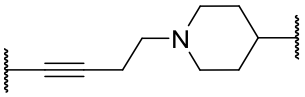
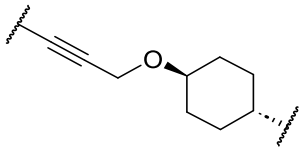
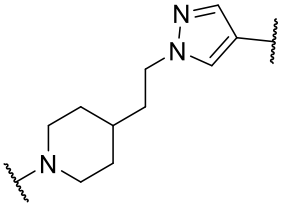
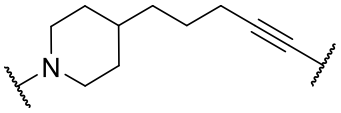
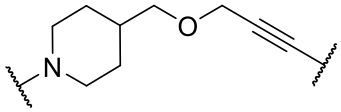
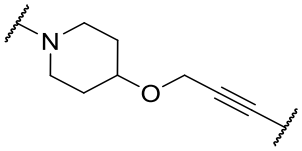
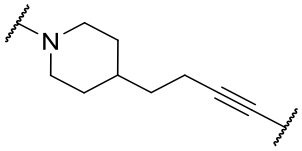
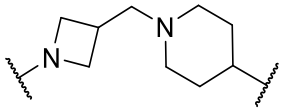
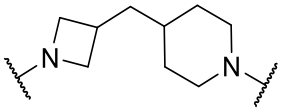
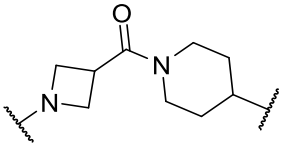
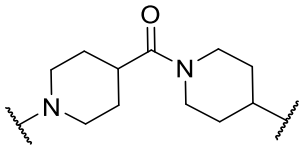
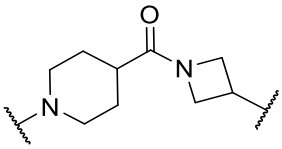
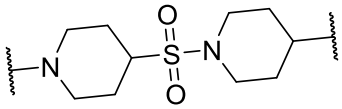
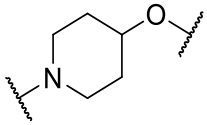
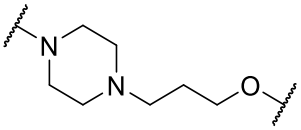
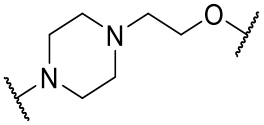
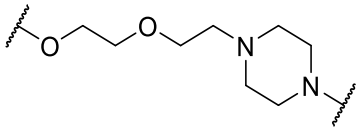
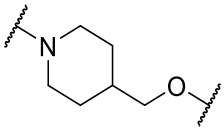
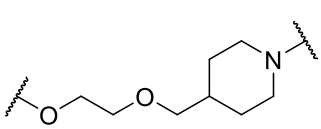
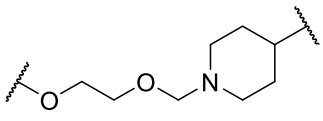
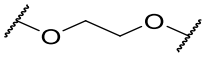
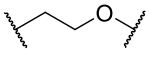
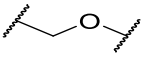
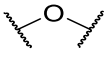
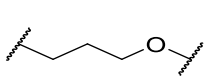
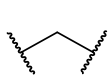
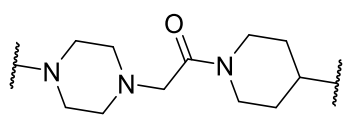
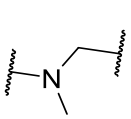
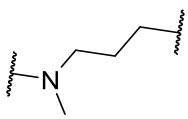

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

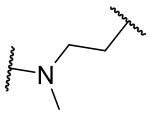
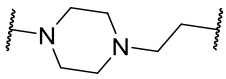
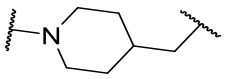
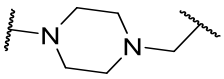
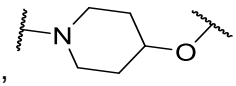
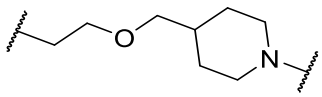
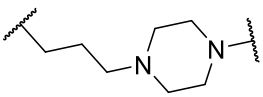
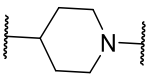
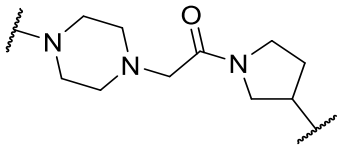
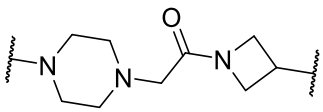
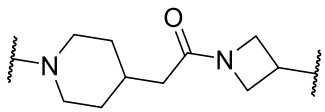
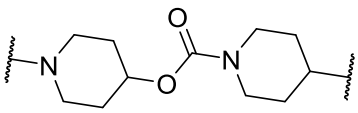
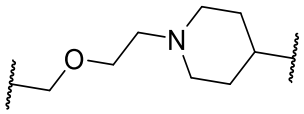
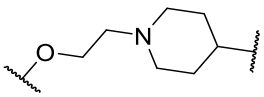
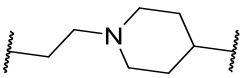
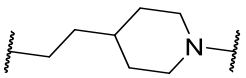
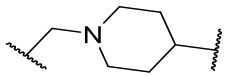
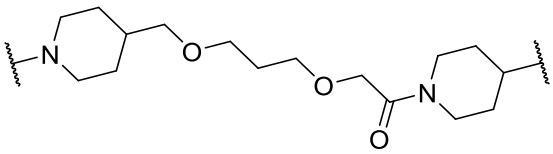
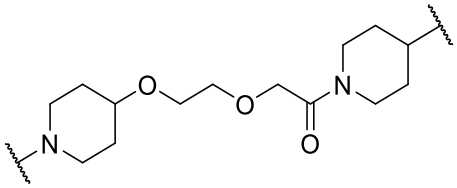
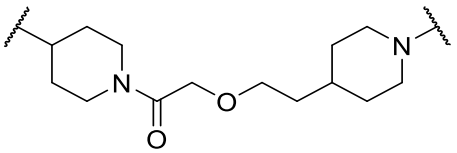
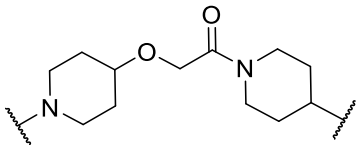
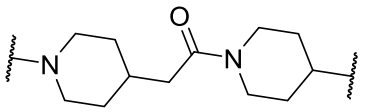
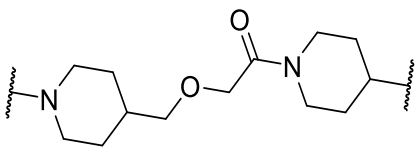
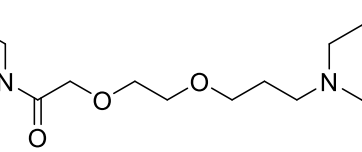
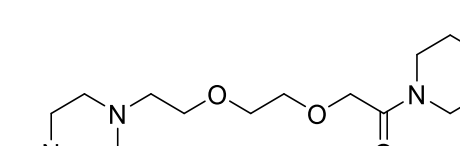
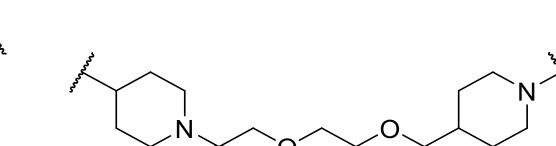
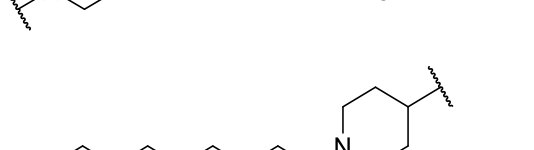
,

,

,

,

,

,

,

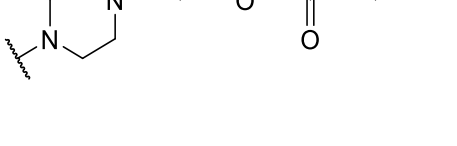
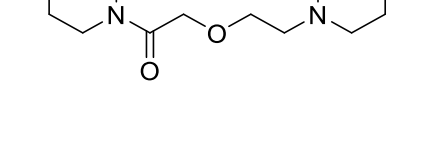
,

,

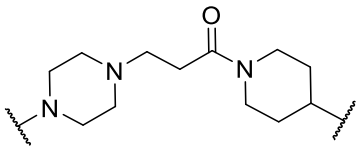
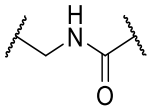
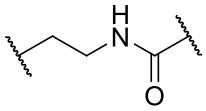
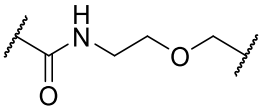
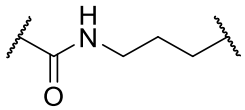
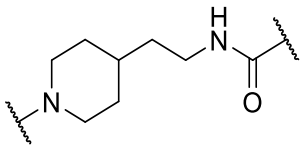
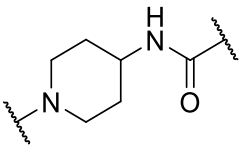
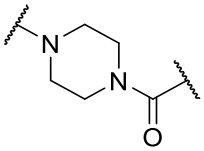
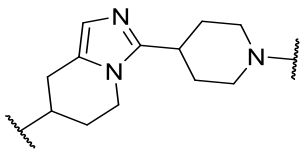
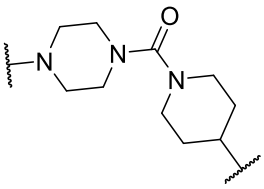
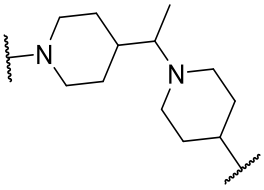
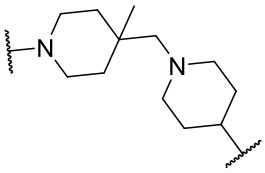
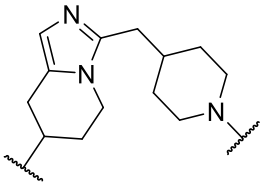
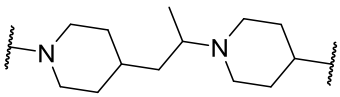
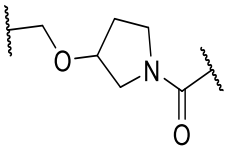
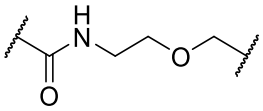
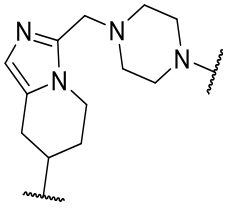
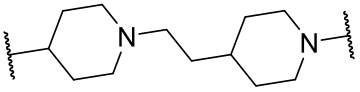
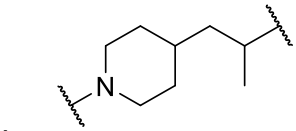
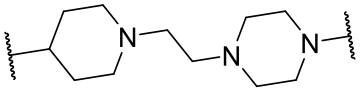
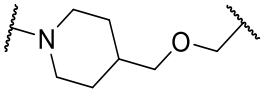
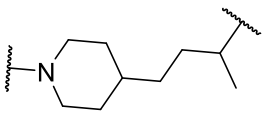
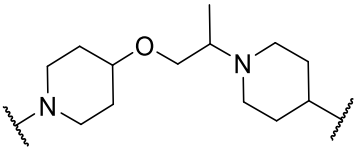
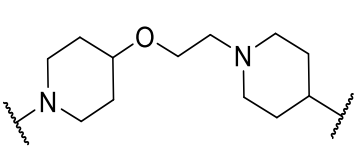
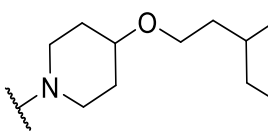
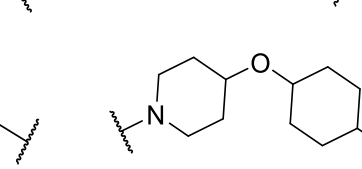
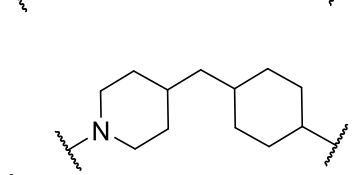
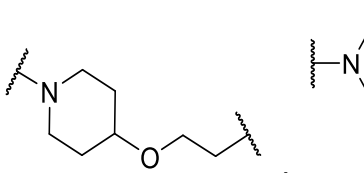
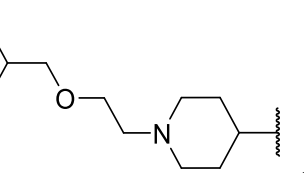
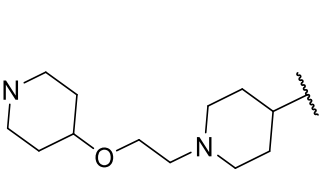
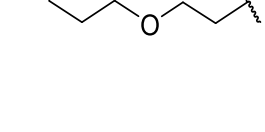
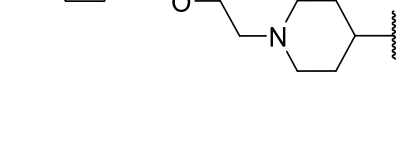
,

,

,

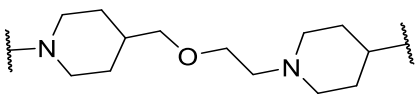
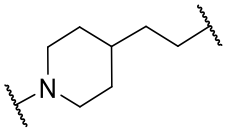
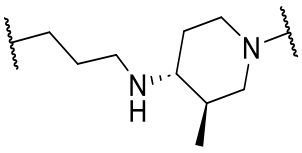
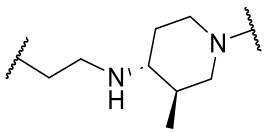
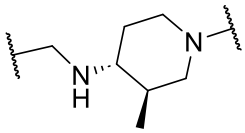
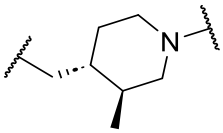
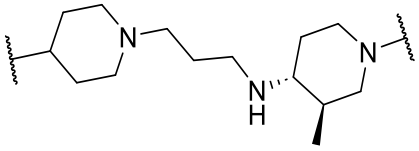
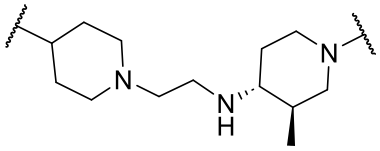
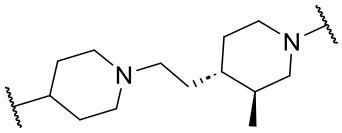
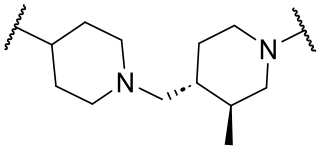
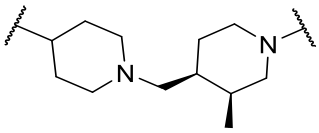
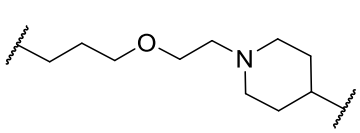
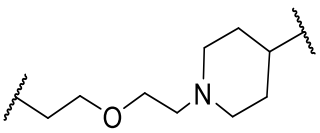
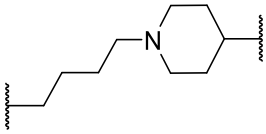
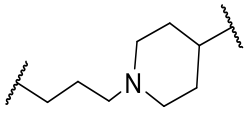
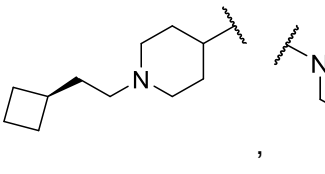

,

,

,

,

,

,

,

,

,

,

,

.

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

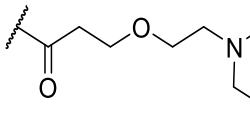

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

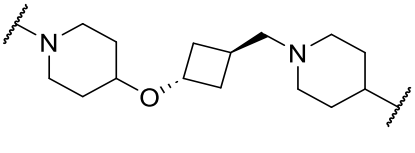
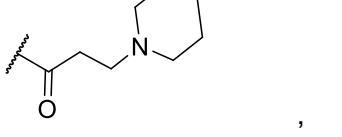
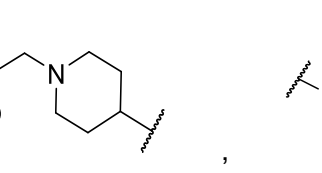
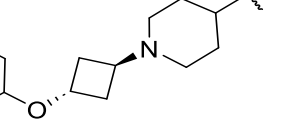
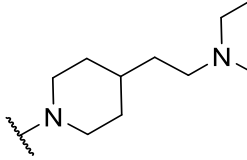
,

,

,

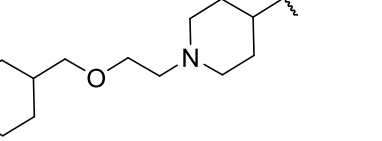

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

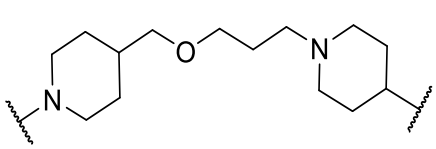
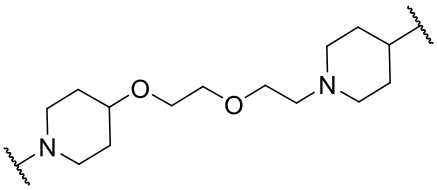
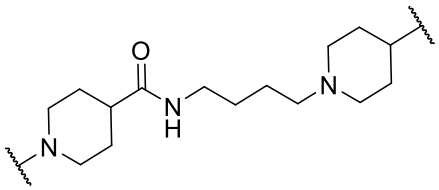
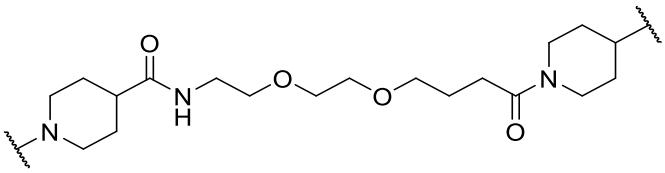
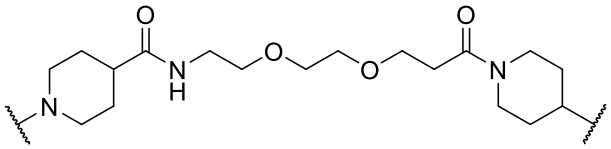
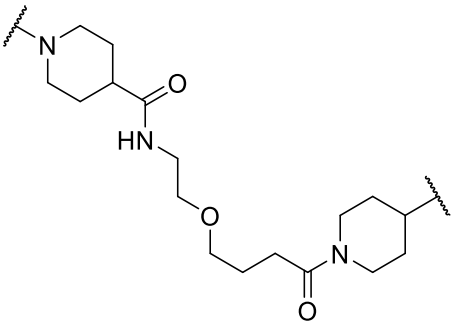
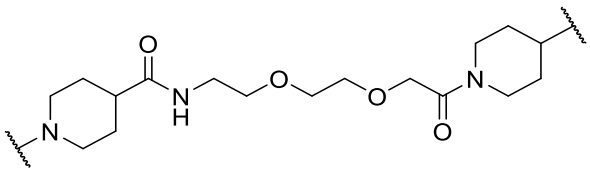
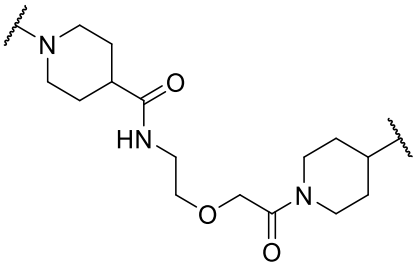
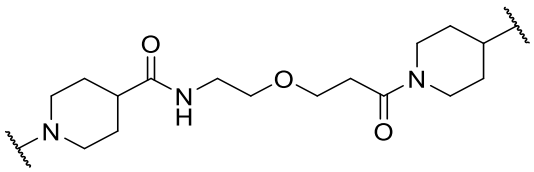
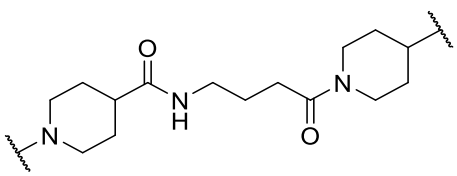
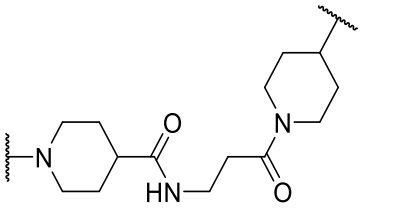
,

,

,

,

,

,

,

,

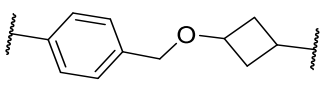
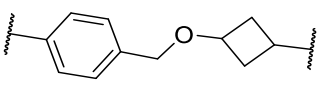
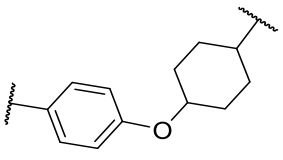
,

,

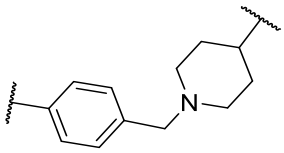
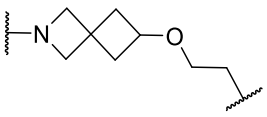
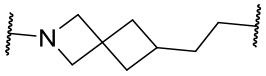
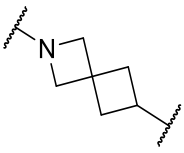
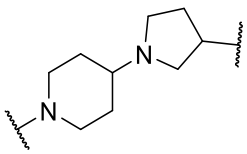
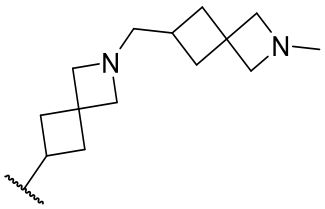
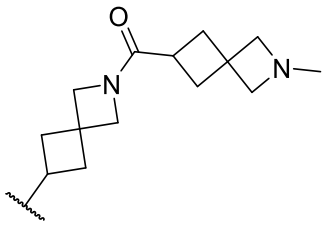
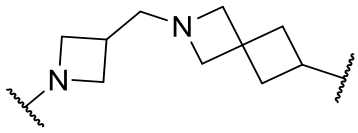
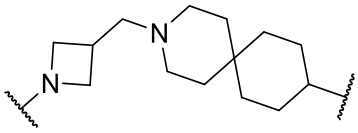
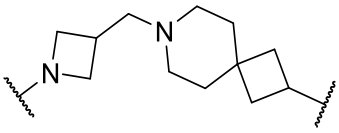
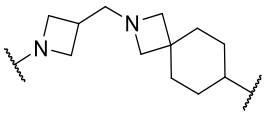
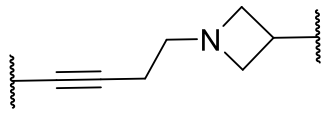
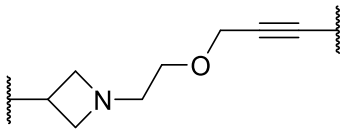
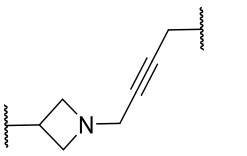
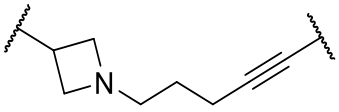
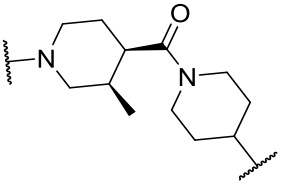
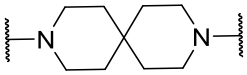
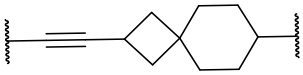
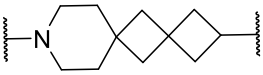
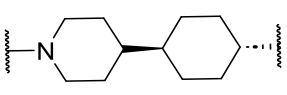
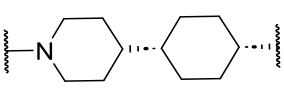
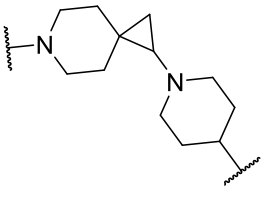
,

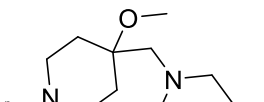
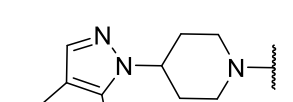
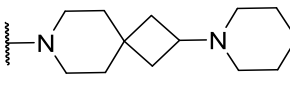
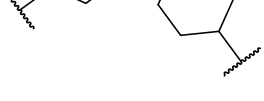
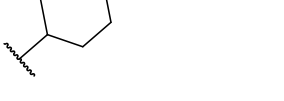
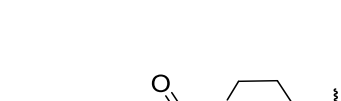
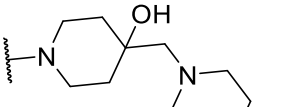
,


,

,

,

,

,


,
,


,
,

,

,

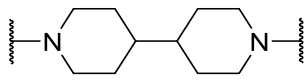
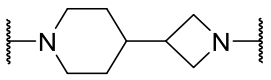
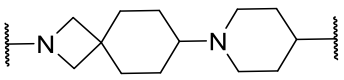
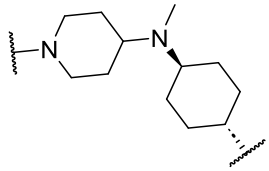
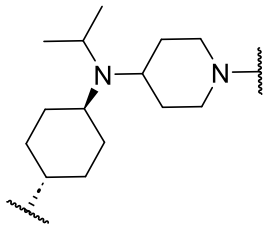
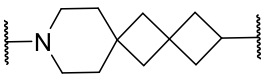
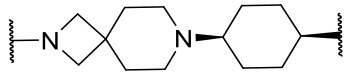
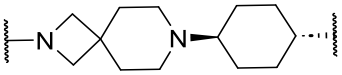
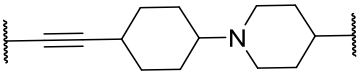
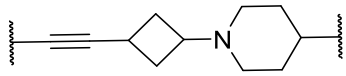
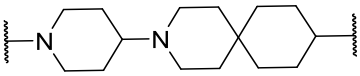
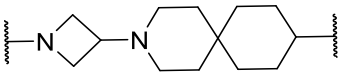
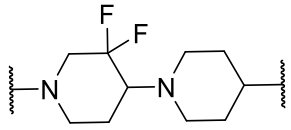
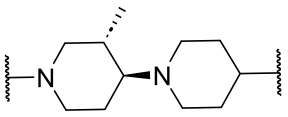
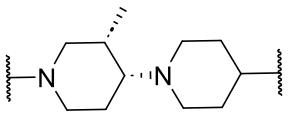
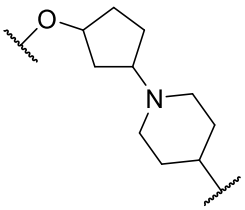
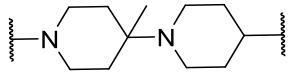
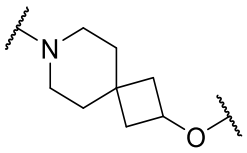
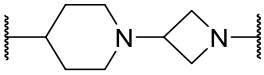
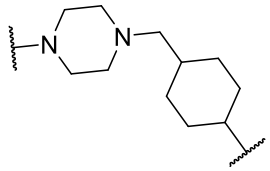
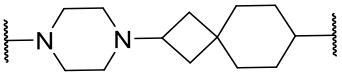
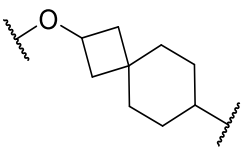
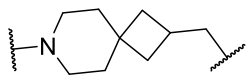
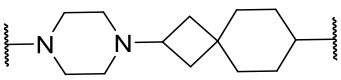
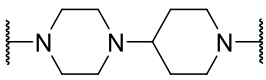
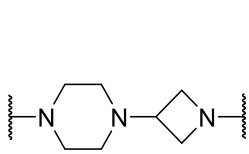
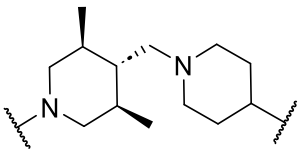
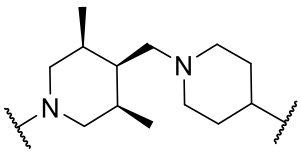
,

,

,

,

,

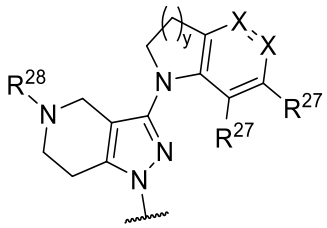

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

, o

, o una sal o solvato farmacéuticamente aceptable de este.

[00171] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIIb), o una sal o solvato farmacéuticamente aceptable de esta:



Fórmula (IIIb)

en donde:

cada X es independientemente -CR^{27}- o -N-;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^b$, -$OC(=O)NR^b$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^b$, -$S(=O)_2OR^a$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -NR^b $C(=O)NR^b$, -N $R^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^b$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -$C(=O)R^b$, o -$C(=O)N(R^b)_2$;

es 1 o 2.

cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00172] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIIb), o una sal o solvato farmacéuticamente aceptable de esta, en la que:

cada X es independientemente -CR^{27}- o -N-;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no

sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -$C(=O)R^b$, o -$C(=O)N(R^b)_2$;

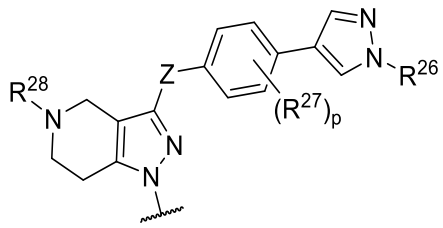
es 1 o 2.

Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo monocíclico;

Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

[00173] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIIc), o una sal o solvato farmacéuticamente aceptable de esta:



Fórmula (IIIc)

en donde:

R^6 es hidrógeno, alquil C_1-C_6 sustituido o no sustituido, fluoroalquilo C_1-C_6 sustituido o no sustituido, heteroalquilo C_1-C_6 sustituido o no sustituido, cicloalquilo C_3-C_8 sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^b$, -$OC(=O)NR^b$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^b$, -$S(=O)_2OR^a$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -NR^b $C(=O)OR^b$, -$NR^bS(=O)_2R^b$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -$C(=O)R^b$, o -$C(=O)N(R^b)_2$;

Z es -NR^c-, -O- o -S-;

R^9 es hidrógeno o alquilo C_{1-6} no sustituido;

cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00174] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIIc), o una sal o solvato farmacéuticamente aceptable de esta, en la que:

R^{26} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$,

o -C(=O)N(R^b)$_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -C(=O)R^a, o -C(=O)N(R^b)$_2$;

Z es -NR^c-, -O- o -S-;

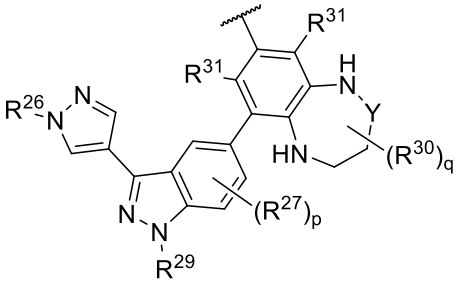
R^9 es hidrógeno o alquilo C_{1-6} no sustituido;

Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo monocíclico;

Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

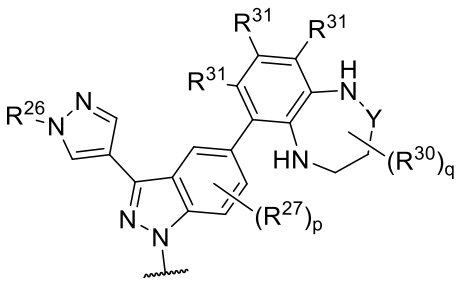
o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

[00175] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIId-1) o (IIId-2), o una sal o solvato farmacéuticamente aceptable de esta:



Fórmula (IIId-1)

o



Fórmula (IIId-2)

en donde:

R^6 es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^b, -OC(=O)NR^b, -SH, -SR^a, -S(=O)R^b, -S(=O)$_2$$R^b$, -S(=O)$_2OR^a$, -S(=O)$_2$N($R^b$)$_2$, -N($R^b$)$_2$, -

$NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^b$, $-C(=O)R^b$, $-C(=O)OR^b$, o $-C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^9 es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{10} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^b$, $-OC(=O)NR^b$, -SH, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^b$, $-C(=O)R^b$, $-C(=O)OR^b$, o $-C(=O)N(R^b)_2$;

q es 1, 2, 3 o 4;

cada R^{11} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^b$, $-OC(=O)NR^b$, -SH, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)NR^b$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^b$, $-C(=O)R^b$, $-C(=O)OR^b$, o $-C(=O)N(R^b)_2$;

Y es $-C(R^{10})_2-$ o C(=O);

cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00176] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIId-1) o (IIId-2), o una sal o solvato farmacéuticamente aceptable de esta, en la que:

R^{26} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{29} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

q es 1, 2, 3 o 4;

cada R^{31} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

Y es -$C(R^{30})_2$- o C(=O);

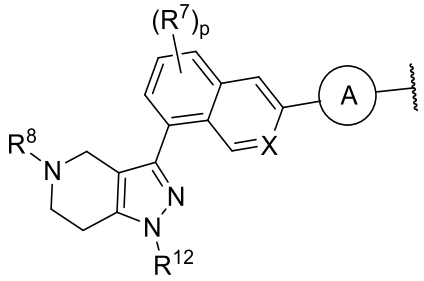
Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo monocíclico;

Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido,

C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

[00177] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIIe), o una sal o solvato farmacéuticamente aceptable de esta:



Fórmula (IIIe)

en donde:

X1 es CR^{27} o N;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^b$, -$OC(=O)NR^b$, -SH, -SR^a, -$S(=O)R^b$, -$S(=O)_2R^b$, -$S(=O)_2OR^a$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^b$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -$C(=O)R^b$, o -$C(=O)N(R^b)_2$;

R^{12} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

El anillo A está ausente, sustituido o no sustituido de 3 a 8 miembros heterocicloalquilo;

cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-

C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00178] En algunas formas de realización, SB-CBP/p300 tiene la estructura de la fórmula (IIIe), o una sal o solvato farmacéuticamente aceptable de esta, en la que:

X1 es CR^{27} o N;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -$C(=O)R^b$, o -$C(=O)N(R^b)_2$;

R^{32} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

El anillo A está ausente o sustituido o no sustituido C_3-C_8cicloalquilo, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido;

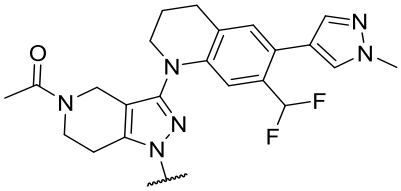
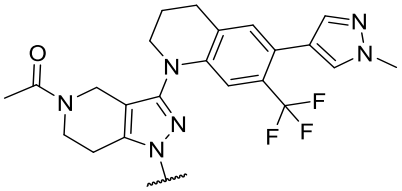
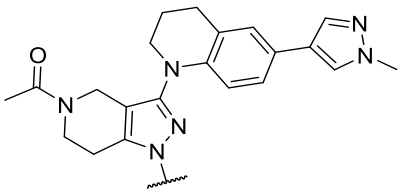
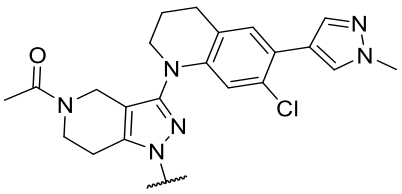
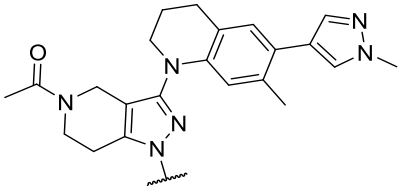
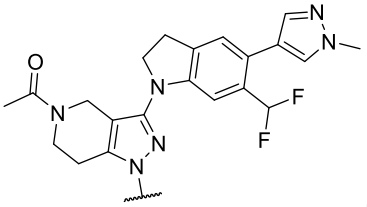
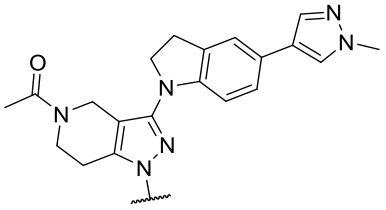
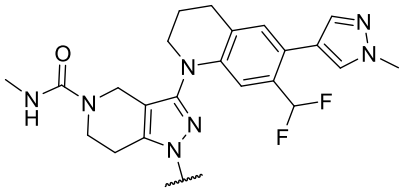
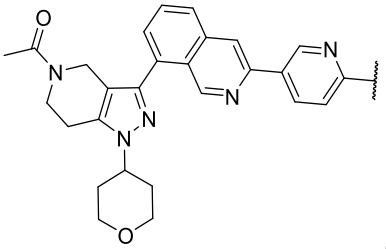
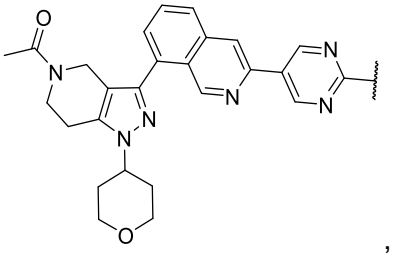
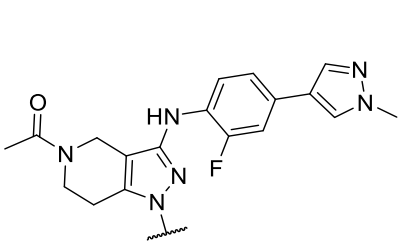
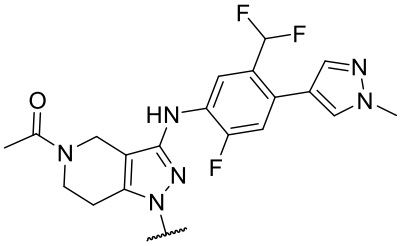
Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo monocíclico;

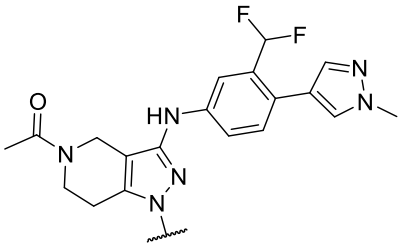
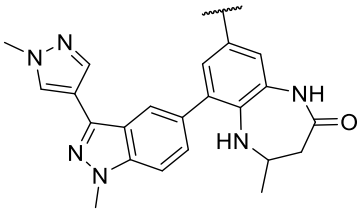
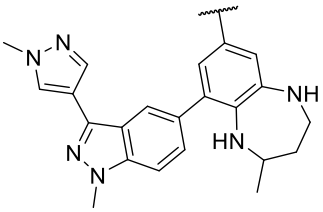
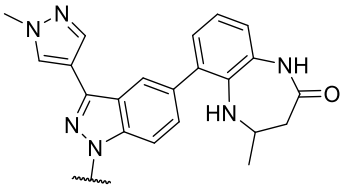
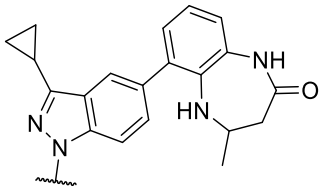
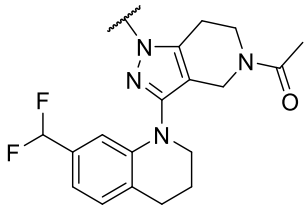
Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo

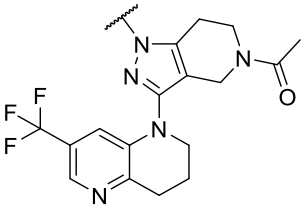
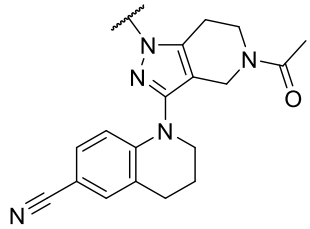
monocíclico sustituido o no sustituido;

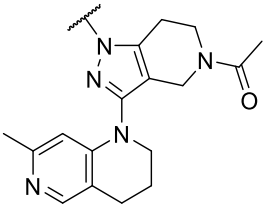
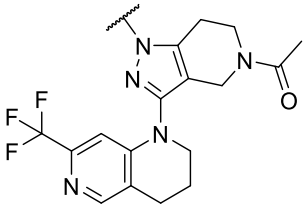
o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

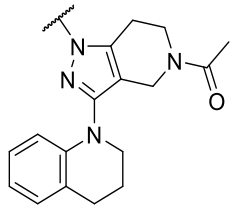
[00179] En algunas formas de realización, p300 tiene una de las siguientes fórmulas:

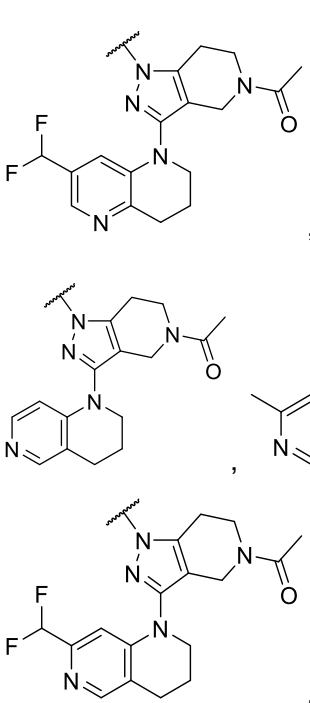
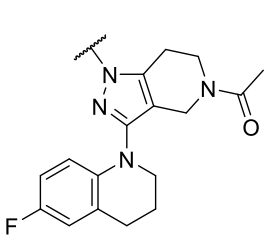
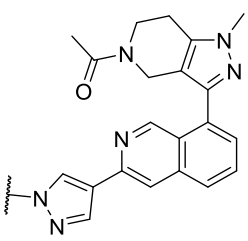
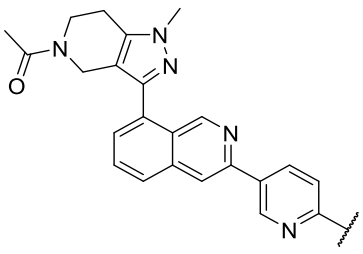

,

,

,

,

,

,

,

,

,

,

,

,

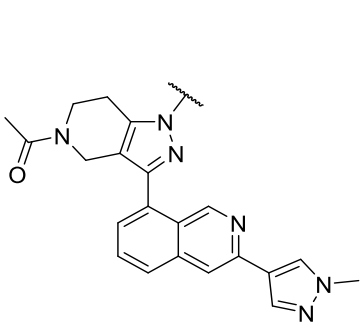
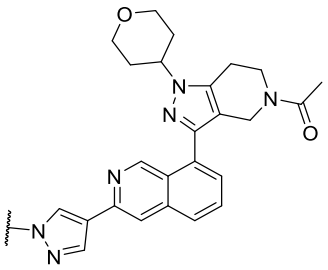
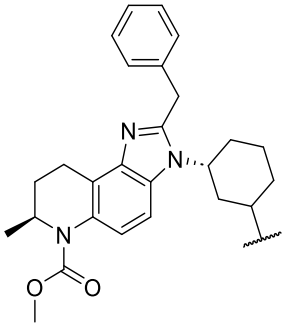

,

,

,

,

,

,

,

,

,

,

,

,

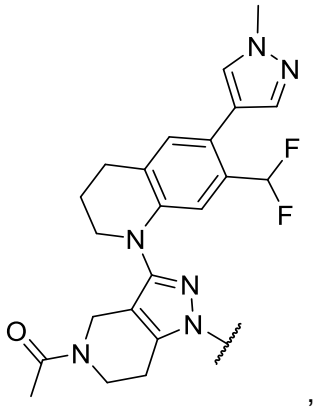
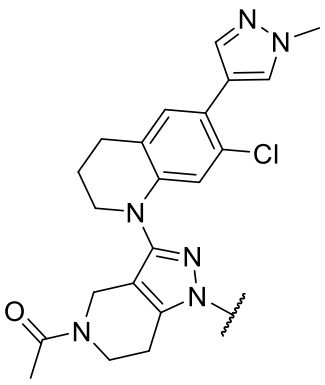
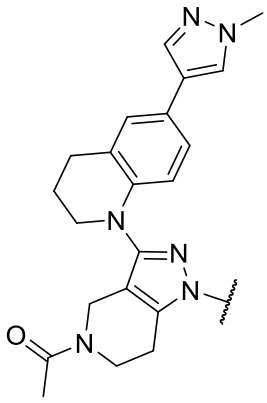
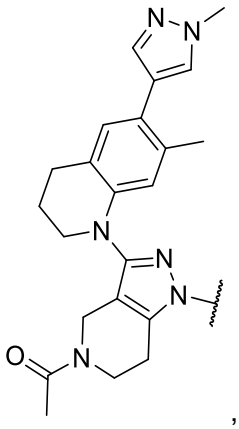
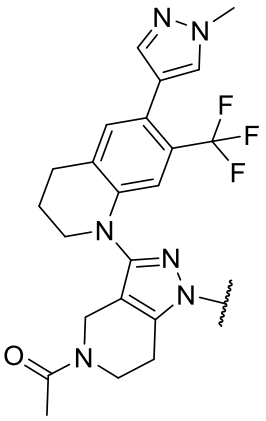
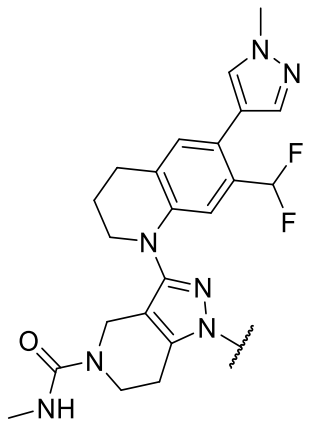
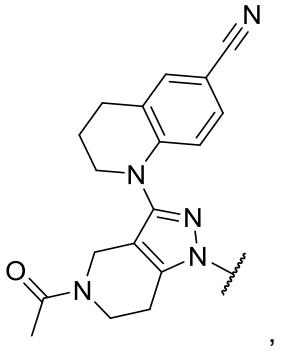
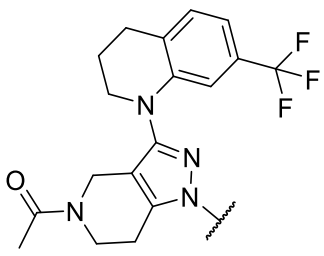
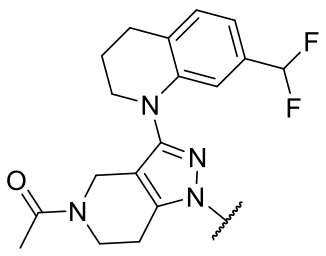
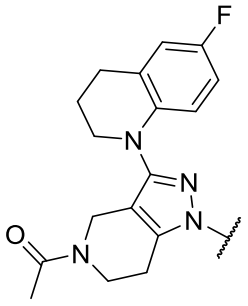
,

,

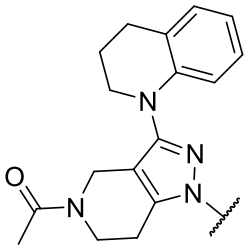
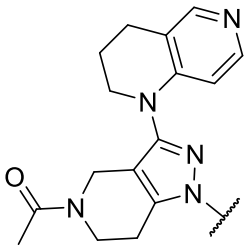
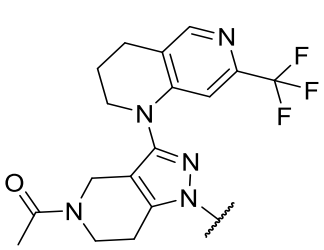
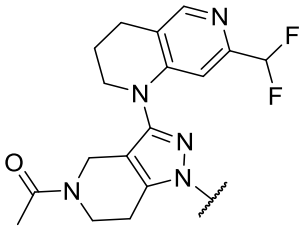
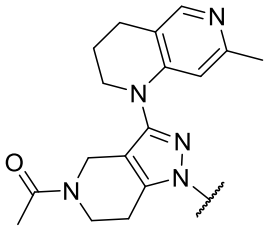
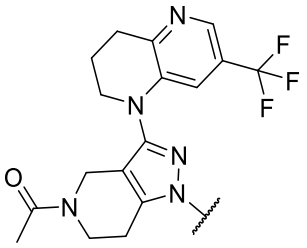
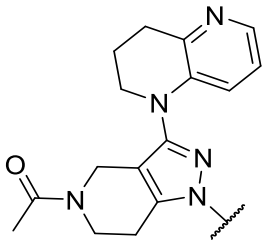
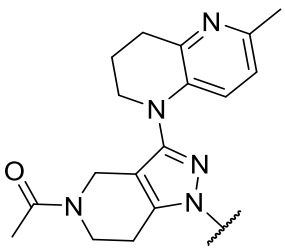
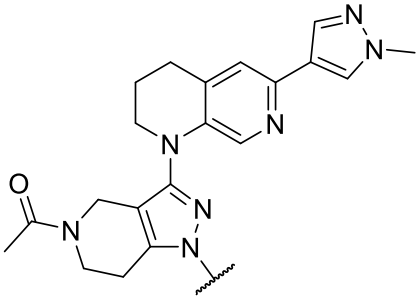
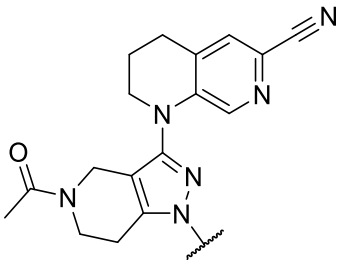
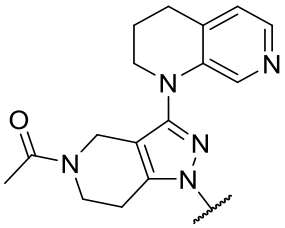
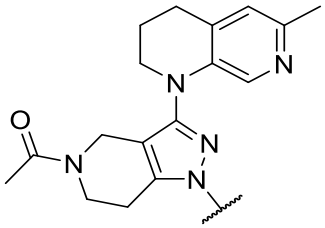
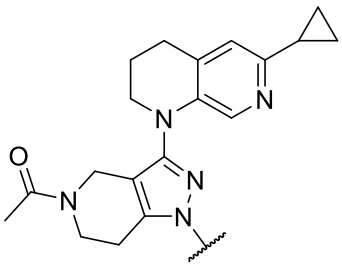
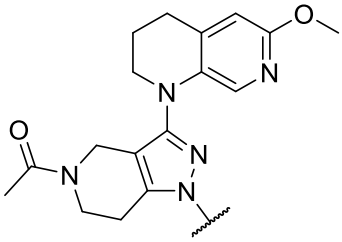
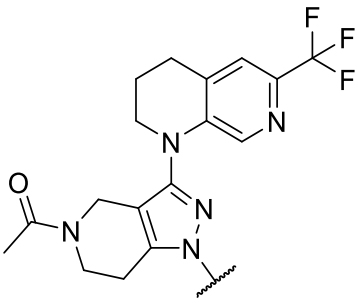
,

,

,

,

,


,

, o


o una sal o solvato farmacéuticamente aceptable de este.

[00180] En algunas formas de realización, p300 tiene una de las siguientes fórmulas:

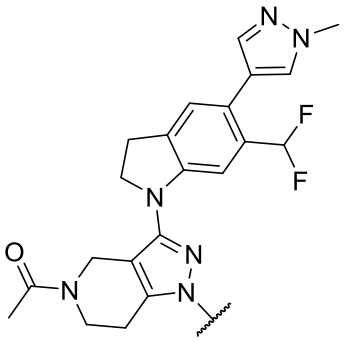
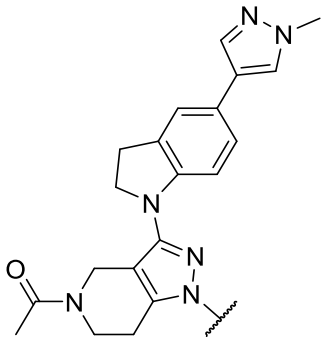
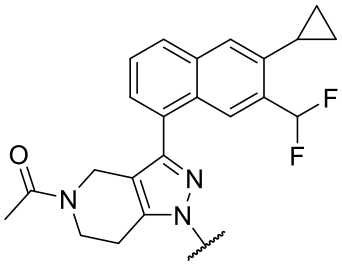
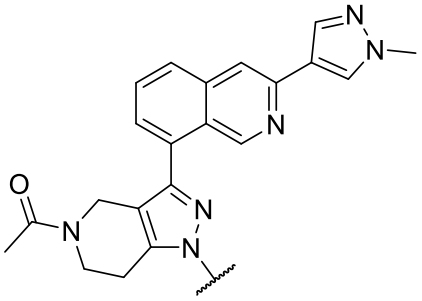
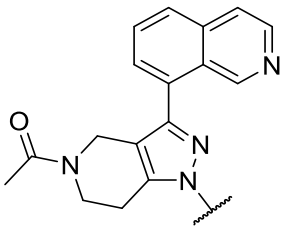
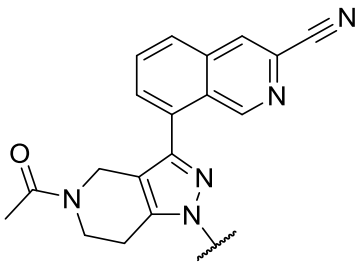
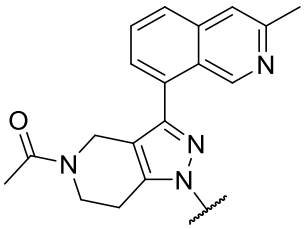
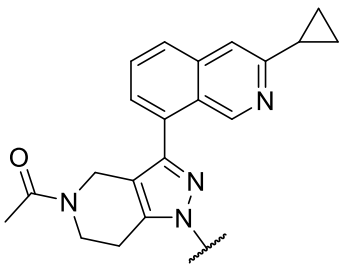
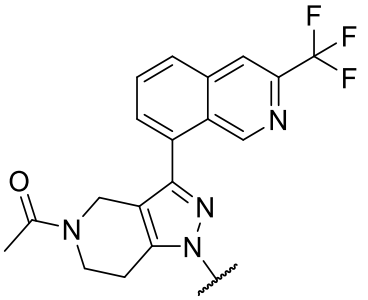
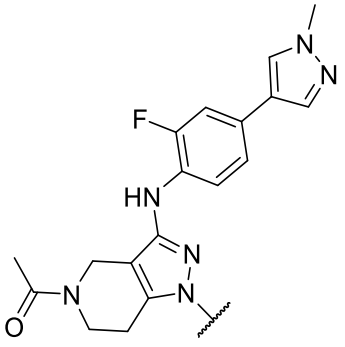
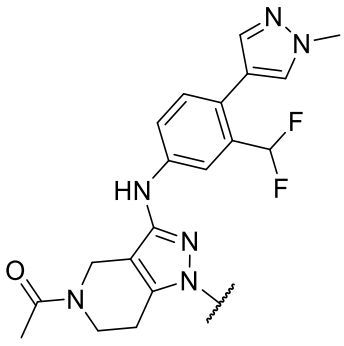
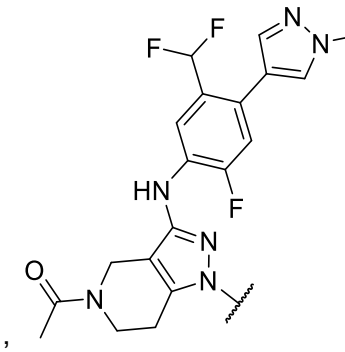

,

,

,

,

,

,

,

,

,

,

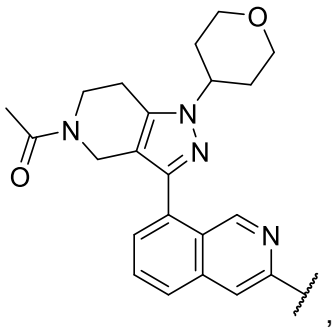
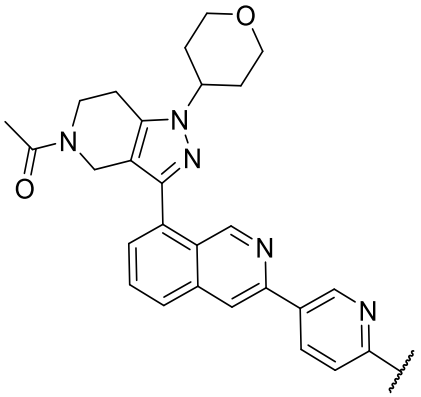
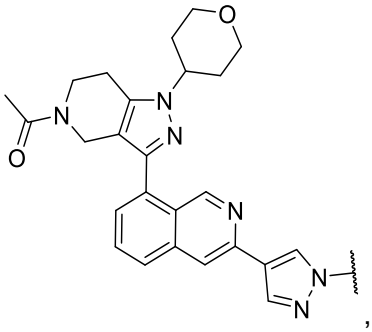
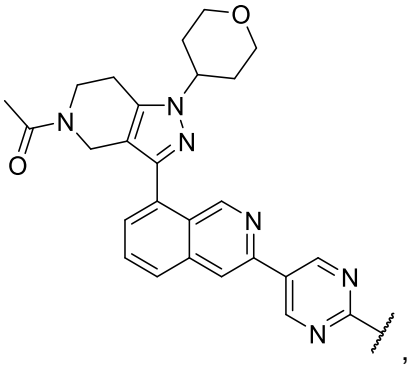
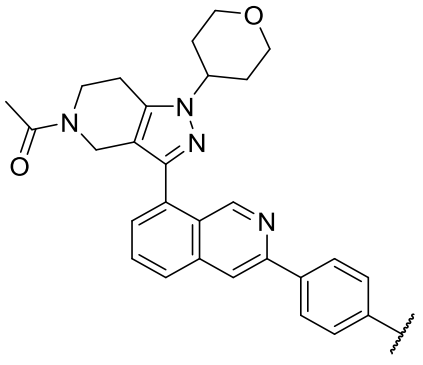
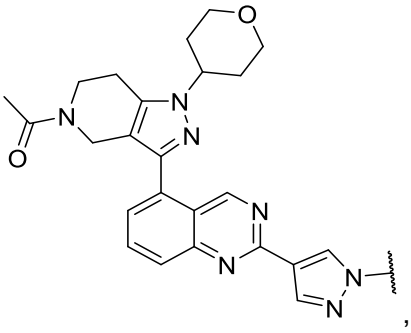
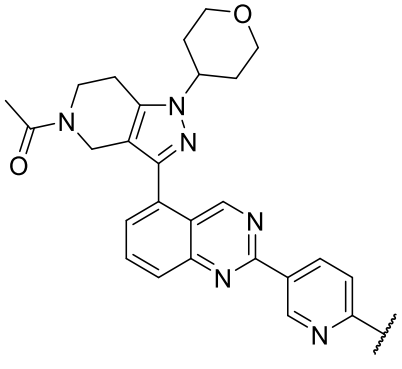
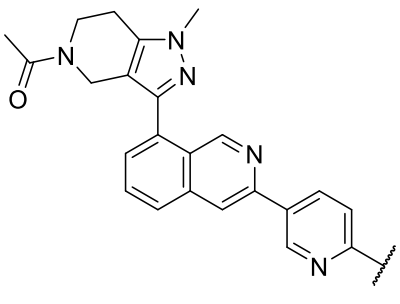

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

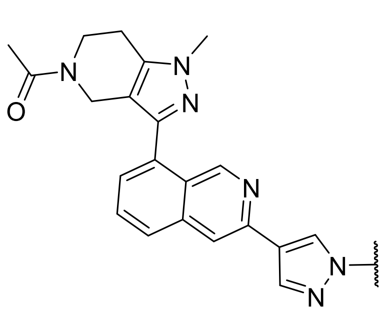
,

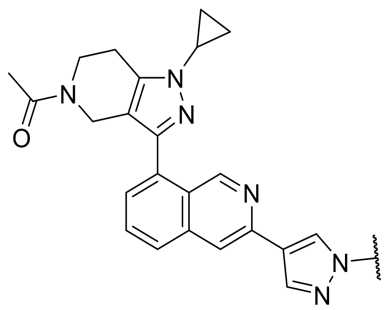
,

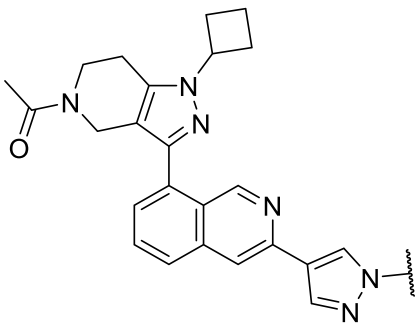
,

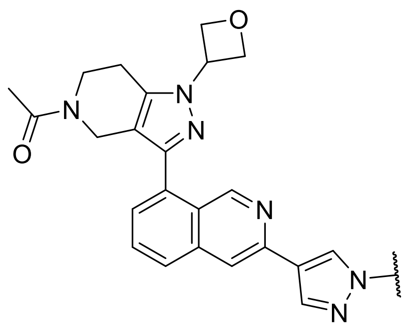

,

,

,

,

,

,

,

,

,

,

,

,

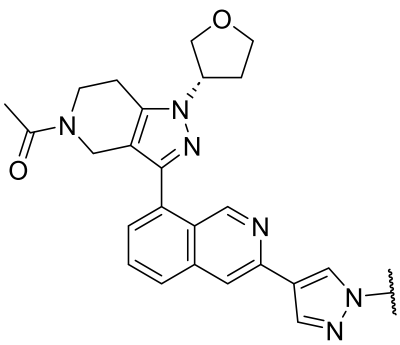

,

,

,

,

,

,

,

,

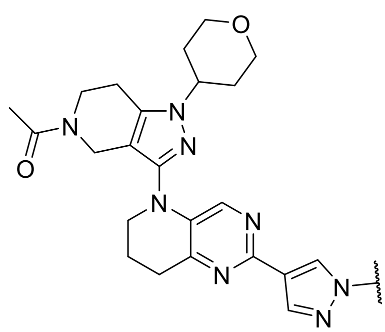
 ,

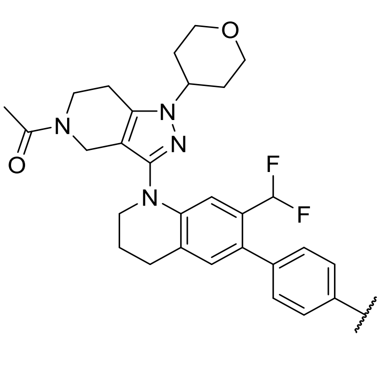
 ,

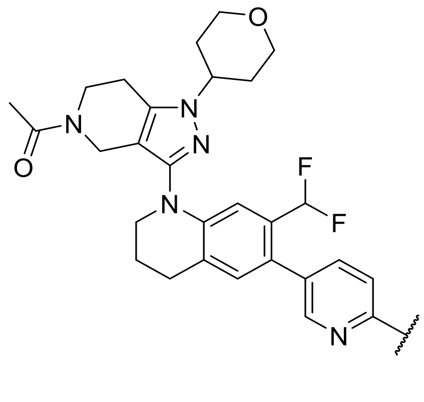
 ,

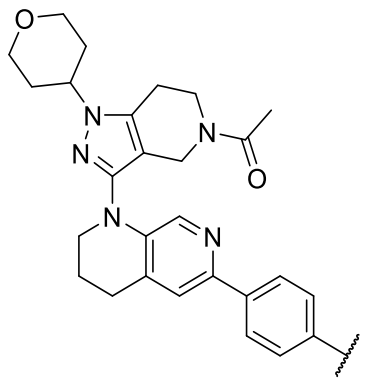
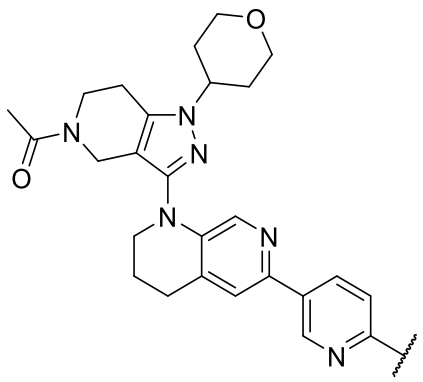
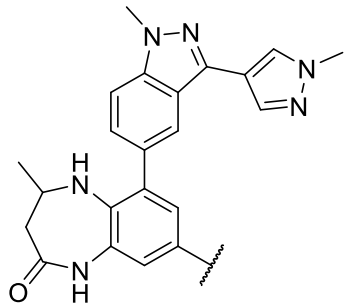
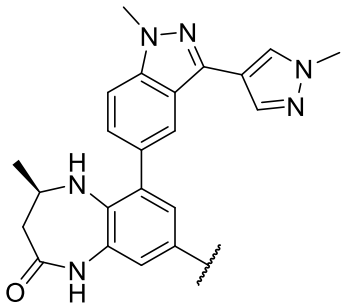
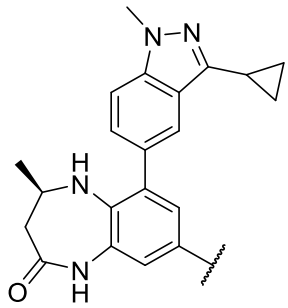
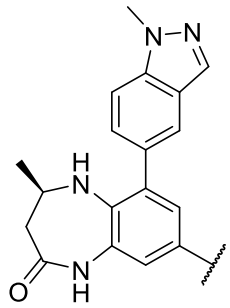
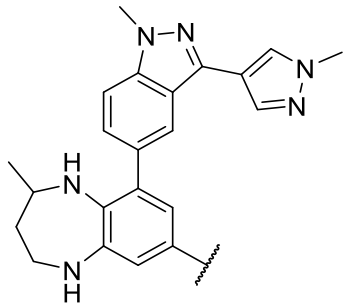
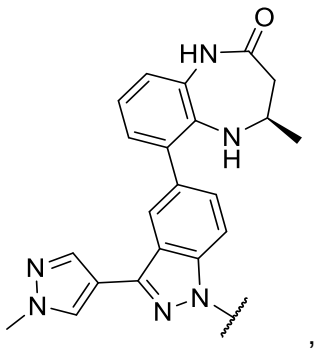
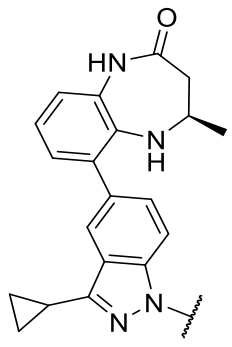
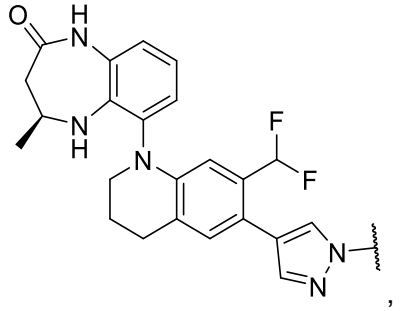
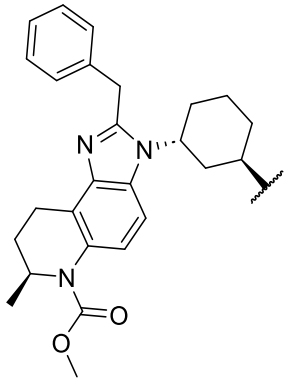
 ,

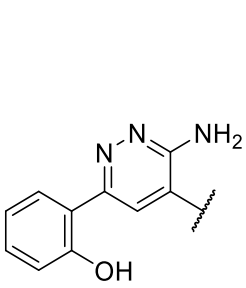
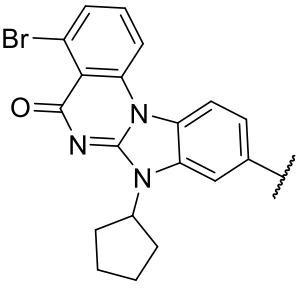
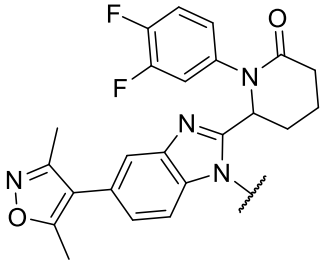
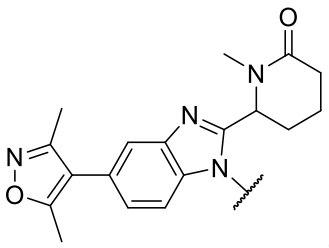
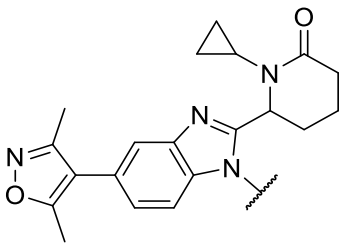
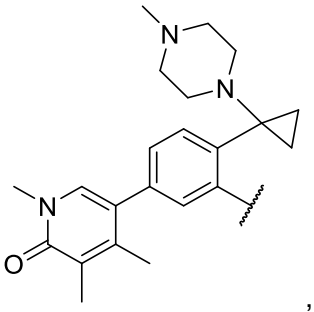
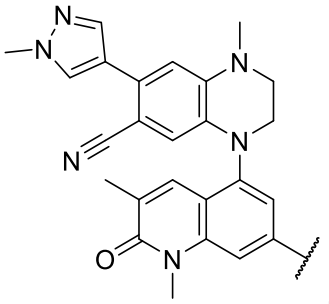
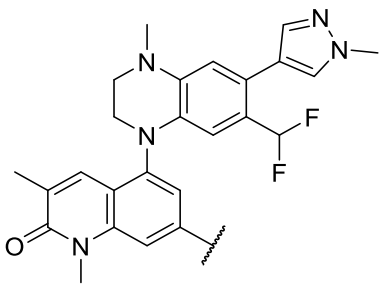
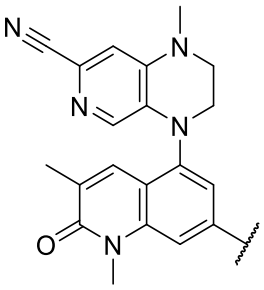
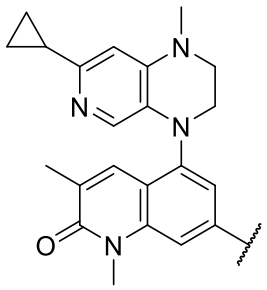
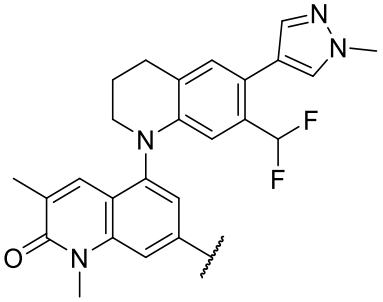
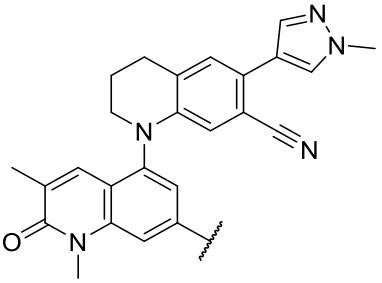
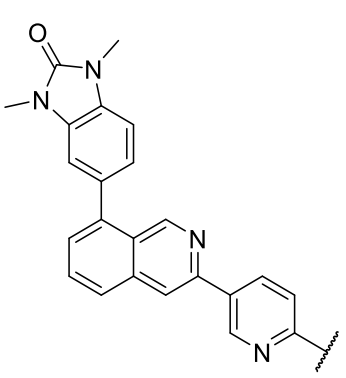
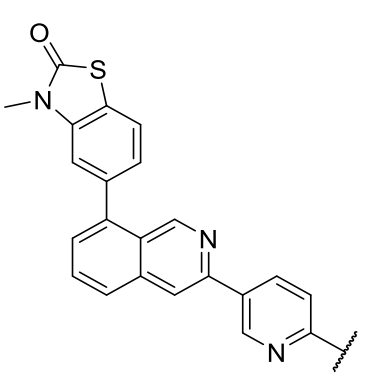
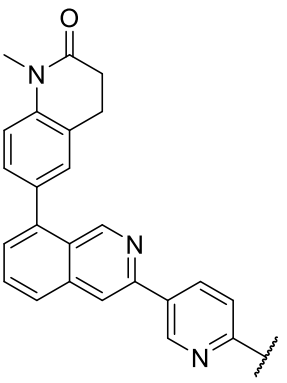
 ,

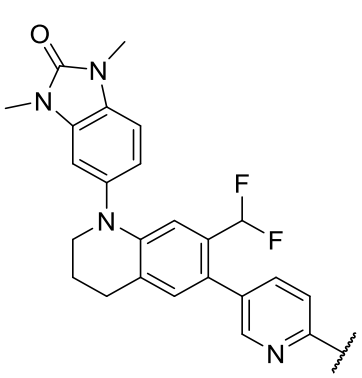
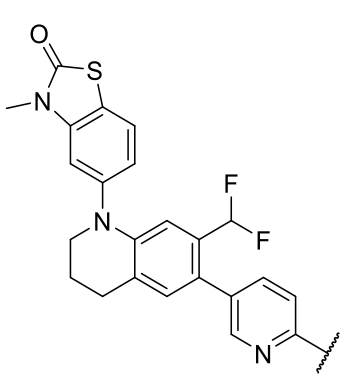
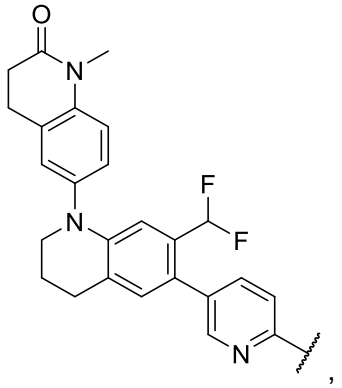
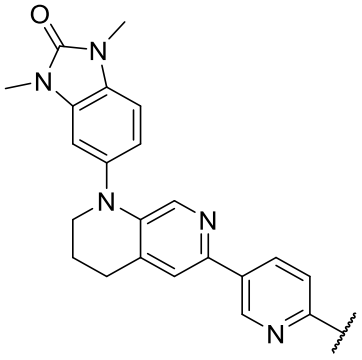
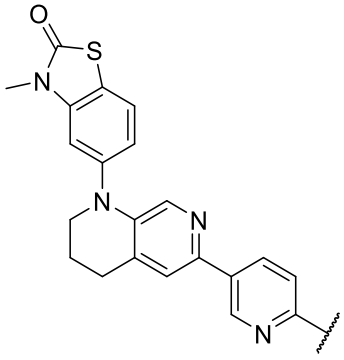
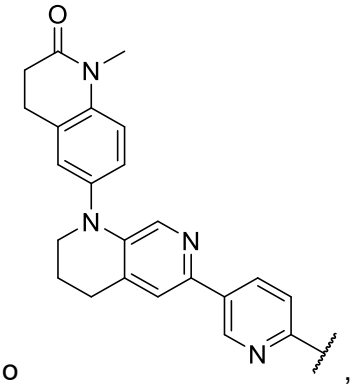
 ,

 ,

 ,

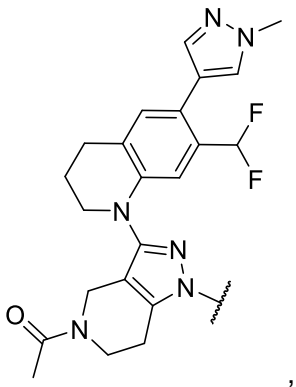
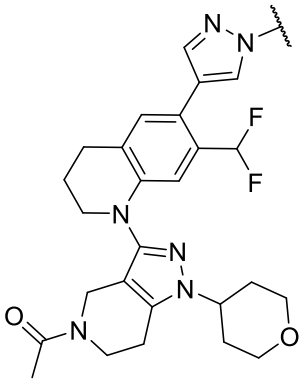
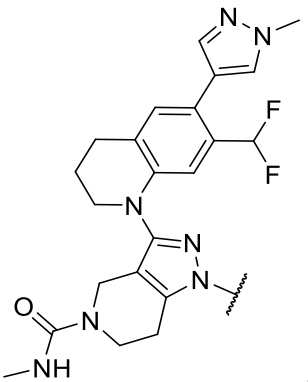
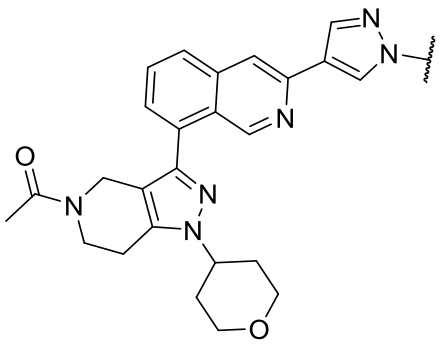
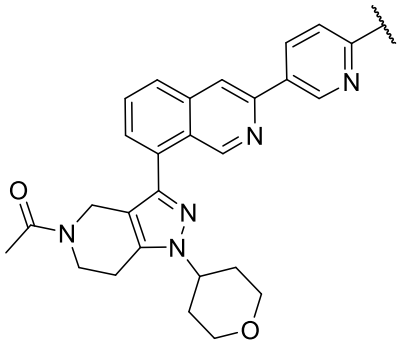













,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

o una sal o solvato farmacéuticamente aceptable de este.

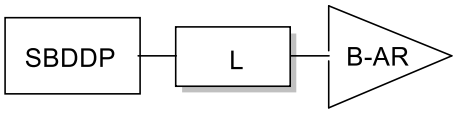
[00181] En algunas formas de realización, p300 tiene una de las siguientes fórmulas:

o una sal o solvato farmacéuticamente aceptable de este.

[00182] Forma de realización 1. un compuesto de la Fórmula (I) o una sal de este

farmacéuticamente aceptable;



en donde:

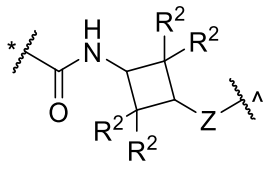
SBDDP es un ligando silencioso de una proteína dependiente de la enfermedad (DDP);

L es un ligador opcional; donde L está unido covalentemente en una posición de SBDDP que está expuesta al disolvente cuando SBDDP se une a DDP;

B-AR es un ligando del receptor de andrógenos (AR), en el que B-AR comprende:

1) un grupo principal que ocupa el dominio de unión al ligando (LBD) del AR y está unido covalentemente a una porción central; y

2) una porción de cola opcional unida covalentemente a la porción central; donde el núcleo comprende un ciclobutilo opcionalmente sustituido que tiene la estructura de Fórmula (C):



, Fórmula (C);

El grupo principal está unido covalentemente a Z en la posición (^);

La porción de cola opcional comprende un anillo D que está unido covalentemente a la amida (*), donde el anillo D es un arilo de 5, 6, 8, 9 o 10 miembros o un heteroarilo de 5, 6, 8, 9 o 10 miembros que está opcionalmente sustituido con s R^3;

en donde:

X es O o NR^5;

cada R^2 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$; o

dos R^2 en el mismo átomo de carbono se toman junto con el átomo de carbono al que están unidos para formar un cicloalquilo C_3-C_8 sustituido o no sustituido o un heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido;

cada R^3 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^4 o -$N(R^5)_2$.

cada R^4 es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o

no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^5 es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^5 en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido; y

cada s es 1, 2 o 3;

donde L está unido covalentemente a la porción central en la posición (*) si la porción de cola opcional está ausente, o L está unido covalentemente a la porción de cola si está presente;

donde DDP y AR se expresan en una célula de interés (COI), y donde la abundancia relativa de AR en la COI es mayor que la abundancia relativa de DDP en la COI; o la COI es una célula enferma, y el AR está sobreexpresado, hiperactivo, o sobreexpresado e hiperactivo a la vez, o amplificado en la célula enferma en comparación con cuando la COI es una célula no enferma.

[00183] Forma de realización 2. El compuesto del ejemplo 1, o una sal o solvato farmacéuticamente aceptable de este, donde DDP es Ataxia-telangiectasia mutada (ATM), Ataxia telangiectasia y proteína relacionada con Rad3 (ATR), Aurora quinasa A (AurkA), AurkB, proteína quinasa relacionada con el ciclo de división celular 7 (CDC7), quinasa de punto de control 1 (CHK1), CHK2, quinasa dependiente de ciclina 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, ADN metiltransferasa 1 (DNMT1), Exportina 1 (XPO1), histona deacetilasa 1 (HDAC1), HDAC2, HDAC3, miembro 11 de la familia de la kinesina (KIF11), proteína quinasa activada por mitógeno quinasa 1 (MEK1), MEK2, Myc, proteína 8 regulada negativamente durante el desarrollo expresada en células precursoras neuronales (NEDD8), SMARCA2/4, proteína de unión a CREB (CBP)/p300, proteína 5 que contiene repeticiones WD (WDR5), factor 1 asociado a DDB1 y CUL4 (DCAF1), fosfatidilinositol-3 quinasa (PI3K), proteína arginina metiltransferasa 5 (PRMT5), subunidad 1 del factor de empalme 3b (SF3B1), WEE1, subunidades del proteasoma 20S, coactivador 1 del receptor de esteroides (SRC1), SRC2 o SRC3.

[00184] Forma de realización 3. El compuesto de la realización 1 o realización 2, o una sal o solvato farmacéuticamente aceptable de este, donde DDP es Aurora Kinase A

(AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphodilinositol-3 kinase (PI3K) o WEE1.

[00185] Forma de realización 4. El compuesto de cualquiera de las formas de realización 1-3, o una sal o solvato farmacéuticamente aceptable de este, en donde Y es -CBP.

[00186] Forma de realización 5. El compuesto del ejemplo 4, o una sal o solvato farmacéuticamente aceptable de este, en el que el SBDDP se une al sitio de unión de la acetil-lisina (KAc) del bromodominio de CBP/p300.

[00187] Forma de realización 6. El compuesto del ejemplo 4, o una sal o solvato farmacéuticamente aceptable de este, en el que el SBDDP comprende una porción mimética de acetil-lisina que se une al sitio de unión de acetil-lisina (KAc) del bromodominio de CBP/p300.

[00188] Forma de realización 7. El compuesto de la forma de realización 6, o una sal o solvato farmacéuticamente aceptable de este, en donde:

la porción que comprende un mimético de acetil-lisina establece o imita una interacción de enlace de hidrógeno con Asn1168 en el bolsillo de unión a Asn del bromodominio de CBP, o establece o imita una interacción de enlace de hidrógeno con Asn1132 en el bolsillo de unión a Asn del bromodominio de p300; y

El grupo principal de B-AR forma enlaces de hidrógeno con las cadenas laterales de Gln 711 y Arg752 del LBD de AR.

[00189] Forma de realización 8. El compuesto de cualquiera de las formas de realización 1-7, o una sal o solvato farmacéuticamente aceptable de este, en el que: SBDDP comprende además una porción que interactúa con Arg1173 en el bromodominio de CBP o Asn1137 en el bromodominio de p300.

[00190] Forma de realización 9. El compuesto de cualquiera de las formas de realización 1-8, o una sal o solvato farmacéuticamente aceptable de este, en donde r es 0.

1) una porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300; o

2) una porción que ocupa la región del bucle BC del bromodominio de CBP/p300; o

3) tanto 1) como 2).

[00191] Forma de realización 10. El compuesto de cualquiera de las formas de realización 6-9, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende una porción

seleccionada de pirrolidonilo, fenilo, piridinilo, piridinol, triazolilo, pirrolilo, isoxazolilo, pirazolilo, quinolinilo, tetrahidroquinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, quinazolonilo, quinazolinilo, dihidroquinazolinonilo, imidazo[4,5-c]quinolinilo fusionado a un dimetilisoxazolilo, triazoloftalazinilo, indolizinilo, benzoimidazolilo, isoxazol-indolizinilo, tienodiazepina-indolizinilo, benzodiazepina-indolizinilo, 5-isoxazolilbenzimidazolilo, 6-isoxazolilbenzimidazolilo, 7-isoxazolo-quinolinilo, diazobencilo, triazoloftalazinilo, isoxazoloquinolinilo, 2-tiazolidinonilo, triazolopirimidinilo, tienodiazepinilo, benzodiazepinilo, benzotriazepinilo, triazolobenzodiazepinilo, triazolotienodiazepinilo, triazolotienodiazepinilo e isoxazol-azepinilo.

[00192] Forma de realización 11. El compuesto de la forma de realización 9 o 10, o una sal o solvato farmacéuticamente aceptable de este, en donde q es 0.

- la porción mimética de acetil-lisina; o
- la porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300, si está presente; o
- la porción que ocupa la región del bucle BC del bromodominio de CBP/p300, si está presente;

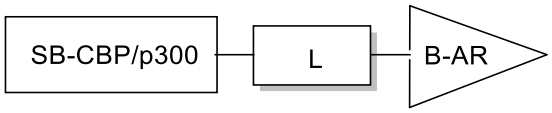
en la que L está unido covalentemente a SBDDP en una posición que no interfiere con la unión de la porción mimética de acetil-lisina en el sitio de unión de lisina acetilada (KAc) de CBP/p300.

[00193] Forma de realización 12. El compuesto de cualquiera de las formas de realización 1-11, o una sal o solvato farmacéuticamente aceptable de este, en donde
el grupo principal de B-AR comprende 4-cianofenilo; 3-fluoro-4-cianofenilo; 3-cloro-4-cianofenilo; 3-metoxi-4-cianofenilo; 3-metil-4-cianofenilo; 3-trifluorometil-4-cianofenilo; 3-trifluorometoxi-4-cianofenilo; 5-fluoro-6-cianopiridin-3-ilo; 5-cloro-6-cianopiridin-3-ilo; 5-metoxi-6-cianopiridin-3-ilo; 5-metil-6-cianopiridin-3-ilo; 5-trifluorometil-6-cianopiridin-3-ilo; 5-trifluorometoxi-6-cianopiridin-3-ilo; [1,2,4]triazolo[4,3-b]piridazin-6-ilo; o 3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-ilo; y
cada R^2 es $-CH_3$.

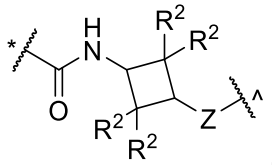
[00194] Forma de realización 13. El compuesto de cualquiera de las formas de realización 1 a 12, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción mimética de acetil-lisina que se une al sitio de unión de acetil-lisina (KAc) del bromodominio de CBP/p300 comprende:
1-(1,4,6,7-tetrahidro-5H-pirazolo[4,3-c]piridin-5-il)etan-1-ona; o N-metil-1,4,6,7-tetrahidro-5H-pirazolo[4,3-c]piridina-5-carboxamida; donde la porción mimética de acetil-lisina comprende opcionalmente además:

1) una porción en la posición 1 del grupo 1,4,6,7-tetrahidro-5H-pirazolo[4,3-c]piridin-5-ilo que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300; o
2) una porción que en la posición 3 del grupo 1,4,6,7-tetrahidro-5H-pirazolo[4,3-c]piridin-5-ilo ocupa la región del bucle BC del bromodominio de CBP/p300; o
3) tanto 1) como 2).

[00195] Forma de realización 14. (a) poner en contacto un compuesto de fórmula (II) o una sal farmacéuticamente aceptable de este



en donde:
SB-CBP/p300 es un ligando silencioso de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300);
L es un ligador opcional; donde L está unido covalentemente en una posición de SB-CBP/p300 que está expuesta al disolvente cuando SB se une a CBP/p300;
El B-AR es un ligando del receptor de andrógenos (AR), en el que el B-AR comprende:
1) un grupo principal que ocupa el dominio de unión al ligando (LBD) del AR y está unido covalentemente a una porción central; y
2) una porción de cola opcional unida covalentemente a la porción central; donde el núcleo comprende un ciclobutilo opcionalmente sustituido que tiene la estructura de Fórmula (C):



, Fórmula (C);

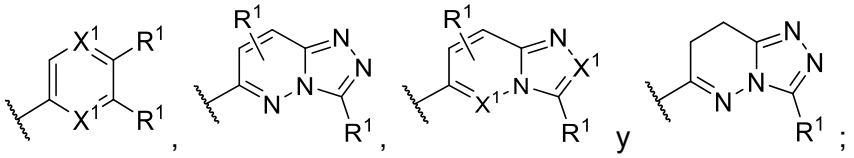
en donde:
El grupo principal está unido covalentemente a Z en la posición (^);
La porción de cola opcional comprende un anillo D que está unido covalentemente a la amida (*), donde el anillo D es un arilo de 5, 6, 8, 9 o 10 miembros o un heteroarilo de 5, 6, 8, 9 o 10 miembros que está opcionalmente sustituido con s R^3;
X es O o NR^5;
cada R^2 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$; o
dos R^2 en el mismo átomo de carbono se toman junto con el átomo de carbono al que

están unidos para formar un cicloalquilo C_3-C_8 sustituido o no sustituido o un heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido;
cada R^3 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^4 o -$N(R^5)_2$.
cada R^4 es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;
cada R^5 es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;
o dos R^5 en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido; y
cada s es 1, 2 o 3;
donde L está unido covalentemente a la porción central en la posición (*) si la porción de cola opcional está ausente, o L está unido covalentemente a la porción de cola si está presente.

[00196] Forma de realización 15. El compuesto de cualquiera de las Formas de realización 1-14, o una sal de este farmacéuticamente aceptable, en donde:
El grupo principal de B-AR forma enlaces de hidrógeno con las cadenas laterales de Gln 711 y Arg752 del LBD de AR; y cada R^2 es independientemente hidrógeno, -CH_3, -CD_3, -CH_2F, -CHF_2 o -CF_3.

[00197] Forma de realización 16. El compuesto de cualquiera de las formas de realización 1-14, o una sal o solvato farmacéuticamente aceptable de este, en donde r es 3.

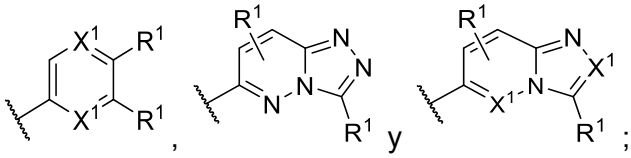
[00198] Forma de realización 17. El compuesto de cualquiera de las formas de realización 1-11 o 14, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR comprende un grupo de cabeza y un núcleo opcional, en el que el grupo de cabeza se selecciona de:



X^1 es CR^1 o N;

cada R^1 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -NO_2, -OH, -OR^4, $OC(=O)R^4$, -$OC(=O)N(R^5)_2$, -$OC(=O)OR^5$, -$OC(=O)NR^5$, -SH, -SR^4, -$S(=O)R^4$, -$S(=O)_2R^5$, -$S(=O)_2OR^4$, -$S(=O)_2N(R^5)_2$, -$N(R^5)_2$, -$NR^5C(=O)NR^5$, -$NR^5C(=O)R^4$, -$NR^5C(=O)OR^5$, -$NR^5S(=O)_2R^5$, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$.

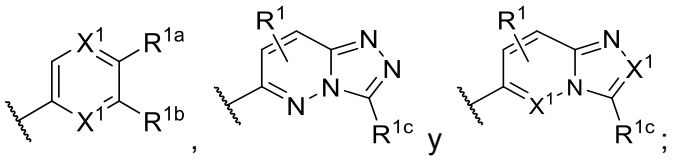
[00199] Forma de realización 18. El compuesto de cualquiera de las formas de realización 1-11 o 14, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR comprende un grupo de cabeza y un núcleo opcional, en el que el grupo de cabeza se selecciona de:



Uno X^1 es -CR^1- y el otro X^1 es -CR^1- o -N-;

cada R^1 es independientemente hidrógeno, F, Cl, Br, I, -CH_3, -CD_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, - CH_2CF_3, -OH, -OCF_3, -OCH_3, -OCD_3, -OCH_2CH_3, -CN, -$C(=O)NH_2$ -$C(=O)NH(CH_3)$o -$C(=O)NH(CD_3)$.

[00200] Forma de realización 19. El compuesto de cualquiera de las formas de realización 1-11 o 14, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR comprende un grupo de cabeza y un núcleo opcional, en el que el grupo de cabeza se selecciona de:



X^1 es CR^1 o N;

R^{1a} es -CN, -NO_2, -$C(=O)R^5$, -$C(=O)OR^5$, o -$C(=O)N(R^5)_2$;

R^{1b} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH, -OR^4 o -SR^4;

R^{1c} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo o -CN;

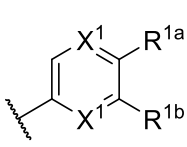
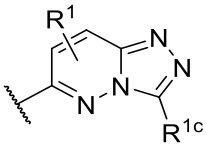
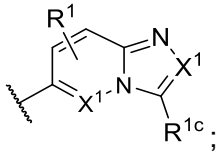
cada R^1 es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -

CN, -OH o -OR^4;

Cada R^4 es independientemente C_1-C_4alquilo, o C_1-C_4fluoroalquilo;

Cada R^5 es independientemente hidrógeno, C_1-C_4alquilo o C_1-C_4fluoroalquilo.

[00201] Forma de realización 20. El compuesto de cualquiera de las formas de realización 1-11 o 14, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR comprende un grupo de cabeza y un núcleo opcional, en el que el grupo de cabeza se selecciona de:


,

y

;

Uno X^1 es -CR^1- y el otro X^1 es -CR^1- o -N-;

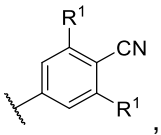
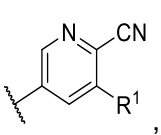
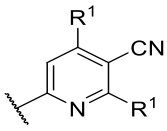
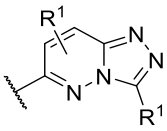
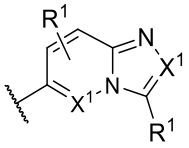
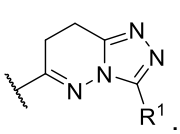
R^{1a} es -CN, -NO_2, -C(=O)NH_2 o -C(=O)$NH(CH_3)$;

R^{1b} es hidrógeno, F, Cl, Br, I, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -OH, -OCF_3, -OCH_3, -OCH_2CH_3 o -CN;

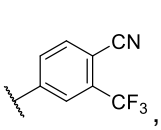
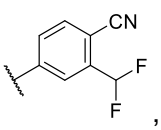
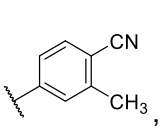
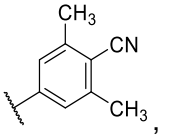
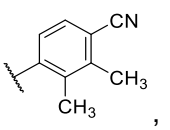
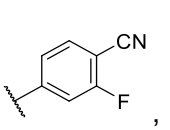
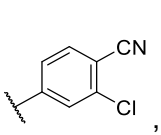
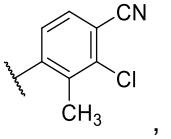
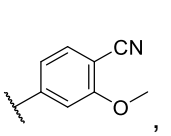
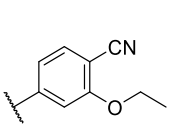
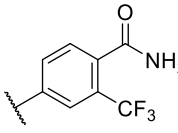
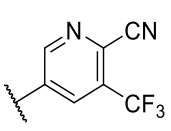
cada R^{1c} es hidrógeno, F, Cl, Br, -CH_3, -CH_2F, -CHF_2 o -CF_3;

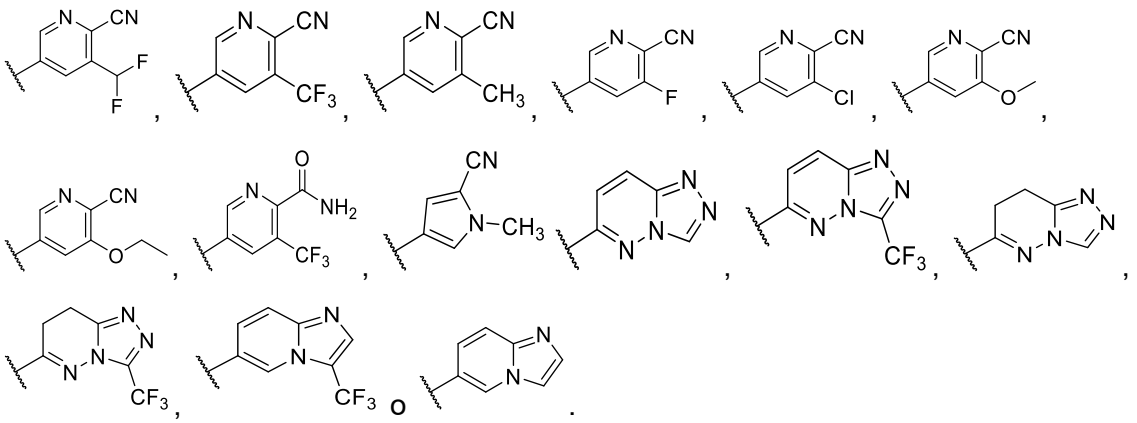
Cada R^1 es independientemente hidrógeno, F, Cl, Br, I, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -OH, -OCF_3, -OCH_3 o -OCH_2CH_3.

[00202] Forma de realización 21. El compuesto de cualquiera de las formas de realización 1-11 o 14, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR comprende un grupo de cabeza y un núcleo opcional, en el que el grupo de cabeza se selecciona de:

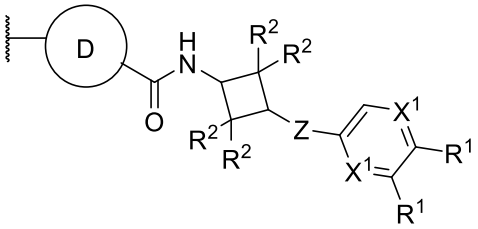

,

,

,

,

y

.

[00203] Forma de realización 22. El compuesto de cualquiera de las formas de realización 1-11 o 14, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR comprende un grupo de cabeza y un núcleo opcional, en el que el grupo de cabeza se selecciona de:


,

,

,

,

,

,

,

,

,

,

,

,



[00204] Forma de realización 23. El compuesto de cualquiera de las formas de realización 1-11 o 14-20, o una sal o solvato farmacéuticamente aceptable de este, donde B-AR tiene la estructura de la Fórmula (IIa), o una sal o solvato farmacéuticamente aceptable de este:



Fórmula (IIa)

en donde:

X^1 es CR^1 o N;

X es O o NR^5;

cada R^1 es independientemente hidrógeno, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$ o $-C(=O)NH(CH_3)$;

R^2 es alquil C_1-C_6;

anillo D que es un arilo de 5, 6, 8, 9 o 10 miembros o un heteroarilo de 5, 6, 8, 9 o 10 miembros que opcionalmente está sustituido con s R^3;

cada R^3 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, $-OR^4$ o $-N(R^5)_2$;

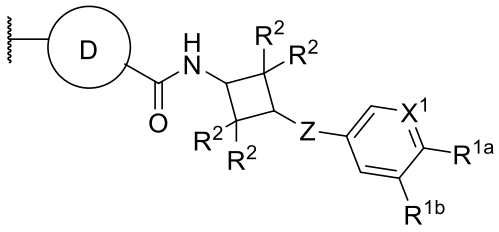
es 0, 1, 2 o 3;

[00205] Forma de realización 24. El compuesto de la forma de realización 23, o una sal o solvato farmacéuticamente aceptable de este:

Uno X^1 es $-CR^1-$ y el otro X^1 es $-CR^1-$ o -N-;

cada R^2 es $-CH_3$.

[00206] Forma de realización 25. El compuesto de cualquiera de las formas de realización 1-11 o 14-20, o una sal o solvato farmacéuticamente aceptable de este, donde B-AR tiene la estructura de la Fórmula (IIIa), o una sal o solvato farmacéuticamente aceptable de este:



Fórmula (IIIa)

en donde:

X^1 es CR^1 o N;

X es O o NR^5;

R^{1a} es -CN, $-NO_2$, $-C(=O)R^5$, $-C(=O)OR^5$, o $-C(=O)N(R^5)_2$;

R^{1b} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH o $-OR^4$;

cada R^1 es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH o $-OR^4$;

cada R^2 es $-CH_3$;

anillo D que es un arilo de 5, 6, 8, 9 o 10 miembros o un heteroarilo de 5, 6, 8, 9 o 10 miembros que opcionalmente está sustituido con s R^3;

cada R^3 es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH, $-OR^4$ o $-N(R^5)_2$;

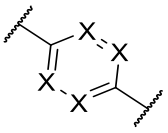
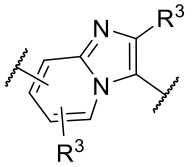
es 0, 1, 2 o 3;

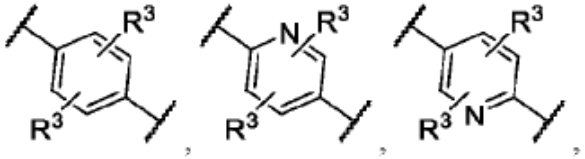
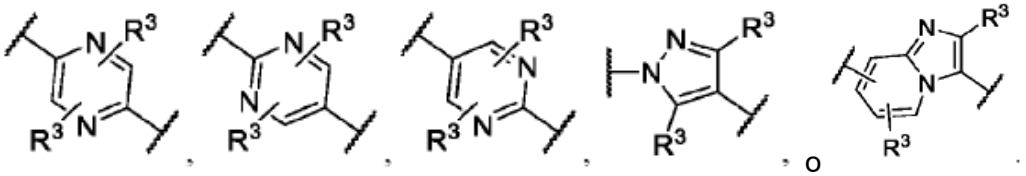
Cada R^4 es independientemente C_1-C_4alquilo, o C_1-C_4fluoroalquilo;

Cada R^5 es independientemente hidrógeno, C_1-C_4alquilo o C_1-C_4fluoroalquilo.

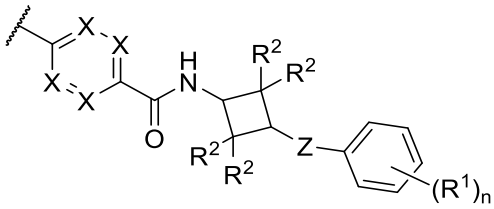
[00207] Forma de realización 26. El compuesto de cualquiera de las formas de realización 23-25, o una sal o solvato farmacéuticamente aceptable de este, en el que el anillo D es fenilo, naftilo, piridinilo, pirimidinilo, piridazinilo, pirazinilo, triazinilo, pirrolilo, tiazolilo, oxazolilo, isoxazolilo, oxadiazolilo, imidazolilo, pirazolilo, isotiazolilo, triazolilo y tetrazolilo, en el que cada anillo D está opcionalmente sustituido con s R^3.

[00208] Forma de realización 27. El compuesto de cualquiera de las formas de realización 23-25, o una sal o solvato farmacéuticamente aceptable de este, donde el

anillo D es  ,  o  ; y cada X es independientemente -CR^3- o -N-.

[00209] Forma de realización 28. El compuesto de cualquiera de las formas de realización 23-25, o una sal de este farmacéuticamente aceptable, en donde el anillo D es  ,  o .

[00210] Forma de realización 29. El compuesto de cualquiera de las formas de realización 1-11 o 14-20, o una sal o solvato farmacéuticamente aceptable de este, donde B-AR tiene la estructura de la Fórmula (IVa), o una sal o solvato farmacéuticamente aceptable de este:



Fórmula (IVa)

en donde:

cada X es independientemente -CR^3- o -N-;

X es O o NR^5;

n es 2 y un R^1 es halógeno, -CH_3, -OCH_3 o -CF_3, y el otro R^1 es -CN;

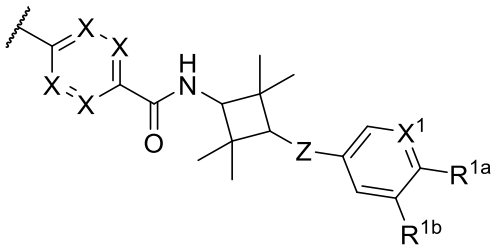
cada R^2 es -CH_3.

[00211] Forma de realización 30. El compuesto de la forma de realización 20, o una sal o solvato farmacéuticamente aceptable de este, en donde:

Uno de los R^1 es -Cl, -CH_3, -OCH_3 o -CF_3, y el otro R^1 es -CN.

[00212] Forma de realización 31. El compuesto de cualquiera de las formas de realización 1-11 o 14-20, o una sal o solvato farmacéuticamente aceptable de este,

donde B-AR tiene la estructura de la Fórmula (Va), o una sal o solvato farmacéuticamente aceptable de este:



Fórmula (Va)

en donde:

cada X es independientemente $-CR^3-$ o -N-;

X es O o NR^5;

X^1 es CR^1 o N;

R^{1a} es

R^{1b} es hidrógeno, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$ o -CN;

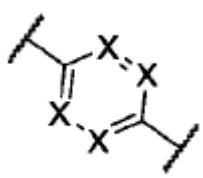
R^1 es hidrógeno, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$ o $-OCH_2CF_3$;

cada R^3 es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, $-OR^4$ o $-N(R^5)_2$;

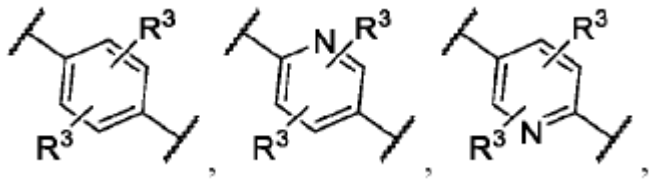
Cada R^4 es independientemente sustituido o no sustituido C_1-C_6alquilo, o C_1-C_6fluoroalquilo;

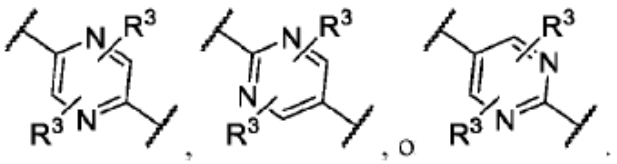
Cada R^5 es independientemente hidrógeno, sustituido o no sustituido C_1-C_6alquilo, C_1-C_6fluoroalquilo.

[00213] Forma de realización 32. El compuesto de cualquiera de las formas de realización 29-31, o una sal o solvato farmacéuticamente aceptable de este, en donde



es

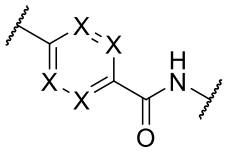
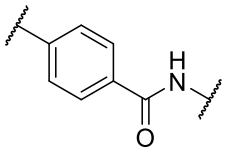
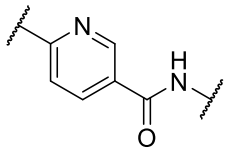
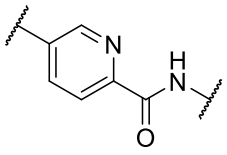
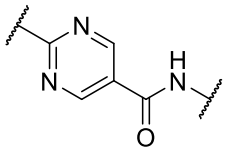
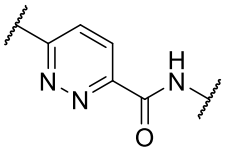
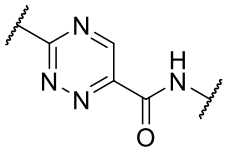




.

[00214] Forma de realización 33. El compuesto de cualquiera de las formas de realización 1-32, o una sal o solvato farmacéuticamente aceptable de este, en donde: cada R^3 es independientemente hidrógeno, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, o $-C(=O)NH(CH_3)$.

[00215] Forma de realización 34. El compuesto de cualquiera de las formas de realización 29-33, o una sal o solvato farmacéuticamente aceptable de este, en donde:


es

,

,

,

,

o

.

[00216] Forma de realización 35. El compuesto de cualquiera de las formas de realización 1-14, o una sal o solvato farmacéuticamente aceptable de este, en donde el grupo principal y central de B-AR es:

N-(3-(3-fluoro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-metoxi-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-metil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-(3-trifluorometoxi-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-((5-fluoro-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

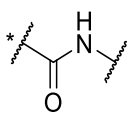
N-(3-((5-cloro-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-((5-metoxi-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

N-(3-((5-metil -6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

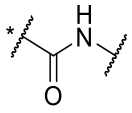
N-(3-((5-trifluorometil-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*; o

N-(3-((5-trifluorometoxi-6-cianopiridin-3-il)oxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

donde la acetamida-* es 
.

[00217] Forma de realización 36. El compuesto de cualquiera de las formas de realización 1-14, o una sal o solvato farmacéuticamente aceptable de este, en donde el grupo principal y el central de B-AR es:

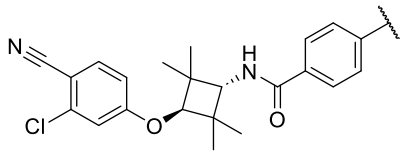
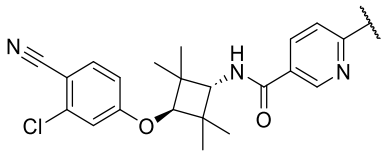
N-(3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-(3-metoxi-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;
N-(3-(3-metil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*; o
N-(3-(3-trifluorometil-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil)acetamida-*;

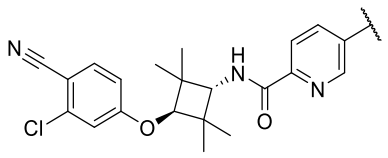
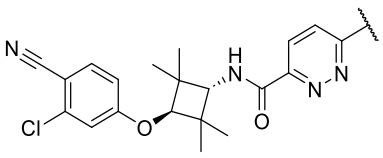
donde la acetamida-* es  .

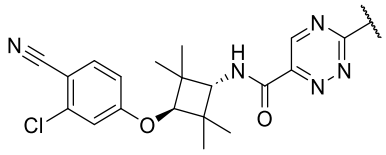
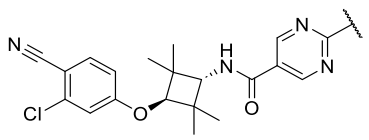
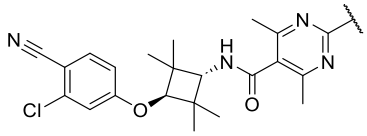
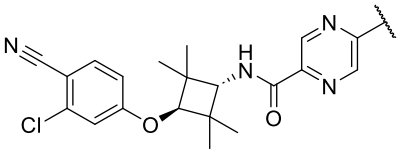
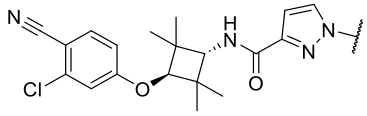
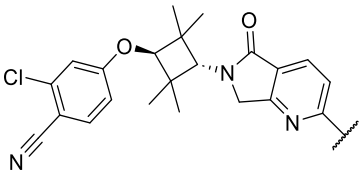
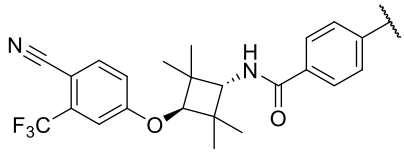
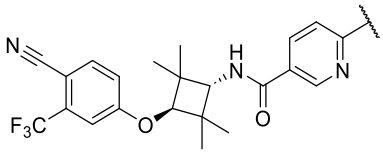
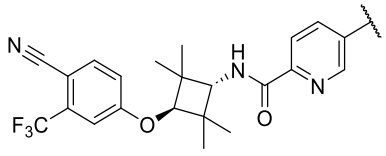
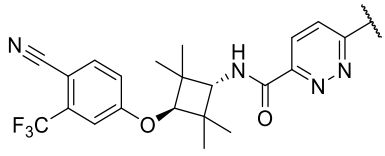
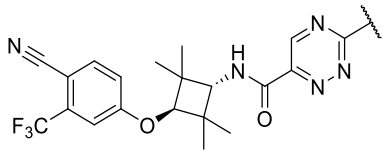
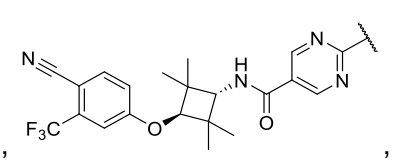
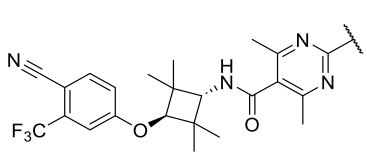
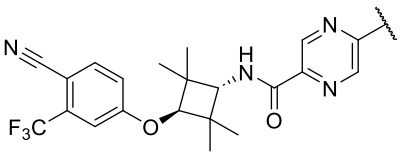
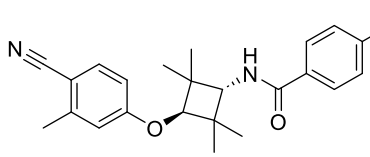
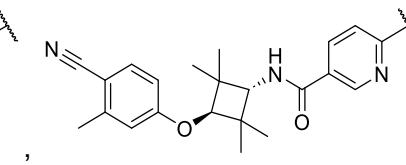
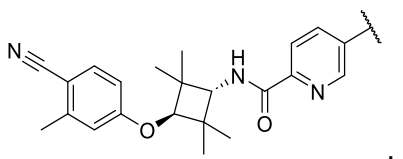
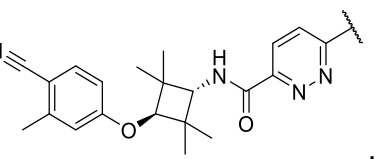
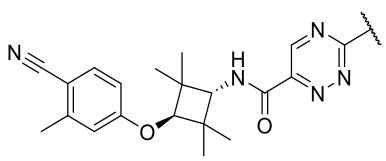
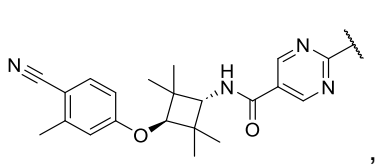
[00218] Forma de realización 37. El compuesto de realización 35 o 36, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR comprende además una porción de cola que está unida covalentemente a la posición (*), en la que la porción de cola es un anillo D que es fenilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, triazolilo, pirrolilo, imidazolilo, pirazolilo, piridilo, indolilo, isoindolilo, indolizinilo, bencimidazolilo, naftilo, quinolilo, isoquinolilo, quinoxalinilo, quinazolinilo, indazolilo o benzotriazolilo; en el que el anillo D está opcionalmente sustituido con s R^3;
es 0, 1, 2 o 3;
cada R^3 es independientemente hidrógeno, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$, -CN, $-C(=O)NH_2$, o $-C(=O)NH(CH_3)$.

[00219] Forma de realización 38. El compuesto de la realización 35 o 36, o una sal o solvato farmacéuticamente aceptable de este, en el que el anillo D es fenilo, piridilo, pirimidinilo, pirazinilo, piridazinilo o triazinilo; en el que el anillo D está opcionalmente sustituido con s R^3; s es 1, 2 o 3;
cada R^3 es independientemente hidrógeno, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCH_2CH_3$ o -CN.

[00220] Forma de realización 39. El compuesto de la forma de realización 1 o 14, o una sal o solvato farmacéuticamente aceptable de este, en donde B-AR tiene una de las siguientes estructuras:

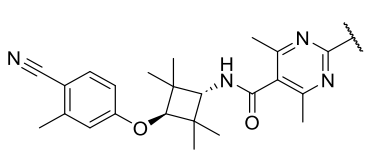
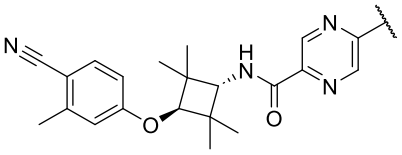
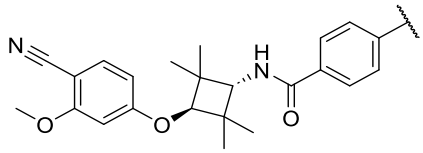
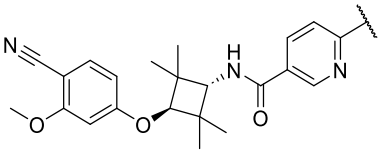
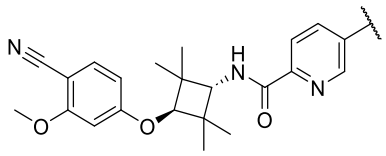
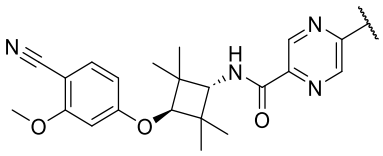
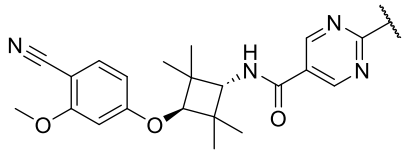
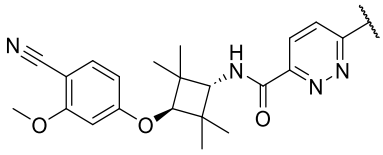
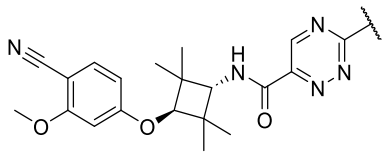
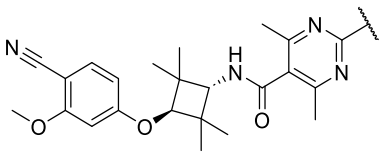
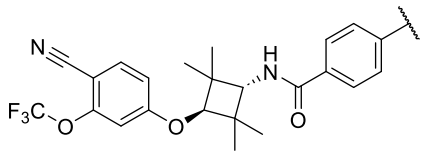
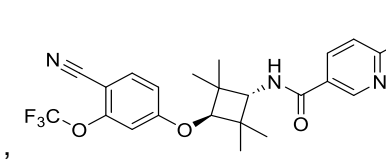
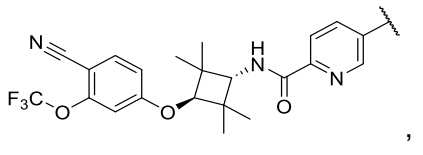
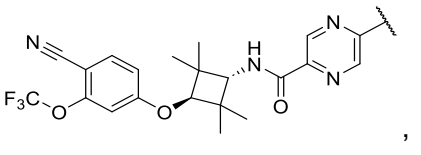
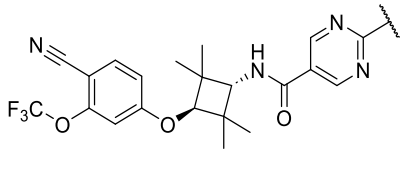
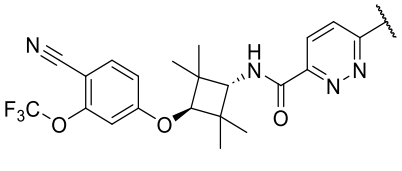
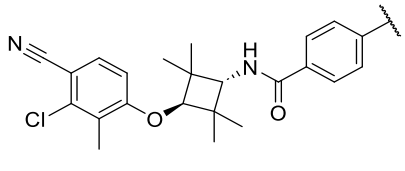
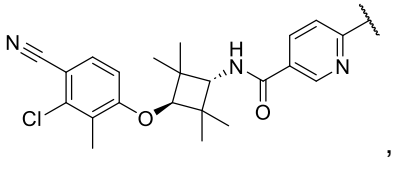
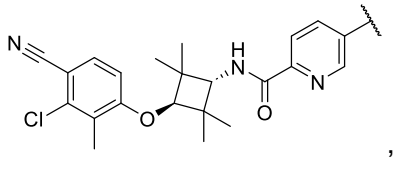
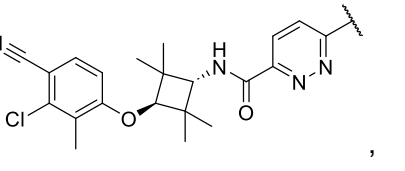
 ,  ,

 ,  ,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

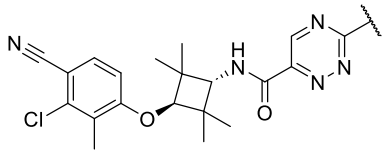
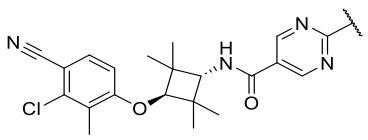
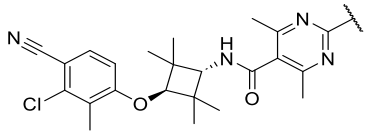
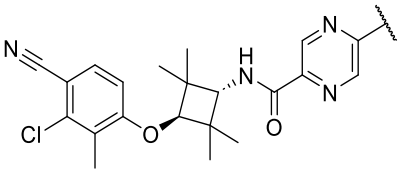
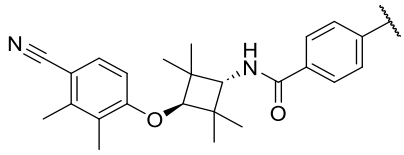
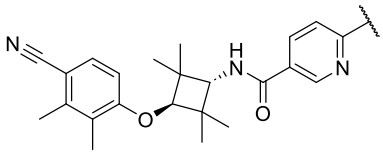
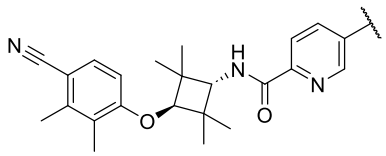
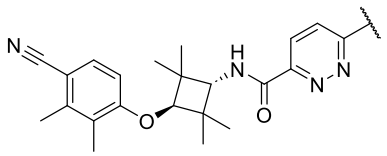
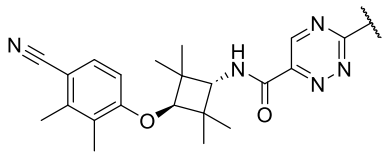
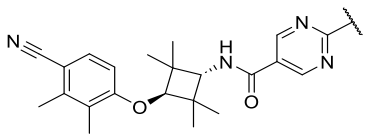
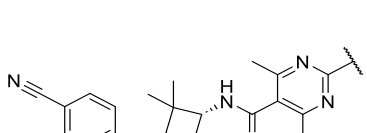
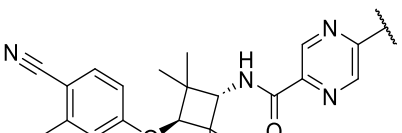
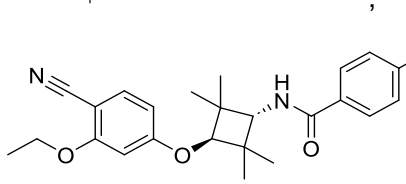
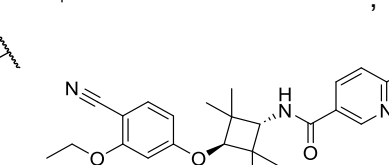
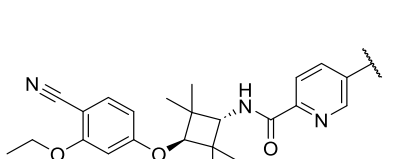
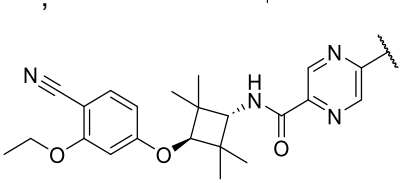
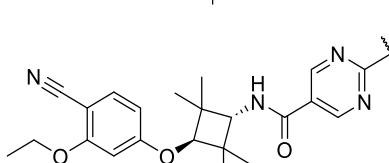
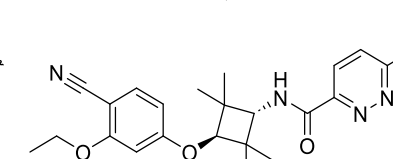
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

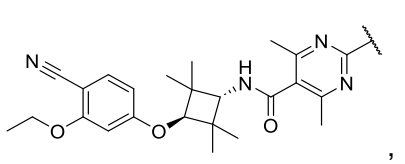
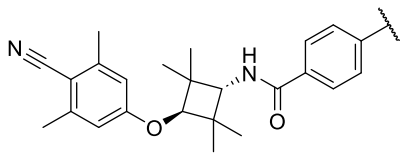
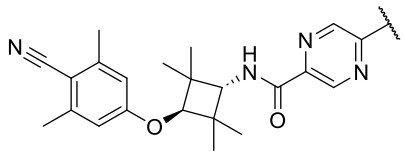
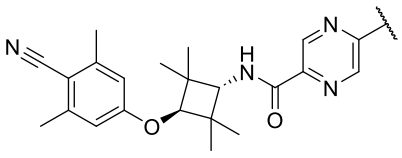
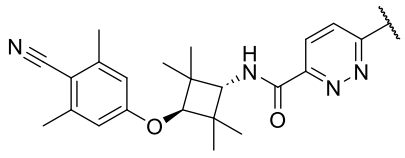
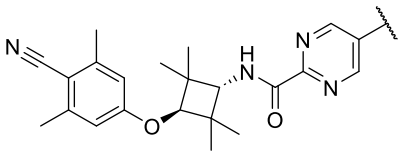
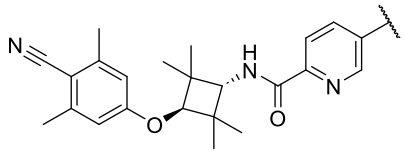
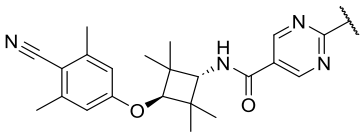
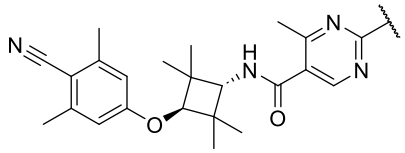
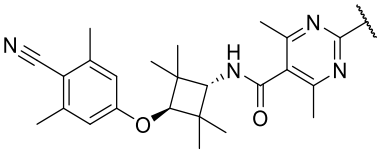
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

o

.

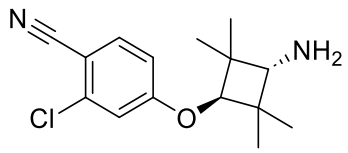
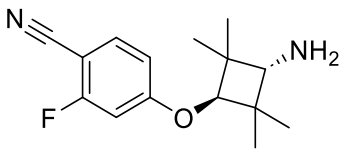
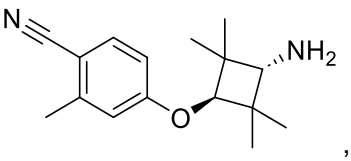
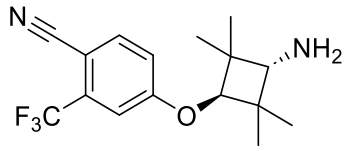
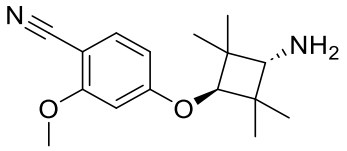
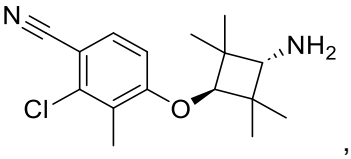
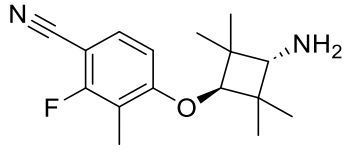
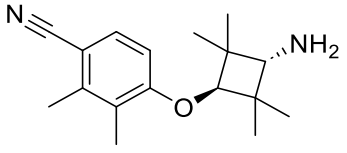
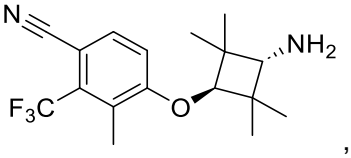
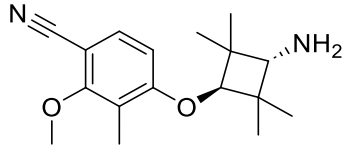
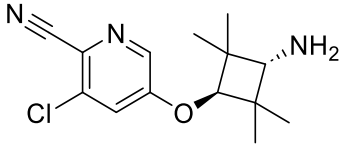
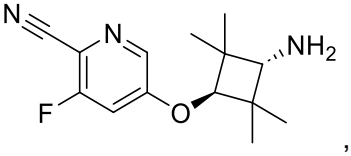
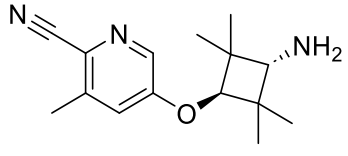
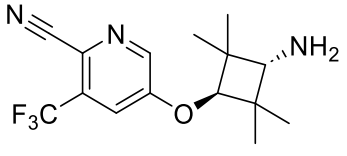
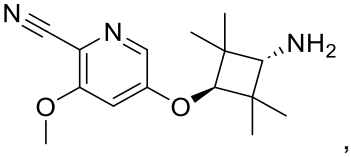
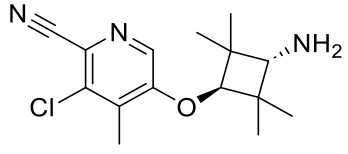
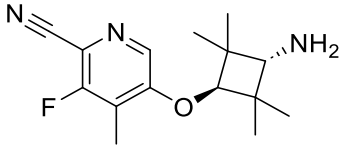
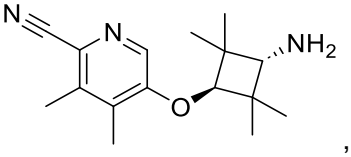
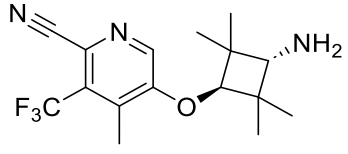
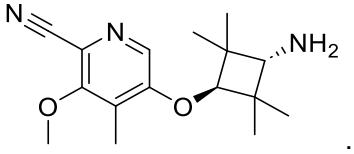
[00221] Forma de realización 39a. El compuesto del ejemplo 39, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR tiene una de las siguientes estructuras del ejemplo 39, en el que  es un haluro.  es un haluro.

[00222] Forma de realización 39b. El compuesto del ejemplo 39a, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR tiene una de las siguientes estructuras del ejemplo 39a, en el que es Cl, Br o I.

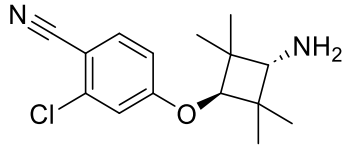
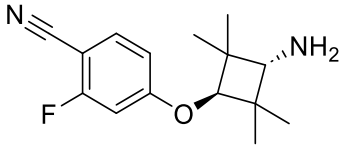
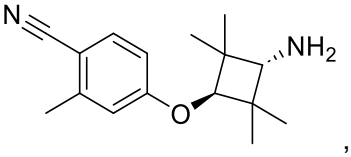
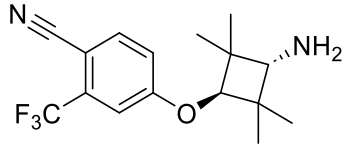
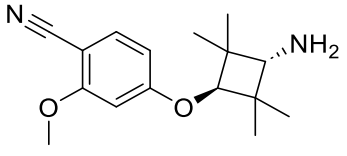
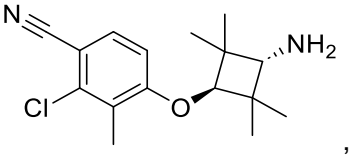
[00223] Forma de realización 39c. El compuesto del ejemplo 39a, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR tiene una de las siguientes estructuras del ejemplo 39a, en el que es Cl.

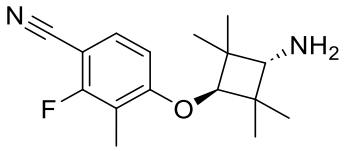
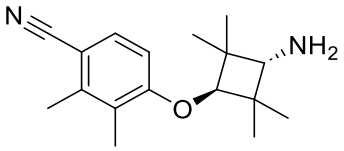
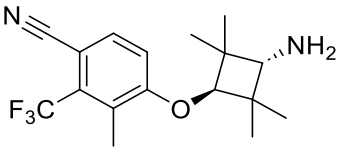
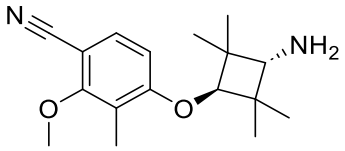
[00224] Forma de realización 39d. El compuesto del ejemplo 39a, o una sal o solvato farmacéuticamente aceptable de este, en el que B-AR tiene una de las siguientes estructuras del ejemplo 39a, en el que es H.

[00225] Forma de realización 39e. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:

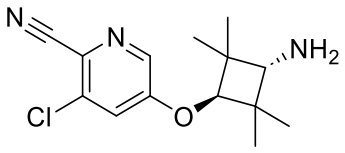
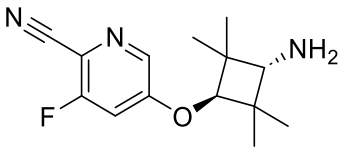
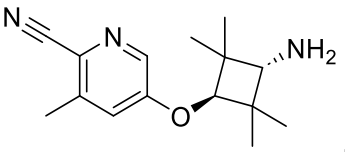
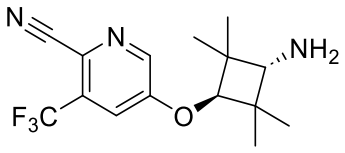
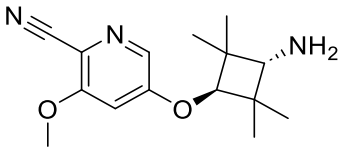
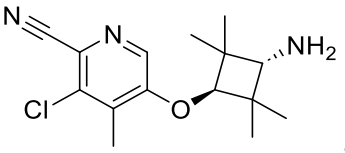
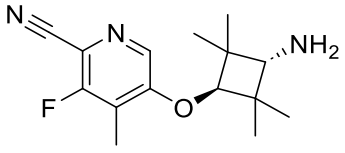
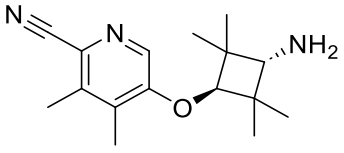
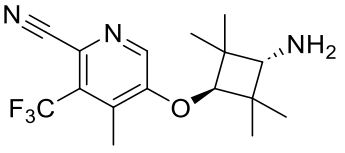
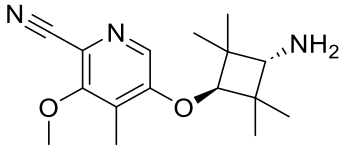

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

o

.

[00226] Forma de realización 39f. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:


,

,

,

,

,

,




o


[00227] Ejemplo de realización 39g. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:










o


[00228] Forma de realización 40. El compuesto de cualquiera de las formas de realización 14-39, o una sal o solvato farmacéuticamente aceptable de este, en el que SB-CBP/p300 se une al sitio de unión de acetil-lisina (KAc) del bromodominio de CBP/p300.

[00229] Forma de realización 41. El compuesto de cualquiera de las formas de realización 14-39, o una sal o solvato farmacéuticamente aceptable de este, en el que SB-CBP/p300 comprende una porción mimética de acetil-lisina que se une al sitio de unión de acetil-lisina (KAc) del bromodominio de CBP/p300.

[00230] Forma de realización 42. El compuesto del ejemplo 41, o una sal o solvato farmacéuticamente aceptable de este, en el que L está unido covalentemente en una posición de a) que está expuesta al disolvente cuando a) se une al sitio de unión de KAc del bromodominio de CBP/p300.

[00231] Forma de realización 43. El compuesto del ejemplo 41, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina hace o imita una interacción de enlace de hidrógeno con Asn1168 en el bolsillo de unión de Asn del bromodominio de CBP, o hace o imita una interacción de enlace de hidrógeno con Asn1132 en el bolsillo de unión de Asn del bromodominio de p300; y el grupo de cabeza de B-AR forma enlaces de hidrógeno con las cadenas laterales de Gln 711 y Arg 752 del LBD de AR.

[00232] Forma de realización 44. El compuesto de cualquiera de las formas de realización 14-43, o una sal o solvato farmacéuticamente aceptable de este, en el que SB-CBP/p300 comprende además una porción que interactúa con Arg1173 en el bromodominio de CBP o Asn1137 en el bromodominio de p300.

[00233] Forma de realización 45. El compuesto de cualquiera de las formas de realización 14-44, o una sal o solvato farmacéuticamente aceptable de este, en donde SB-CBP/p300 también comprende:

1) una porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300; o

2) una porción que ocupa la región del bucle BC del bromodominio de CBP/p300; o

3) tanto 1) como 2).

[00234] Forma de realización 46. El compuesto de realización 41-45, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende una porción seleccionada de pirrolidonilo, fenilo, piridinilo, piridinol, triazolilo, pirrolilo, isoxazolilo, pirazolilo, quinolinilo, tetrahidroquinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, quinazolonilo, quinazolinilo, dihidroquinazolinonilo, imidazo[4,5-c]quinolinilo fusionado a un dimetilisoxazolilo, triazoloftalazinilo, indolizinilo, benzoimidazolilo, isoxazol-indolizinilo, tienodiazepina-indolizinilo, benzodiazepina-indolizinilo, 5-isoxazolilbenzimidazolilo, 6-isoxazolilbenzimidazolilo, 7-isoxazolo-quinolinilo, diazobencilo, triazoloftalazinilo, isoxazoloquinolinilo, 2-tiazolidinonilo, triazolopirimidinilo, tienodiazepinilo, benzodiazepinilo, benzotriazepinilo, triazolobenzodiazepinilo, triazolotienodiazepinilo, triazolotienodiazepinilo e isoxazol-azepinilo.

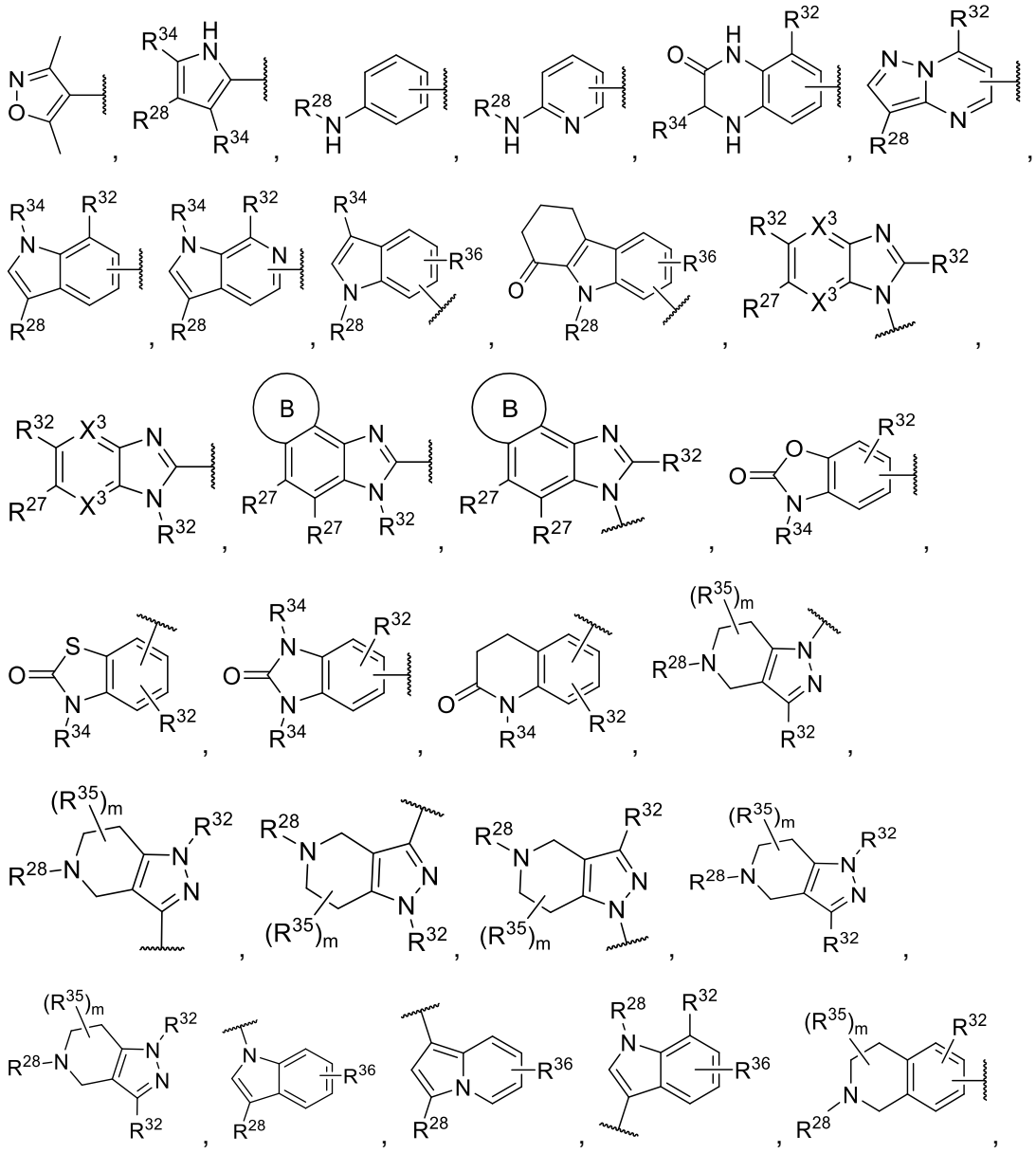
[00235] Forma de realización 47. El compuesto de la forma de realización 45 o 46, o una sal o solvato farmacéuticamente aceptable de este, en donde q es 0.

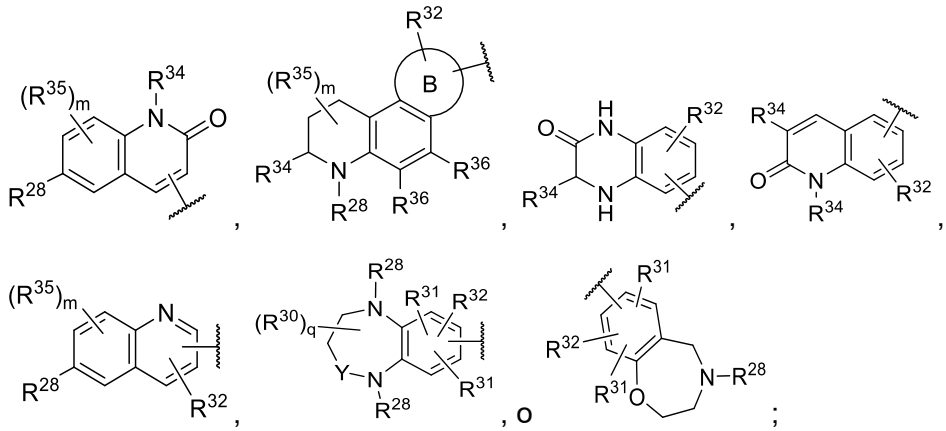
- la porción mimética de acetil-lisina; o
- la porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300, si está presente; o

- la porción que ocupa la región del bucle BC del bromodominio de CBP/p300, si está presente;

en la que L está unido covalentemente a SB-p300/CBP en una posición que no interfiere con la unión de la porción mimética de acetil-lisina en el sitio de unión de lisina acetilada (KAc) de CBP/p300.

[00236] Forma de realización 48. El compuesto de cualquiera de las formas de realización 1 a 47, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende una porción seleccionada de:





Cada R^{32} es independientemente una porción opcional que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300;

o cada R^{32} es independientemente una porción opcional que ocupa la región del bucle BC del bromodominio de CBP/p300;

 es el punto de unión a L que conecta covalentemente SB-CBP/p300 a B-AR;

o R^{32} comprende  y L que conecta covalentemente SB-CBP/p300 a B-AR está unido a R^{32};

cada R^{28} es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -C(=O)R^b, o -C(=O)N(R^b)$_2$;

cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

cada R^{35} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -OH, -OR^a o -N(R^b)$_2$;

m es 0, 1, 2, 3 o 4;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, OC(=O)R^a, -OC(=O)N(R^b)$_2$, -OC(=O)OR^a, -OC(=O)N(R^b)$_2$, -SR^b, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2$OR^b, -S(=O)$_2$N(R^b)$_2$, -N(R^b)$_2$, -NR^bC(=O)N(R^b)$_2$, -NR^bC(=O)R^a, -NR^bC(=O)OR^a, -NR^bS(=O)$_2R^a$, -C(=O)R^b, -C(=O)OR^b, o -C(=O)N(R^b)$_2$;

Y es -C(R^{30})$_2$- o C(=O);

X^3 es CR^{27} o N;

cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

q es 1, 2, 3 o 4;

cada R^{31} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

cada R^{36} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido,C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^a o -$N(R^b)_2$;

El anillo B es un heterocicloalquilo fusionado, sustituido o no sustituido, de 5 o 6 miembros;

cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_8cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

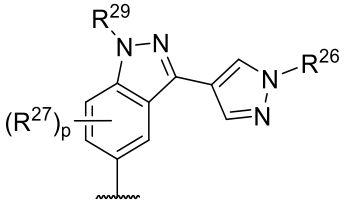
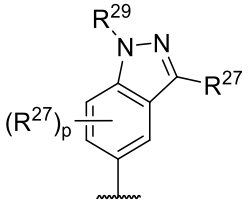
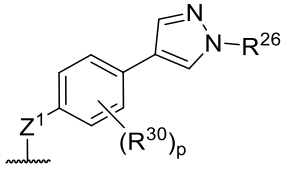
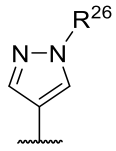
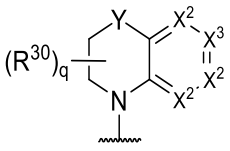
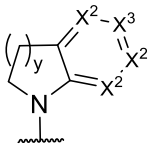
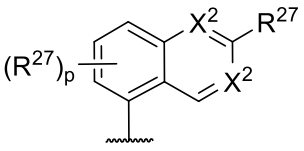
cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00237] Forma de realización 49. El compuesto de la realización 45-48, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que ocupa la región del estante lipofílico (LPF) del bromodominio de CBP/p300 es R^{32}, en el que:

R^{32} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_2-C_6alquenilo sustituido o no sustituido, C_2-C_6alquinilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_{12}cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 12

miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido;

o R^{32} es  ,  ,  ,  ,  ,  , o  ;

es 1 o 2.

Q^1 es NR, O o S;

R^9 es hidrógeno o alquilo C_{1-6} no sustituido;

R^{26} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

X^2 es CR^{30} o N;

X^3 es CR^{27} o N;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno o alquilo C_{1-6} no sustituido;

R^{29} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

Y es -CH^{30}-, -O- o -$N(R_{28})$-,

cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -

$S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, o $-C(=O)N(R^b)_2$;

q es 1, 2, 3 o 4;

o R^{32} es -LC;

L es un alquilo C_1-C_6 sustituido o no sustituido, o un heteroalquilo C_1-C_6 sustituido o no sustituido;

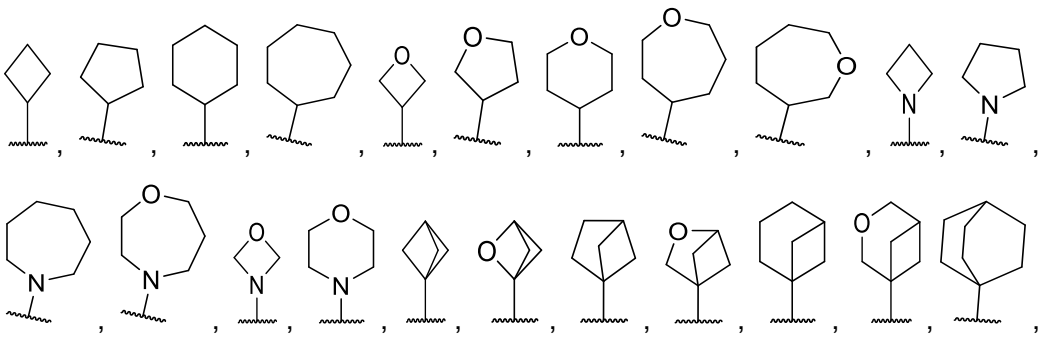
C es C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido;

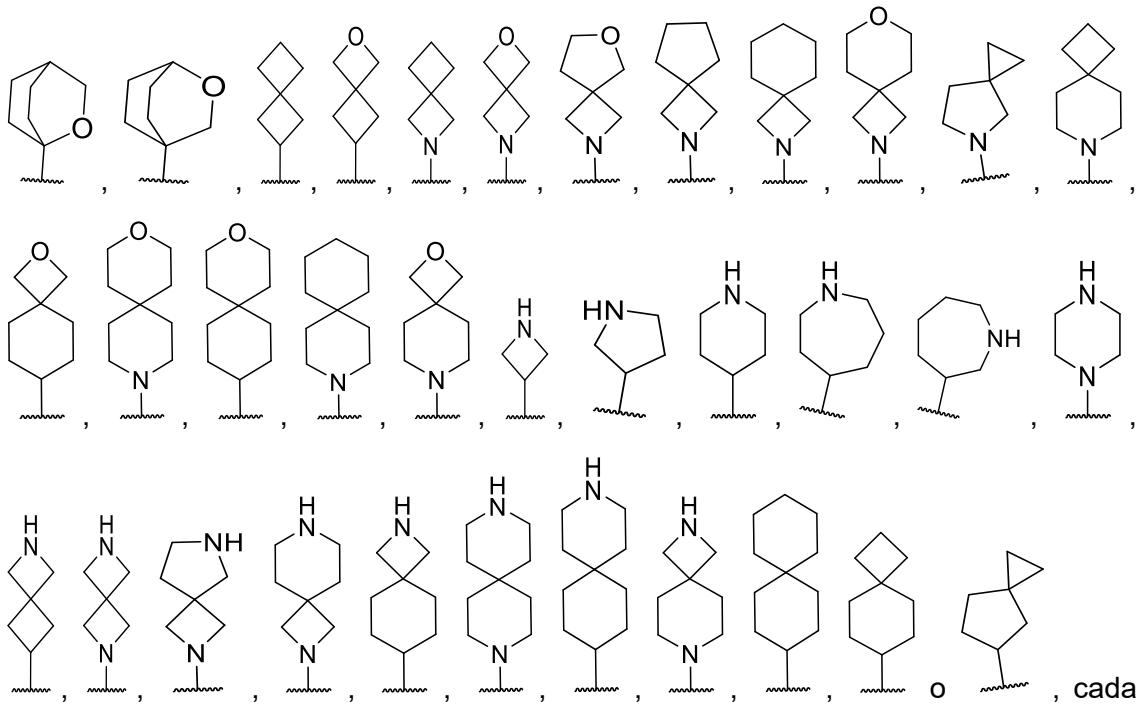
Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_8cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

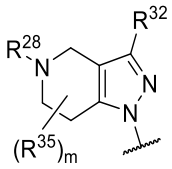
cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

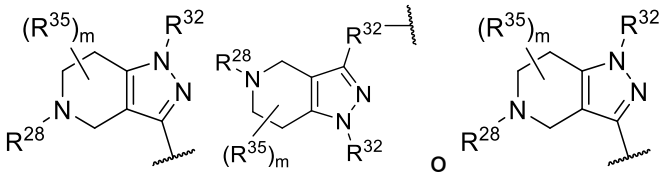
o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00238] Forma de realización 50. El compuesto de cualquiera de las formas de realización 45-49, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que ocupa la región del bucle BC del bromodominio de CBP/p300 es R^{32}, en el que:

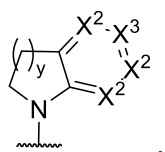
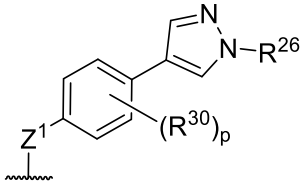
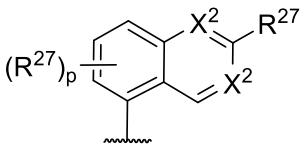
R^{32} es 


o , cada uno de los cuales está sustituido o no.

[00239] Forma de realización 51. El compuesto de cualquiera de las formas de realización 41-50, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende  ,


o .

[00240] Forma de realización 52. El compuesto de la forma de realización 51, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es  , 
o  ;

R^{27} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -OH o -OR^a; y

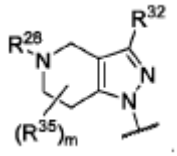
cada R^{27} es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH o -OR^a; y

cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

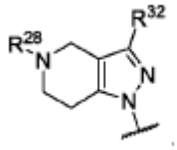
[00241] Forma de realización 53. El compuesto de la forma de realización 52, o una sal o solvato farmacéuticamente aceptable de este, en donde:

cada R^{27} es independientemente hidrógeno, -CH_3, -CH_2CH_3, -F, -CHF_2, -CF_3, -CN, -OH, -OCH_3, ciclopropilo, ciclobutilo, oxetanilo, tetrahidrofurano, tetrahidropiranilo, fenilo, pirazolilo, 1-metilpirazolilo, piridinilo o pirimidinilo.

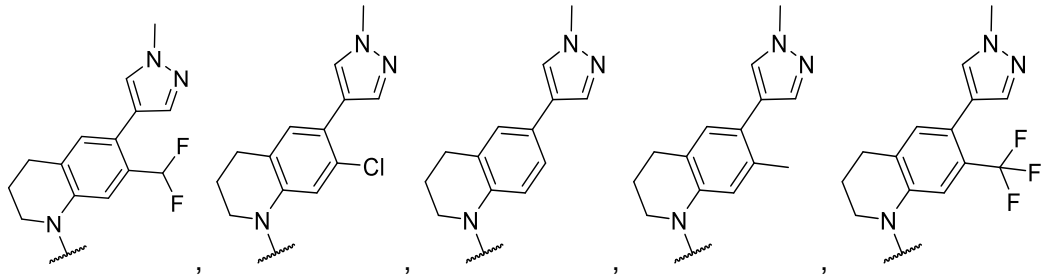
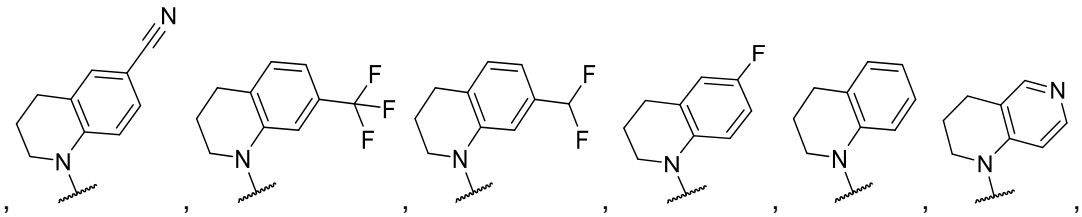
[00242] Forma de realización 54. El compuesto de cualquiera de las formas de realización 51-53, o una sal o solvato farmacéuticamente aceptable de este, en donde

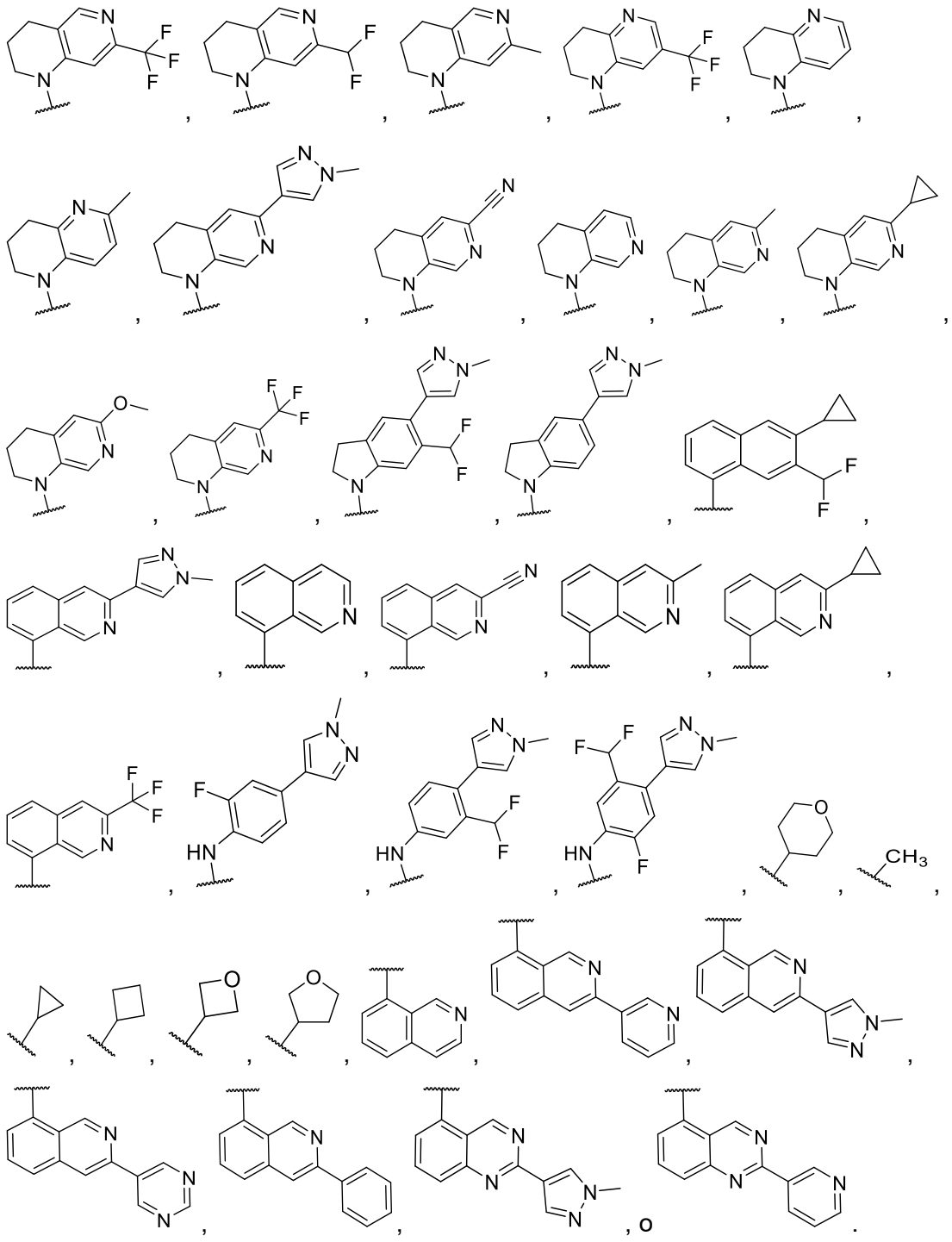


[00243] Forma de realización 55. El compuesto de cualquiera de las formas de realización 51-53, o una sal o solvato farmacéuticamente aceptable de este, en donde

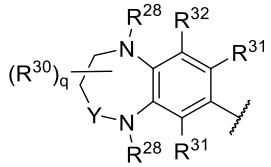


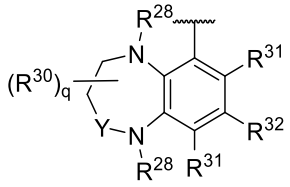
[00244] Forma de realización 56. El compuesto de cualquiera de las formas de realización 51-55, o una sal o solvato farmacéuticamente aceptable de este, en donde

R^{32} es  ,  ,

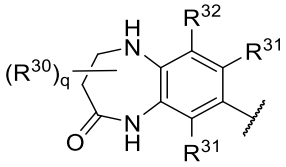
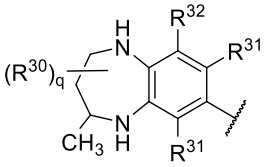
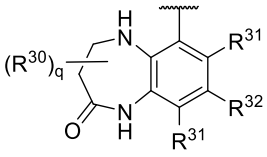
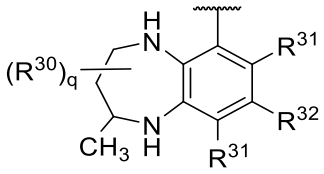


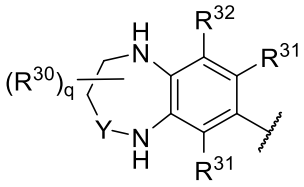
[00245] Forma de realización 57. El compuesto de cualquiera de las formas de realización 41-50, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende



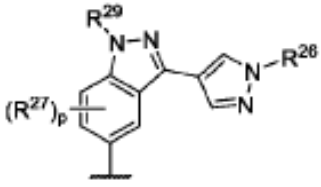
o  .

[00246] Forma de realización 58. El compuesto de la forma de realización 57, o una sal o solvato farmacéuticamente aceptable de este, en donde la porción que comprende un mimético de acetil-lisina comprende:

 ,  ,  o  .

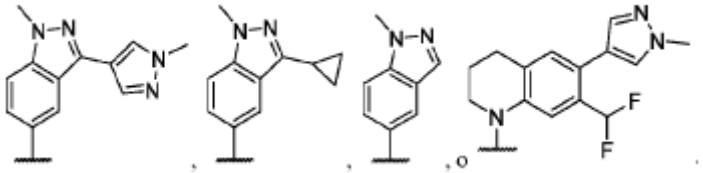
[00247] Forma de realización 59. El compuesto del ejemplo 57, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende  ;

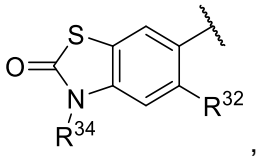
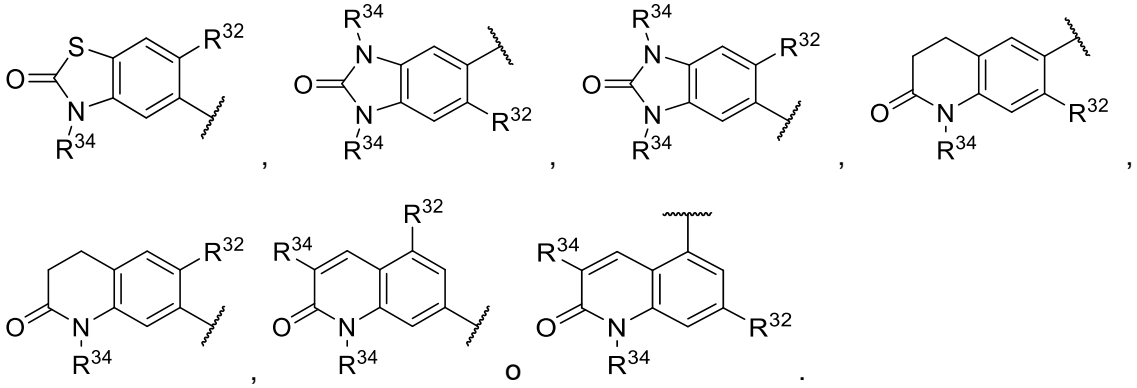
en donde:

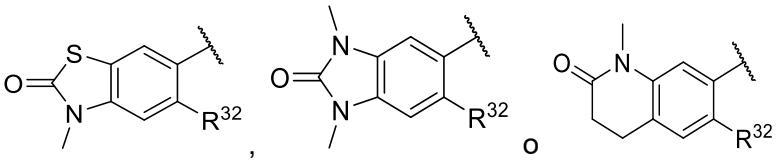
R^{32} es  ; y

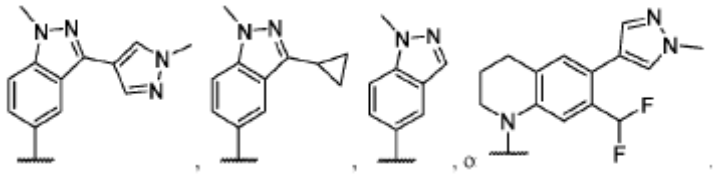
cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$.

[00248] Forma de realización 60. El compuesto de cualquiera de las formas de realización 57-59, o una sal o solvato farmacéuticamente aceptable de este, en donde

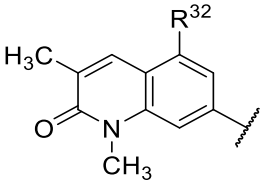
R^{32} es  .

[00249] Forma de realización 61. El compuesto de cualquiera de las formas de realización 41-50, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende  ,  .

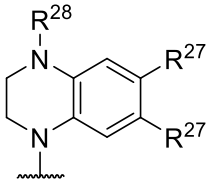
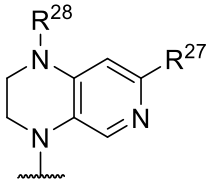
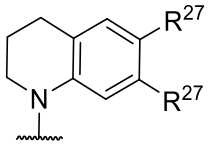
[00250] Forma de realización 62. El compuesto del ejemplo 61, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende  .

[00251] Forma de realización 63. El compuesto de cualquiera de las formas de realización 61-62, o una sal o solvato farmacéuticamente aceptable de este, en donde: R^{32} es  .

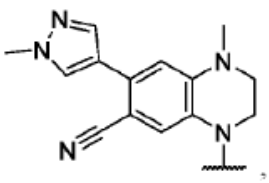
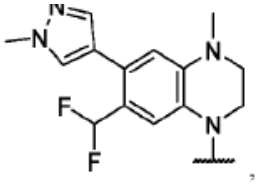
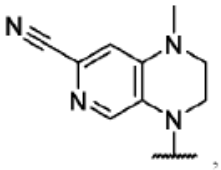
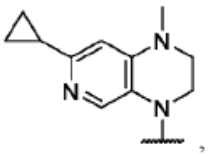
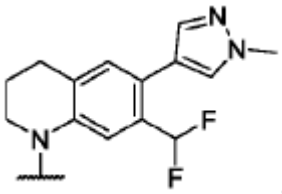
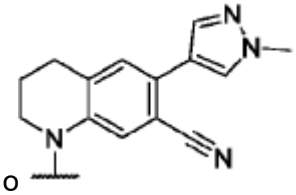
[00252] Forma de realización 64. El compuesto del ejemplo 61, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético

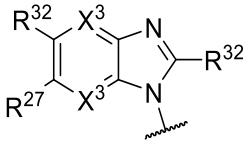
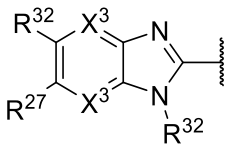
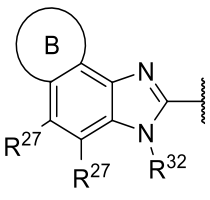
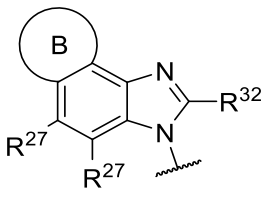
de acetil-lisina comprende:  .

[00253] Forma de realización 65. El compuesto de la forma de realización 61 o 64, o una sal o solvato farmacéuticamente aceptable de este, en donde q es 0.

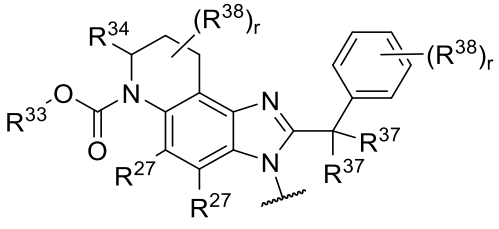
R^{32} es  ,  o  ;

[00254] Forma de realización 66. El compuesto de cualquiera de las formas de realización 61, 62, 64 o 65, o una sal de este farmacéuticamente aceptable, en donde:

R^{32} es  ,  ,  ,  ,  , o  .

[00255] Forma de realización 67. El compuesto de cualquiera de las formas de realización 41-50, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende  ,  ,  o  .

[00256] Forma de realización 68. El compuesto del ejemplo 67, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético

de acetil-lisina comprende  , en el que:

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH, -OR^a o -$N(R^b)_2$;

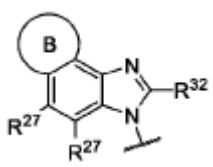
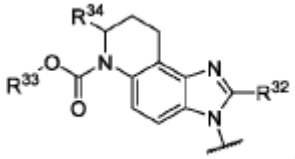
R^{33} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, o C_1-C_6heteroalquilo sustituido o no sustituido;

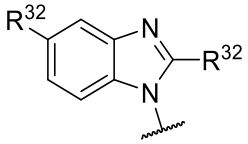
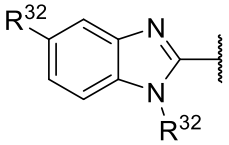
R^{34} es hidrógeno o alquilo C_{1-6} no sustituido;

cada R^{38} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

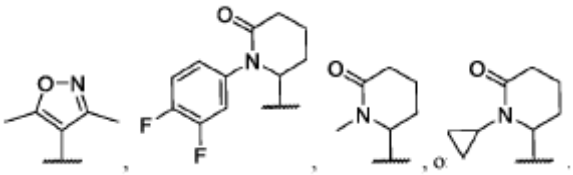
n es 0, 1, 2, 3 o 4;

[00257] Forma de realización 69. El compuesto de la forma de realización 67, o una sal o solvato farmacéuticamente aceptable de este, en donde:

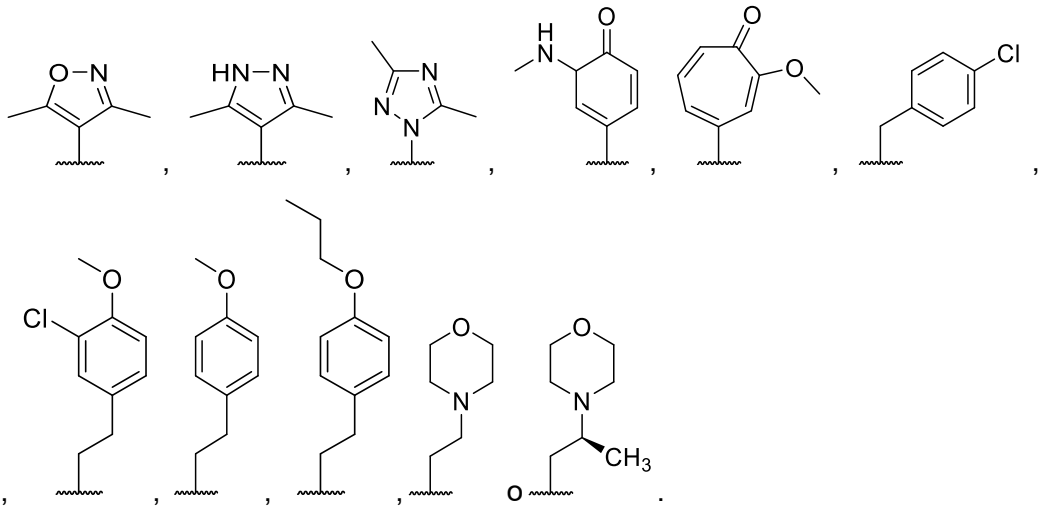
 es 

[00258] Forma de realización 70. El compuesto del ejemplo 67, o una sal o solvato farmacéuticamente aceptable de este, en el que la porción que comprende un mimético de acetil-lisina comprende  o  .

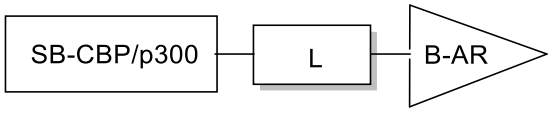
[00259] Forma de realización 71. El compuesto de cualquiera de las formas de realización 67-70, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es 

[00260] Forma de realización 72. El compuesto de cualquiera de las formas de realización 67-70, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es 

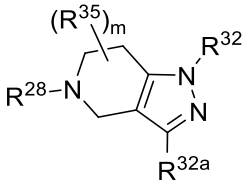
[00261] Forma de realización 73. un compuesto de la Fórmula (I) o una sal de este farmacéuticamente aceptable;



en donde:

SB-CBP/p300 es un ligando silencioso del bromodominio de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300), en el que el ligando de CBP/p300 comprende:

- una porción mimética de acetil-lisina que se une al sitio de unión de acetil-lisina (KAc) del bromodominio de la proteína de unión a CREB humana (CBP) o de la proteína de unión a E1A humana p300 (p300) (CBP/p300) y tiene la siguiente estructura:



R^{28} es -C(=O)CH_3, -C(=O)CH_2CH_3, -C(=O)NH_2, -C(=O)NH(CH_3); o -C(=O)NH(CH_2CH_3);

R^{32} es una porción que ocupa la región del bucle BC del bromodominio de CBP/p300;

R^{32a} es una porción que ocupa la región del estante lipofílico (LPF) del bromodominio de

CBP/p300;

cada R^{35} es independientemente hidrógeno, C_1-C_4alquilo, o C_1-C_4fluoroalquilo;

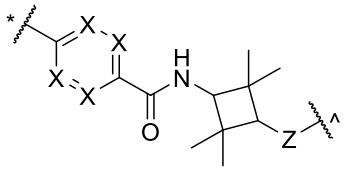
m es 0, 1, 2, 3 o 4;

L es un ligador opcional;

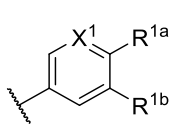
donde L está unido covalentemente al grupo R^{32}, o en la posición ocupada por R^{32}, o el grupo R^{32a};

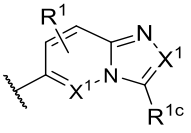
El B-AR es un ligando del receptor de andrógenos (AR), en el que el B-AR comprende:

- un grupo de cabeza que ocupa el dominio de unión al ligando (LBD) del AR y está unido covalentemente a un núcleo con una porción de cola unida covalentemente a la porción del núcleo; donde B-AR tiene la estructura de la fórmula (D):



, Fórmula (D);

donde el grupo de cabeza es 

o 

, y el grupo de cabeza está unido covalentemente a Z en la posición (^), y L está unido en la posición *;

Z es -O-, -NH- o -N(C_1-C_4alquilo)-;

X^1 es CR^1 o N;

R^{1a} es -CN, -NO_2, -C(=O)R^5, -C(=O)OR^5, o -C(=O)$N(R^5)_2$;

R^{1b} es hidrógeno, halógeno, C_1-C_4alquilo sustituido o no sustituido, C_1-C_4fluoroalquilo, -CN, -OH o -OR^4;

R^{1c} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo o -CN;

cada R^1 es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH o -OR^4;

cada X es independientemente -CR^3- o -N-;

cada R^3 es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH, -OR^4 o -$N(R^5)_2$.

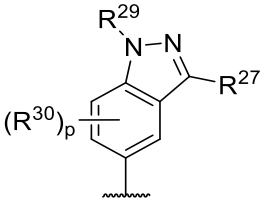
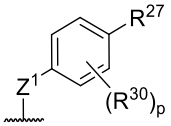
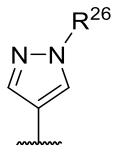
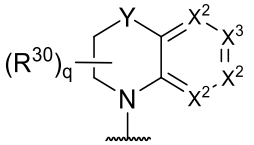
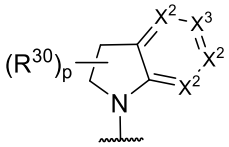
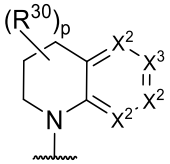
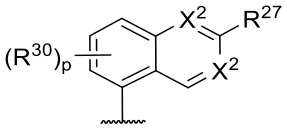
Cada R^4 es independientemente sustituido o no sustituido C_1-C_4alquilo, o C_1-C_4fluoroalquilo;

cada R^5 es independientemente hidrógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo; y

cada s es 1, 2 o 3.

[00262] Forma de realización 74. El compuesto de la forma de realización 73, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es hidrógeno, alquilo C_1-C_6 sustituido o no sustituido, cicloalquilo C_3-C_{12} sustituido o no sustituido, o heterocicloalquilo de 3 a 12 miembros sustituido o no sustituido;

R^{32a} es  ,  ,  ,  ,  ,  o  ;

al menos un X^2 es -CR^{30}- y como máximo dos X^2 son -N-;

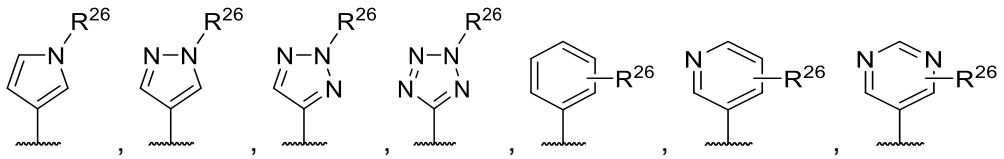
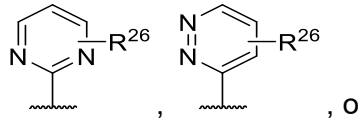
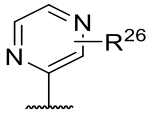
Z^1 es -NR^c- o -O-;

R^4 es: hidrógeno; o alquilo C_{1-6};

R^{26} es hidrógeno, C_1-C_4alquilo sustituido o no sustituido, C_1-C_4fluoroalquilo, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

X^3 es CR^{27} o N;

R^{27} es hidrógeno, halógeno, C_1-C_4alquilo sustituido o no sustituido, C_1-C_4fluoroalquilo, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, fenilo sustituido o no sustituido, heteroarilo monocíclico sustituido o no sustituido, -CN, -OH, -OR^a, -$N(R^b)_2$, -$NR^bC(=O)R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

o R^{27} es  ,  , o  ;

p es 0, 1, 2 o 3;

R^{29} es hidrógeno, C_1-C_4alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

Y es -CH^{30}-, -O- o -$N(R_{28})$-,

cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo,

C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -OH o -OR^a;

q es 1, 2, 3 o 4;

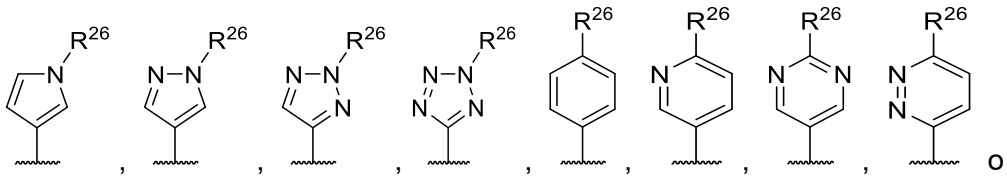
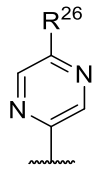
Cada R^a es independientemente C_1-C_4alquilo, C_1-C_6fluoroalquilo, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 6 miembros heterocicloalquilo, fenilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

Cada R^b es independientemente hidrógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, C_3-C_6cicloalquilo sustituido o no sustituido, monocíclico de 3 a 6 miembros heterocicloalquilo, fenilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

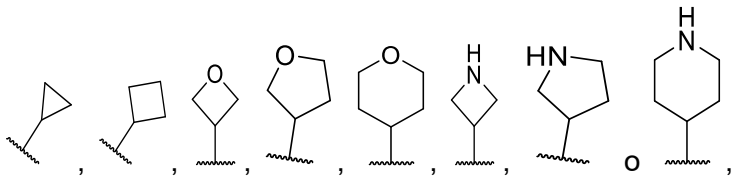
o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

[00263] Forma de realización 75. El compuesto de cualquiera de las formas de realización 73-74, o una sal o solvato farmacéuticamente aceptable de este, en donde:

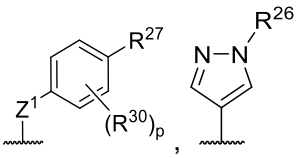
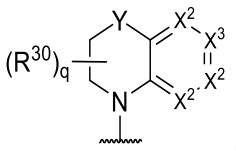
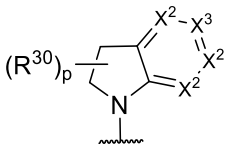
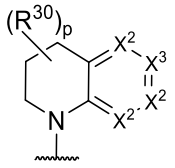
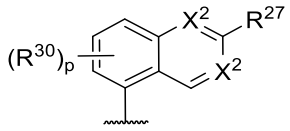
R^{27} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, fenilo sustituido o no sustituido, heteroarilo monocíclico de 5 o 6 miembros sustituido o no sustituido, -CN, -OH, -OR^a, -$N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

o R^{27} es  o  ;

[00264] Forma de realización 76. El compuesto de cualquiera de las formas de realización 73-75, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es  , cada uno de los cuales no está sustituido o está sustituido con F, Cl, Br, -CH_3, -CD_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -CN, -$C(=O)CH_3$, -$C(=O)CH_2CH_3$, -$C(=O)CH_2F$, -$C(=O)CHF_2$, -$C(=O)CF_3$, -$C(=O)CH_2CH_2F$, -$C(=O)CH_2CHF_2$, -$C(=O)CH_2CF_3$, -

$C(=O)CD_3$, o $-SO_2CH_3$, $-SO_2CH_2CH_3$, $-SO_2CD_3$, o $-SO_2CH_2CD_3$.

R^{32a} es  , ,  ,  ,  o  ;

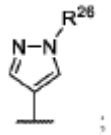
al menos un X^2 es $-CR^{30}-$ y como máximo dos X^2 son -N-;

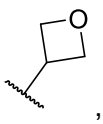
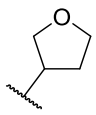
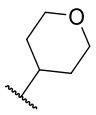
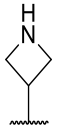
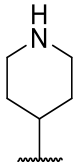
cada R^{27} es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -OH o $-OR^a$; y

cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

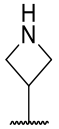
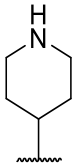
[00265] Forma de realización 77. El compuesto de cualquiera de las formas de realización 73-76, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{27} es hidrógeno, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2(CH_3)_2$, $-(CH_3)_3$, -F, $-CHF_2$, $-CF_3$, -CN, -OH, $-OCH_3$, ciclopropilo, ciclobutilo, oxetanilo, tetrahidrofurano, tetrahidropiranilo, fenilo no sustituido o sustituido, pirazolilo no sustituido o sustituido, piridinilo no sustituido o sustituido, o pirimidinilo no sustituido o sustituido; o

R^{27} es  ;

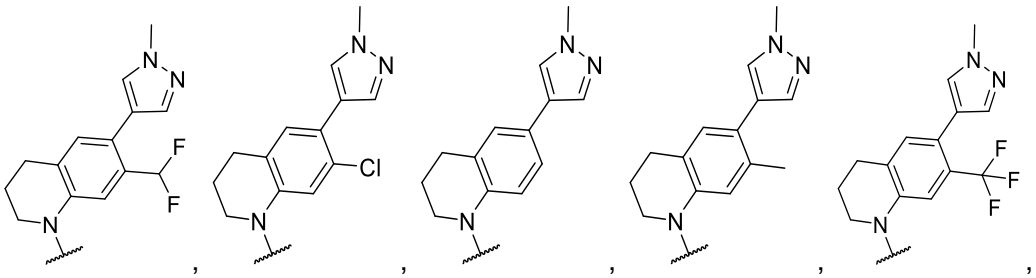
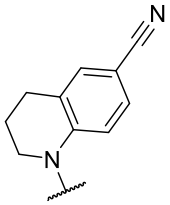
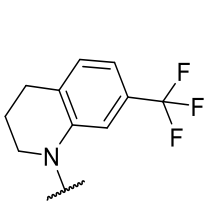
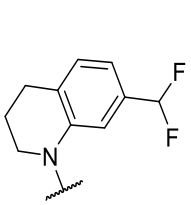
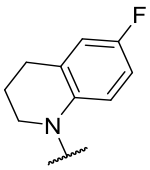
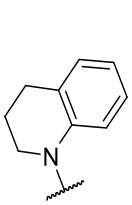
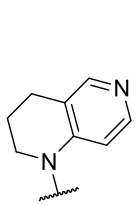
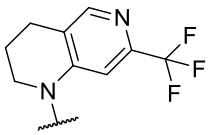
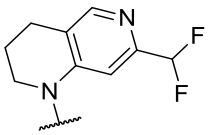
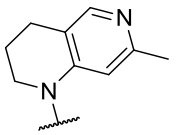
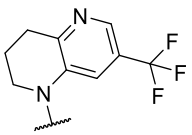
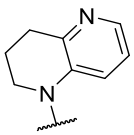
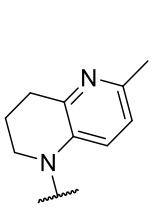
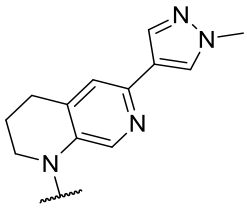
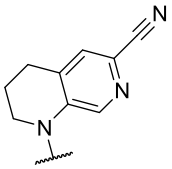
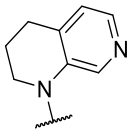
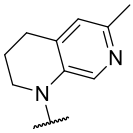
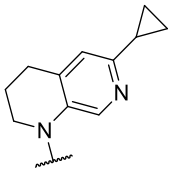
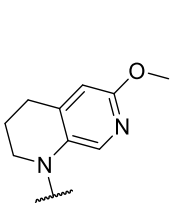
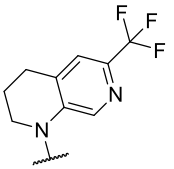
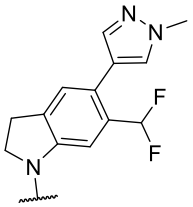
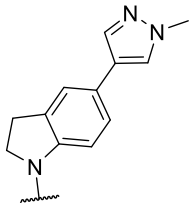
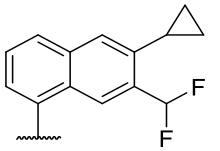
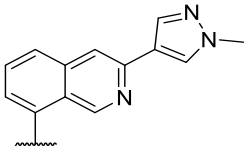
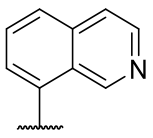
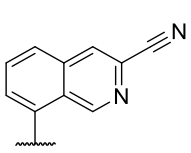
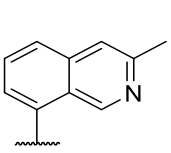
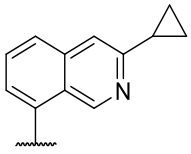
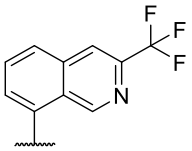
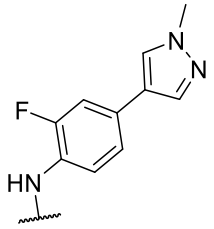
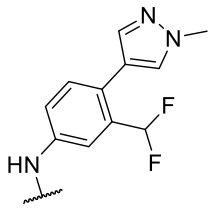
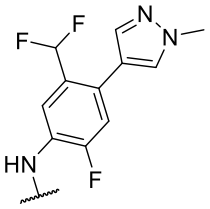
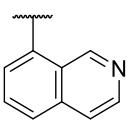
R^{32} es  ,  ,  ,  ,  o  , cada uno de los cuales no está sustituido o está sustituido con F, Cl, Br, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, CN, $-C(=O)CH_3$, $-C(=O)CH_2F$, $-C(=O)CHF_2$, $-C(=O)CF_3$, $-C(=O)CD_3$.

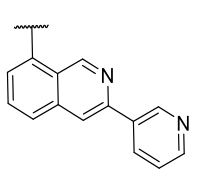
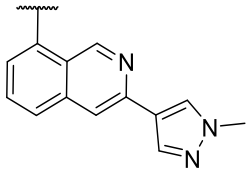
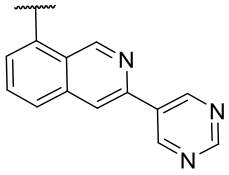
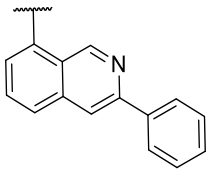
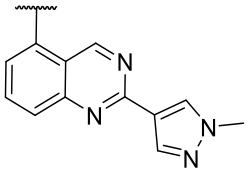
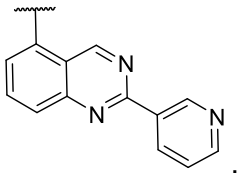
[00266] Forma de realización 78. El compuesto de la forma de realización 77, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es  ,  o  , donde el ligador opcional está unido covalentemente al

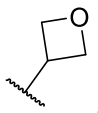
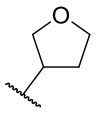
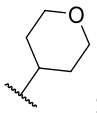
nitrógeno del grupo R^{32};

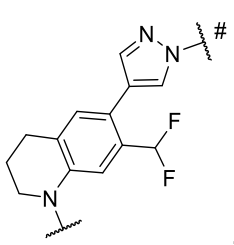
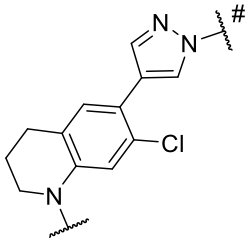
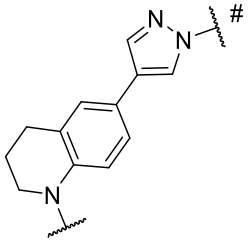
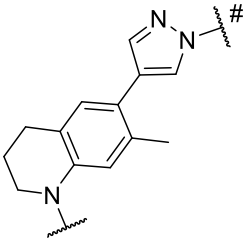
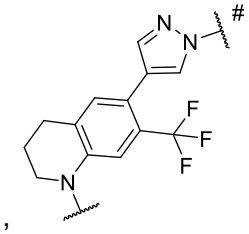
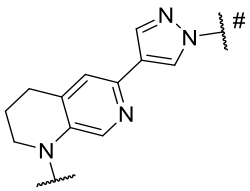
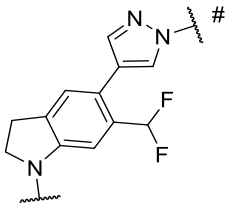
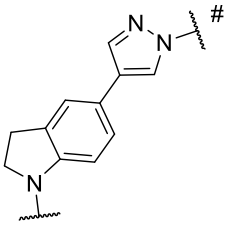
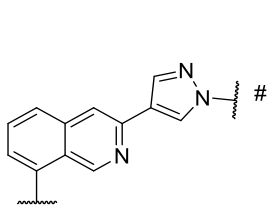
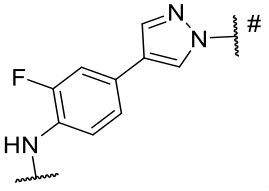
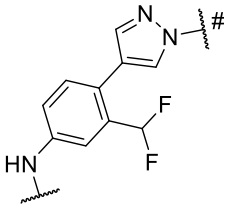
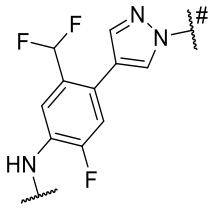
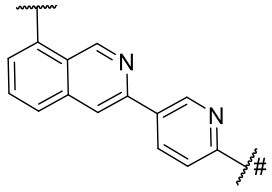
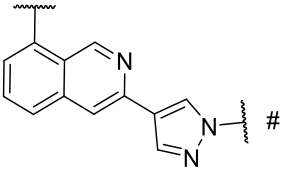
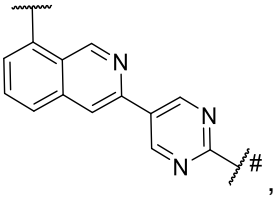
o R^{32} está ausente y L está unido covalentemente a la porción mimética de acetil-lisina en la posición ocupada por R^{32}; y

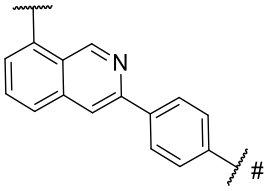
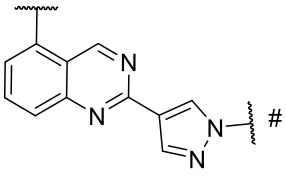
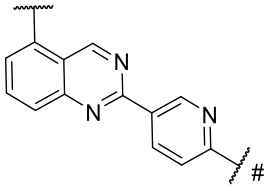
R^{32a} es  , , , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 


,

,

,

,

, o

.

[00267] Forma de realización 79. El compuesto de cualquiera de las formas de realización 73-78, o una sal o solvato farmacéuticamente aceptable de este, en donde:

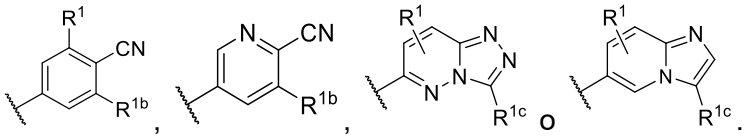
R^{32} es

,

o

;

R^{32a} es

,

,

,

,

,

,

,

,

,

,

,

,

,

,

.




; en donde

 es el punto de unión al ligador opcional.

[00268] Forma de realización 80. El compuesto de la forma de realización 73, o una sal o solvato farmacéuticamente aceptable de este, en donde el grupo principal es:

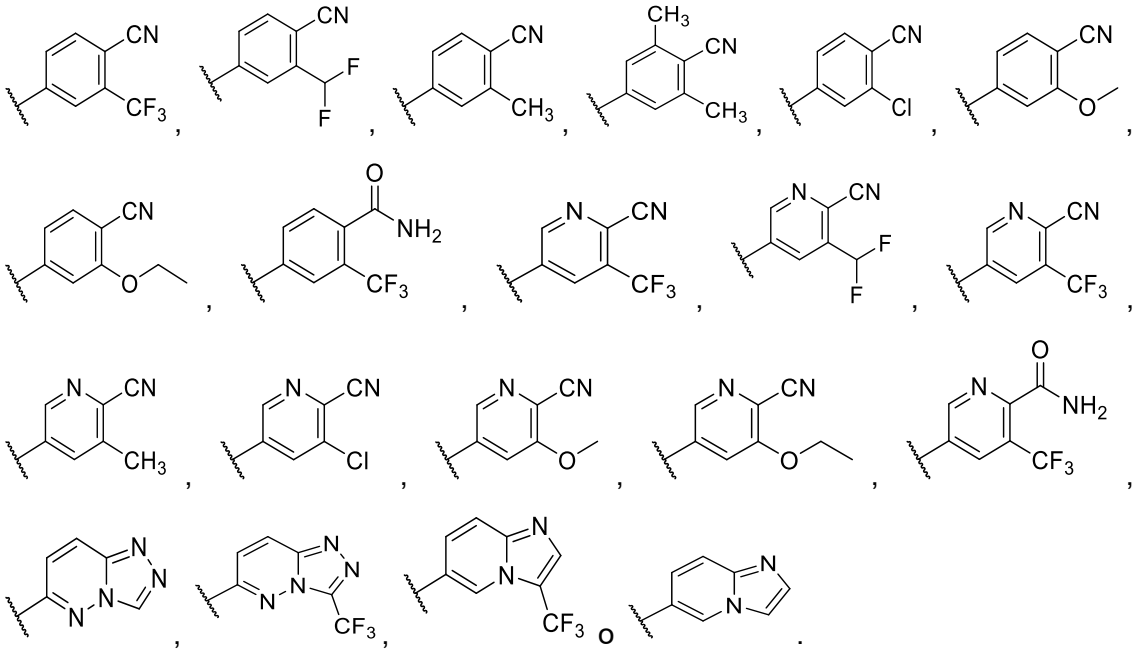


R^{1b} es hidrógeno, F, Cl, Br, I, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-O\ CH_2CH_3$, $-OCD_3$, $-OCH_2CD_3$ o -CN;

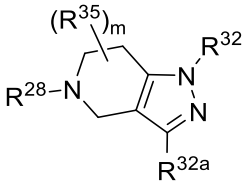
cada R^{1c} es hidrógeno, F, Cl, Br, $-CH_3$, $-CD_3$, $-CH_2F$, $-CHF_2$ o $-CF_3$;

Cada R^1 es independientemente hidrógeno, F, Cl, Br, I, $-CH_3$, $-CD_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCF_3$, $-OCH_3$, $-OCD_3$ o $-OCH_2CH_3$.

[00269] Forma de realización 81. El compuesto de la forma de realización 73 o una sal o solvato farmacéuticamente aceptable de este, en donde el grupo principal se selecciona de:



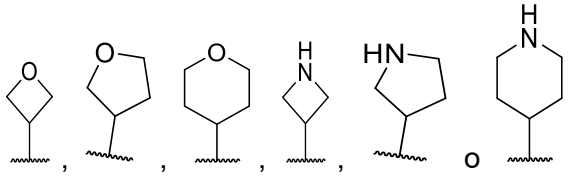
[00270] Forma de realización 82. El compuesto de cualquiera de las formas de realización 14-81, o una sal o solvato farmacéuticamente aceptable de este, en donde:

SB-CBP/p300 tiene la estructura: 

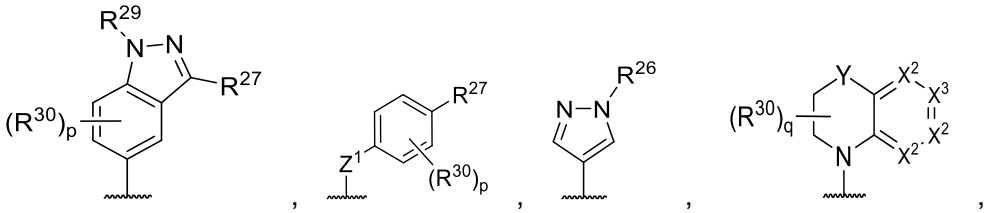
R^{28} es $-C(=O)CH_3$ o $-C(=O)NH(CH_3)$;

cada R^{35} es independientemente hidrógeno, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

m es 0, 1 o 2;

R^{32} es  , cada uno de los cuales no está sustituido o está sustituido con F, $-CH_3$, $-CH_2F$, $-CHF_2$ o $-CF_3$;

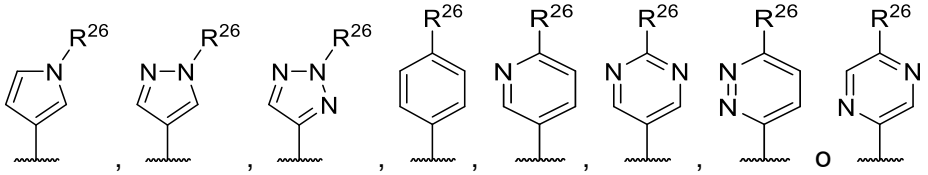
o R^{32} está ausente y el ligador opcional está unido covalentemente a la porción mimética de acetil-lisina en la posición ocupada por R^{32};

R^{32a} es  ;

al menos un X^2 es $-CR^{30}-$ y como máximo dos X^2 son -N-;

R^{26} es hidrógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, C_3-C_6cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 6 miembros sustituido o no sustituido;

R^{27} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 6 miembros sustituido o no sustituido, fenilo sustituido o no sustituido, heteroarilo monocíclico de 5 o 6 miembros sustituido o no sustituido, -CN, -OH, $-OR^a$ o $-N(R^b)_2$;

o R^{27} es  ;

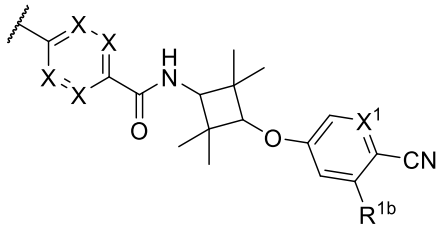
cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo,

-CN, -OH o -OR^a;

R^{13} es alquil C_1-C_4;

cada R^b es independientemente: hidrógeno; o alquilo C_{1-6};

donde L está unido covalentemente al grupo R^{32}, o en la posición ocupada por R^{26}, o en la posición ocupada por R^{27};

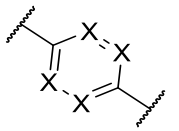
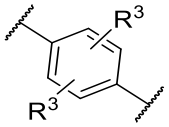
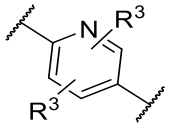
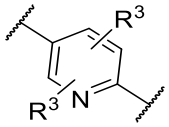
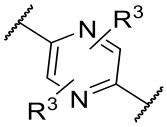
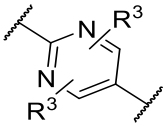
B-AR tiene la estructura:  ;

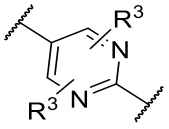
cada X es independientemente -CR^3- o -N-;

X^1 es CR^1 o N;

R^{1b} es hidrógeno, F, Cl, -CH_3, -CH_2F, -CHF_2, -CF_3 o -OCF_3;

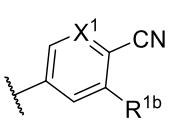
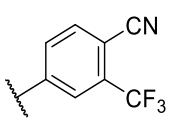
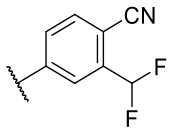
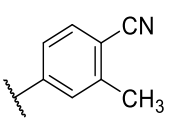
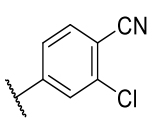
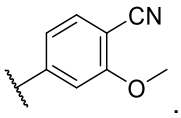
R^1 es hidrógeno, F, Cl, -CH_3, -CH_2F, -CHF_2 o -CF_3;

 es  ,  ,  ,  , 

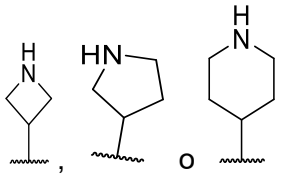
o  ;

cada R^3 es independientemente hidrógeno, F, Cl, Br, -CH_3, -CH_2F, -CHF_2, -CF_3, -OH, -OCF_3, -OCH_3 o -CN.

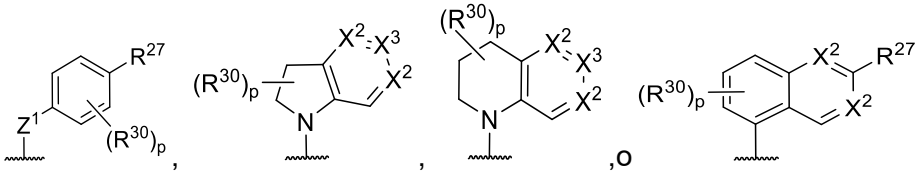
[00271] Forma de realización 83. El compuesto de la forma de realización 82, o una sal o solvato farmacéuticamente aceptable de este, en donde:

 es  ,  ,  ,  o  .

[00272] Forma de realización 84. El compuesto de cualquiera de las formas de realización 82-83, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es  , donde el ligador opcional está unido covalentemente al nitrógeno del grupo R^{32};

o R^{32} está ausente y el ligador opcional está unido covalentemente a la porción mimética de acetil-lisina en la posición ocupada por R^{32};

R^{32a} es  ;

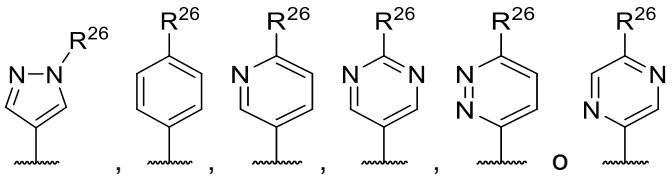
al menos un X^2 es $-CR^{30}-$ y como máximo dos X^2 son -N-;

X1 es CR^{27} o N;

Q^1 es NH u O;

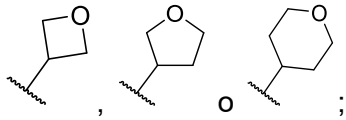
R^{26} es hidrógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, C_3-C_6cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 6 miembros sustituido o no sustituido;

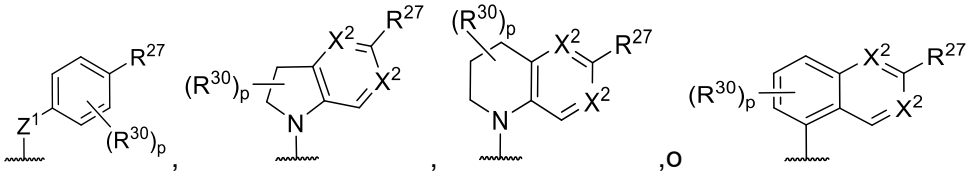
R^{27} es hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 6 miembros sustituido o no sustituido, fenilo sustituido o no sustituido, heteroarilo monocíclico de 5 o 6 miembros sustituido o no sustituido, -CN, -OH, $-OR^a$ o $-N(R^b)_2$;

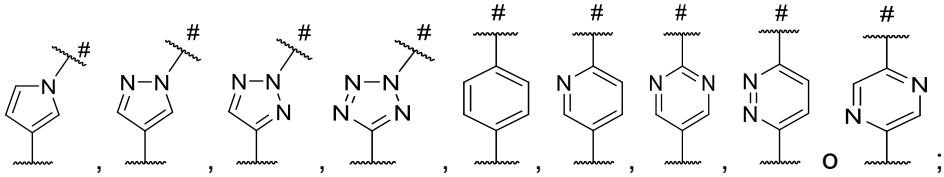
o R^{27} es  ; y

Cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH o $-OR^a$.

[00273] Forma de realización 85. El compuesto de cualquiera de las formas de realización 82-84, o una sal o solvato farmacéuticamente aceptable de este, en donde:

R^{32} es  ;

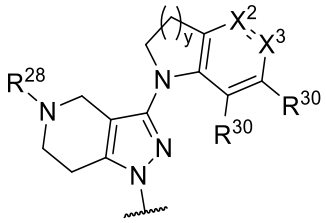
R^{32a} es  ;

R^{27} es  ;

Q^1 es NH u O;

 es el punto de unión al ligador opcional.

[00274] Forma de realización 86. El compuesto de cualquiera de las formas de realización 1-81, o una sal o solvato farmacéuticamente aceptable de este, en donde SB-CBP/p300 tiene la estructura de la Fórmula (IIIb):



Fórmula (IIIb)

en donde:

X^2 es CR^{30} o N;

X^3 es CR^{27} o N;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -$C(=O)R^b$, o -$C(=O)N(R^b)_2$;

cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_4alquilo, C_1-C_4fluoroalquilo, -CN, -OH o -OR^a;

es 1 o 2.

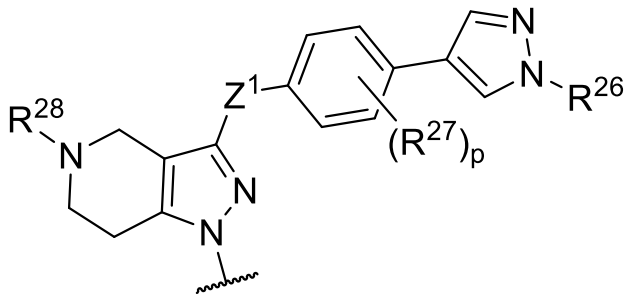
Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo

monocíclico;

Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

[00275] Forma de realización 87. El compuesto de cualquiera de las formas de realización 1-81, o una sal o solvato farmacéuticamente aceptable de este, en donde SB-CBP/p300 tiene la estructura de la Fórmula (IIIc):



Fórmula (IIIc)

en donde:

R^{26} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -$C(=O)R^a$, o -$C(=O)N(R^b)_2$;

Q^1 es NR, O o S;

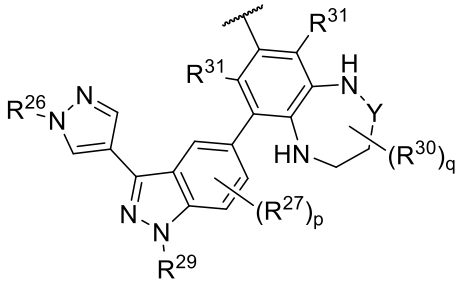
R^9 es hidrógeno o alquilo C_{1-6} no sustituido;

Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo monocíclico;

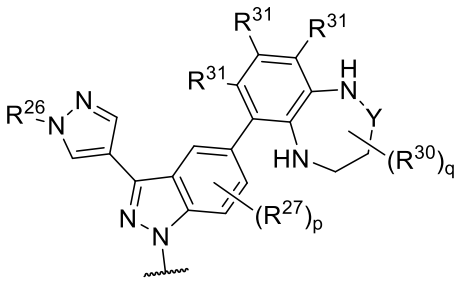
Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

[00276] Forma de realización 88. El compuesto de cualquiera de las formas de realización 14-81, o una sal o solvato farmacéuticamente aceptable de este, que tiene una estructura de fórmula (IIId-I) o (IIId-2):



Fórmula (IIId-1)



o Fórmula (IIId-2)

en donde:

R^{26} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -$OC(=O)N(R^b)_2$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{29} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

cada R^{30} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

q es 1, 2, 3 o 4;

cada R^{31} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, $OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)NR^b$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)_2$;

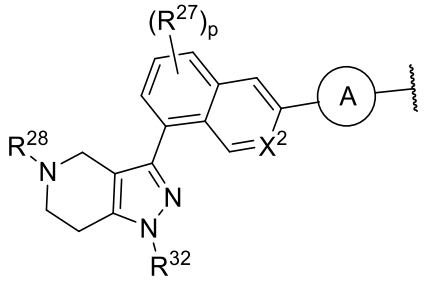
Y es -$C(R^{30})_2$- o C(=O);

Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo monocíclico;

Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

[00277] Forma de realización 89. El compuesto de cualquiera de las formas de realización 1-81, o una sal o solvato farmacéuticamente aceptable de este, en donde SB-CBP/p300 tiene la estructura de la Fórmula (IIIc):



Fórmula (IIIc)

en donde:

X^2 es CR^{27} o N;

cada R^{27} es independientemente hidrógeno, halógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, $-NO_2$, -OH, $-OR^a$, $OC(=O)R^a$, $-OC(=O)N(R^b)_2$, $-OC(=O)OR^a$, $-OC(=O)N(R^b)_2$, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2N(R^b)_2$, $-N(R^b)_2$, $-NR^bC(=O)N(R^b)_2$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^a$, $-NR^bS(=O)_2R^a$, $-C(=O)R^b$, $-C(=O)OR^b$, o $-C(=O)N(R^b)_2$;

p es 0, 1, 2 o 3;

R^{28} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, $-C(=O)R^b$, o $-C(=O)N(R^b)_2$;

R^{32} es hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, o heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido;

El anillo A está ausente o sustituido o no sustituido C_3-C_8cicloalquilo, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido;

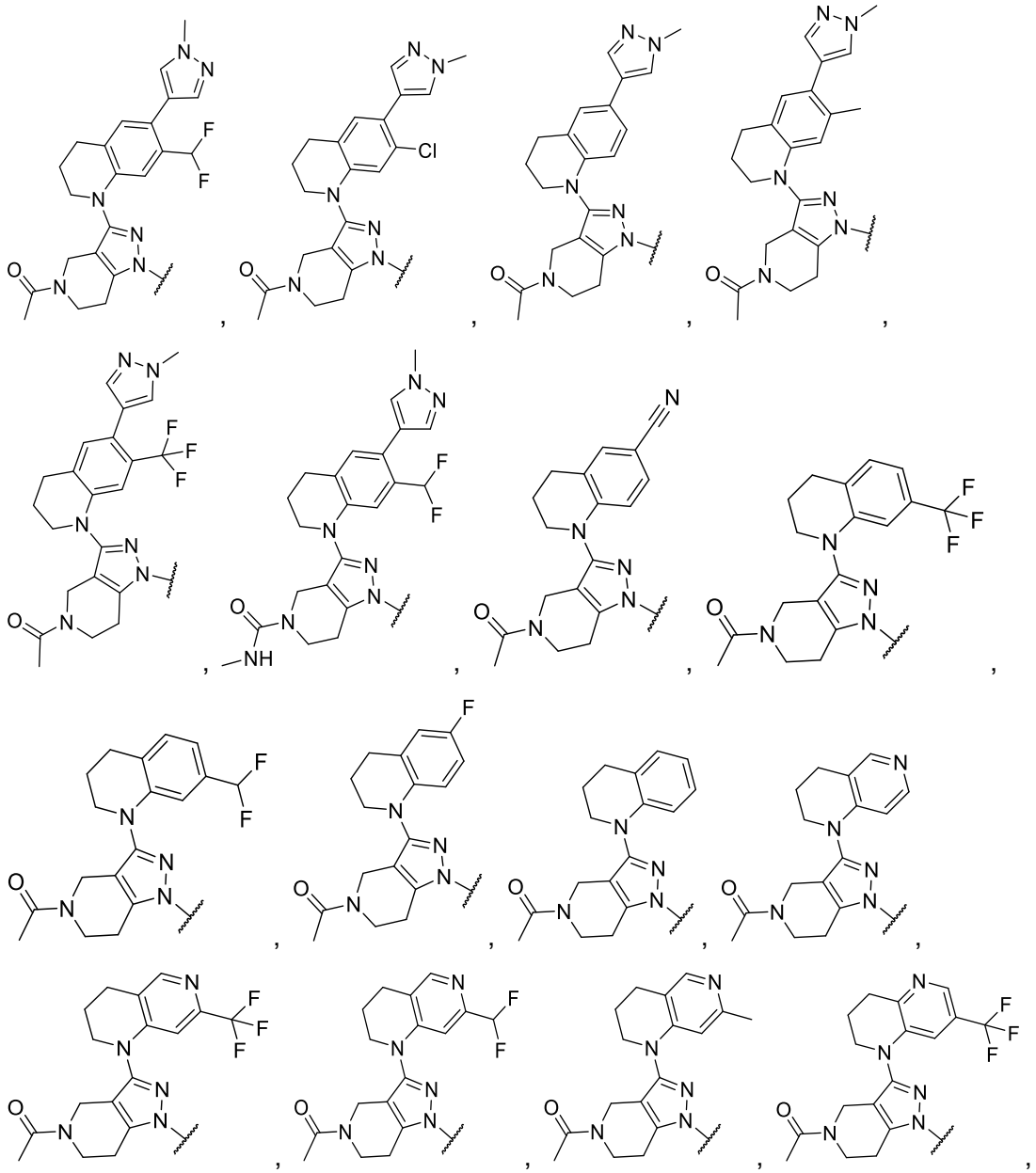
Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_6cicloalquilo, sustituido o no sustituido heterocicloalquilo monocíclico de 3 a 8 miembros, sustituido o no sustituido arilo, sustituido o no sustituido heteroarilo monocíclico;

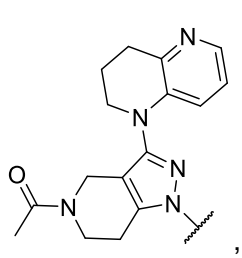
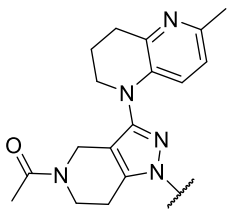
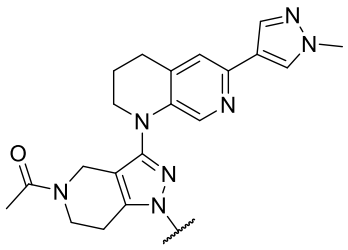
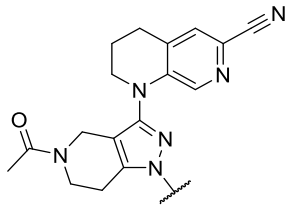
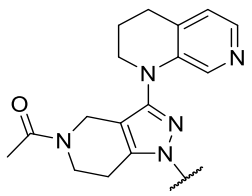
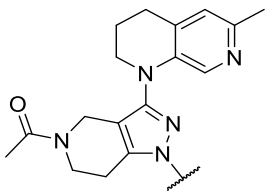
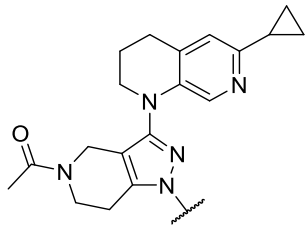
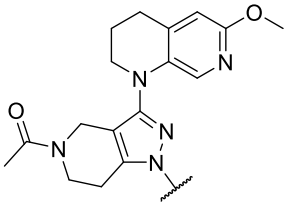
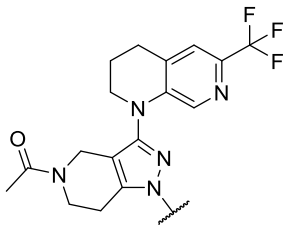
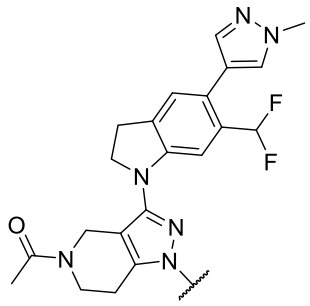
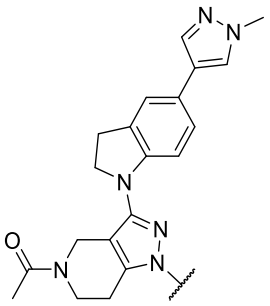
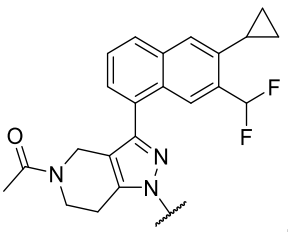
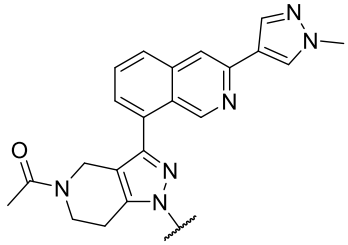
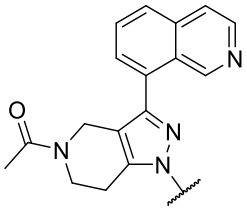
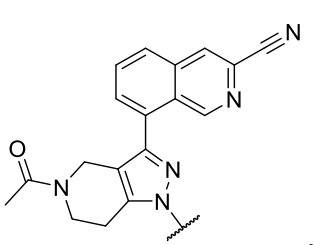
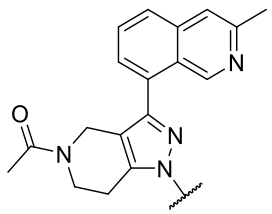
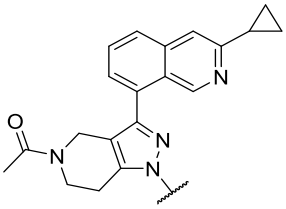
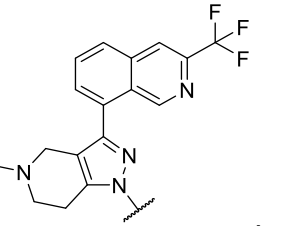
Cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_6cicloalquilo sustituido o no sustituido, heterocicloalquilo monocíclico de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo

monocíclico sustituido o no sustituido;

o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N sustituido o no sustituido.

[00278] Forma de realización 90. El compuesto de cualquiera de las formas de realización 14-89, o una sal o solvato farmacéuticamente aceptable de este, en donde SB-CBP/p300 tiene una de las siguientes estructuras:

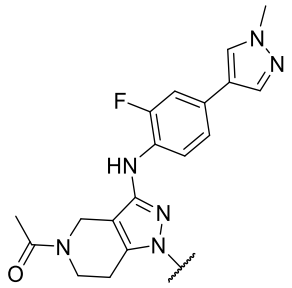
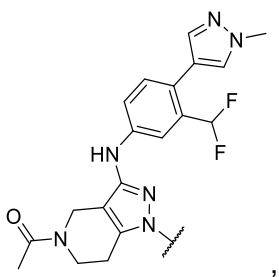
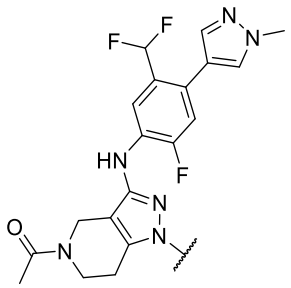
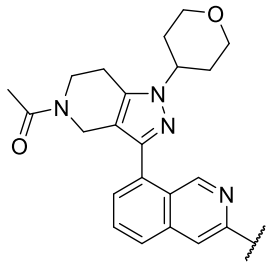
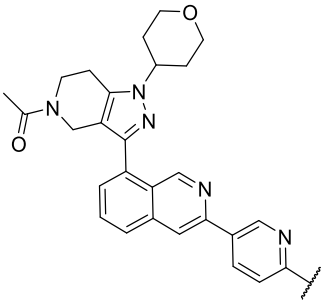
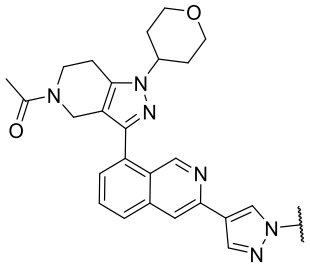
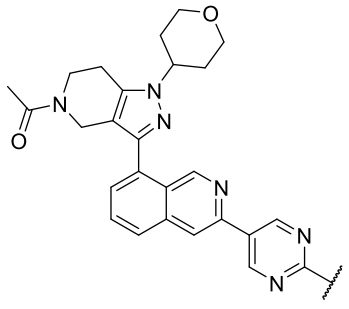
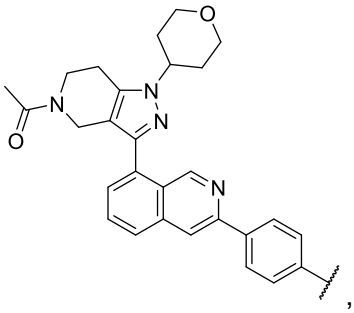
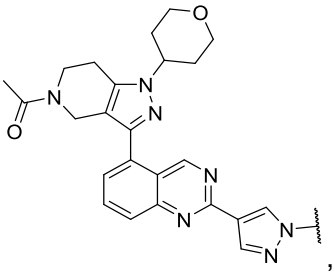
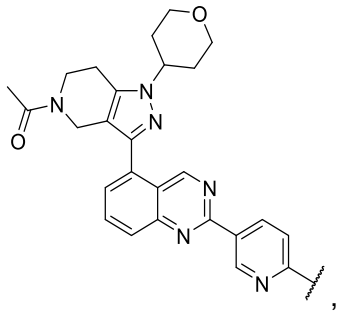
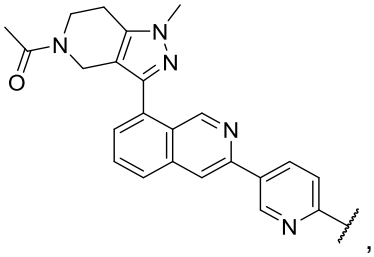
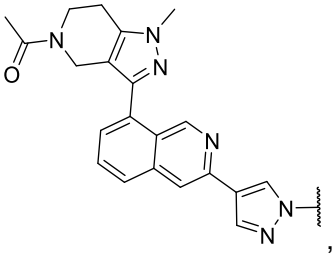
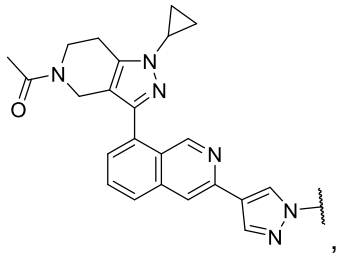
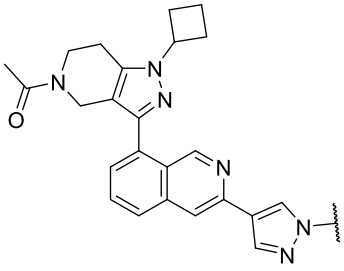
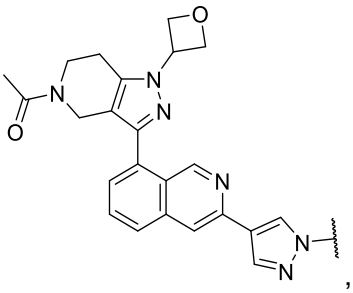


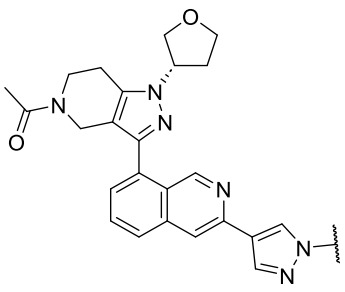
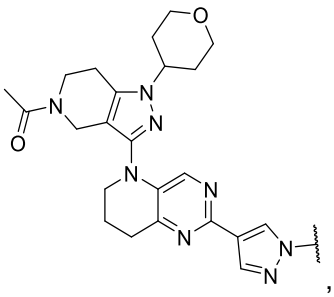
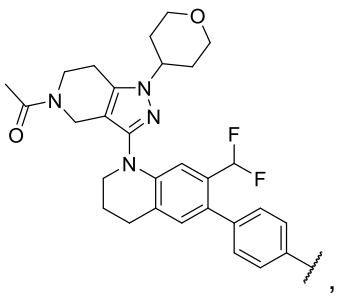
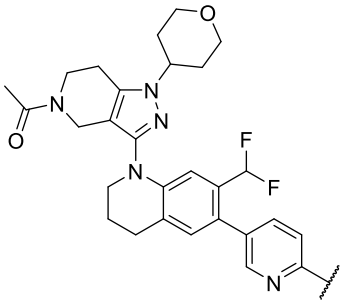
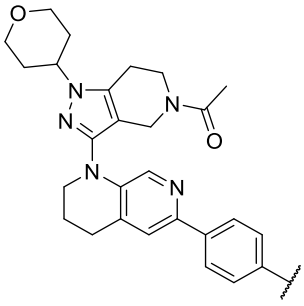
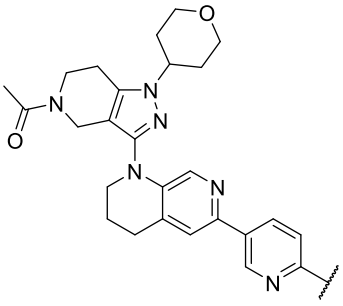
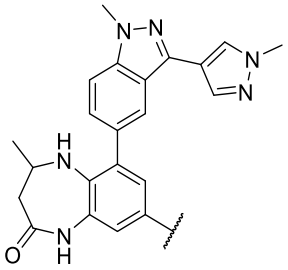
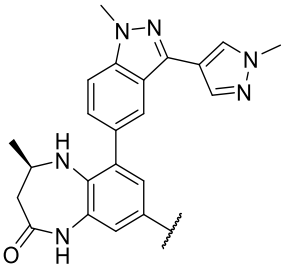
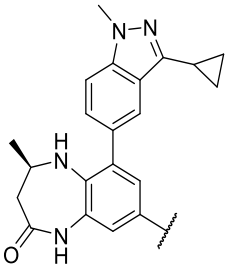
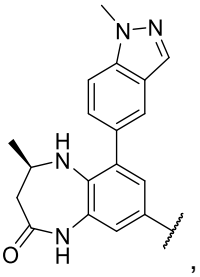
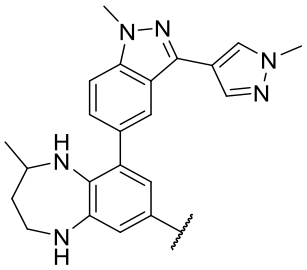
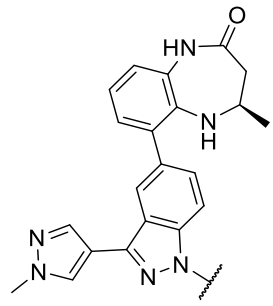
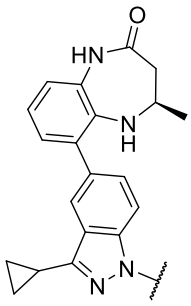
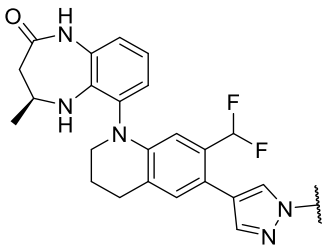
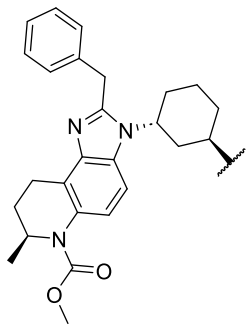
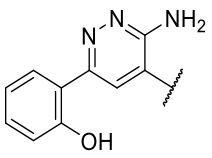
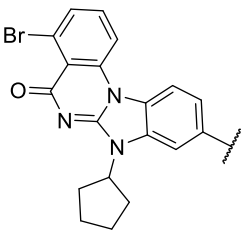

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

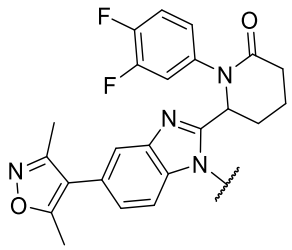
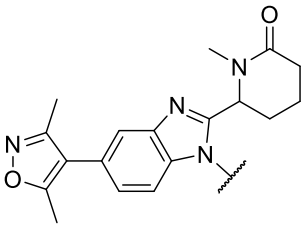
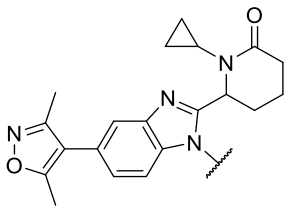
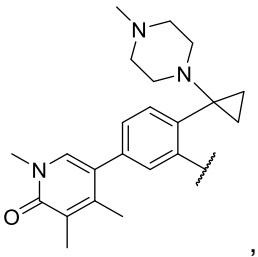
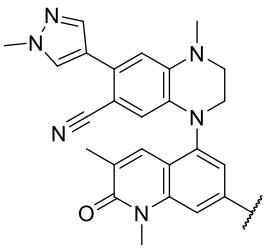
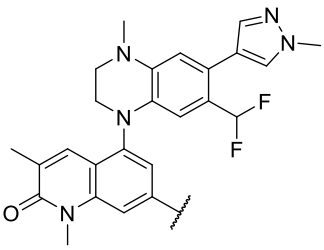
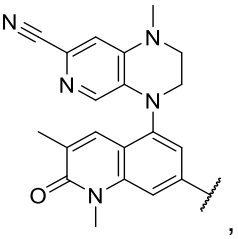
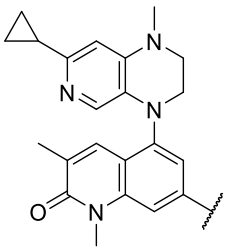
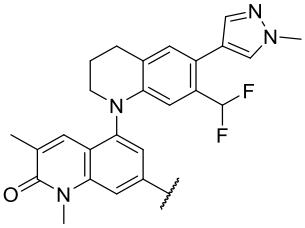
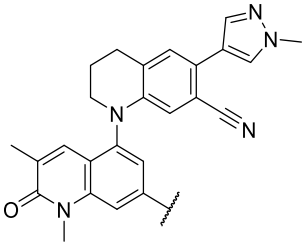
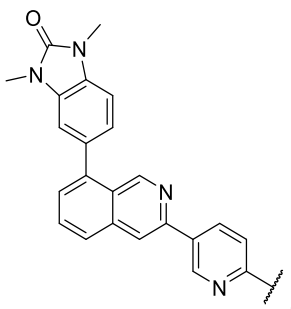
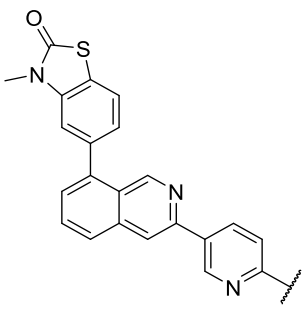
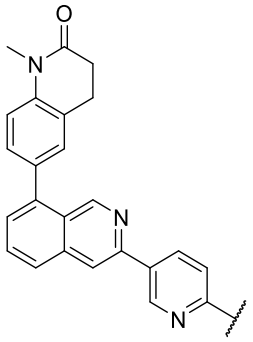
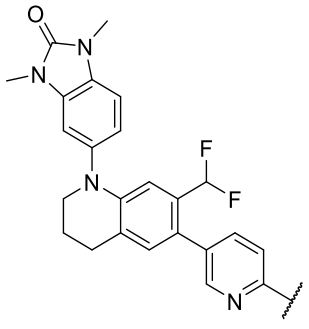
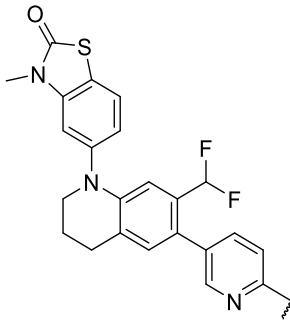
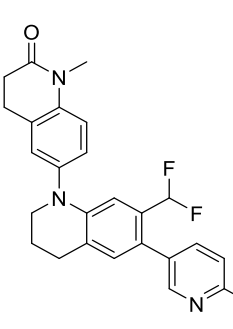
,

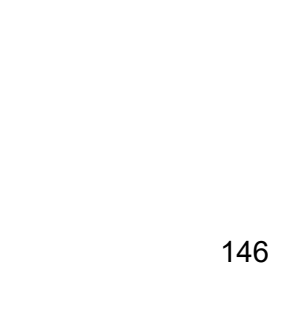
,

,

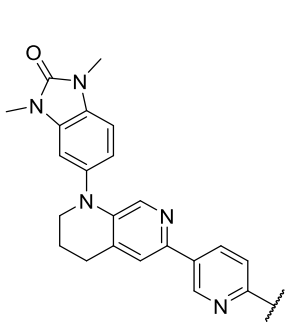
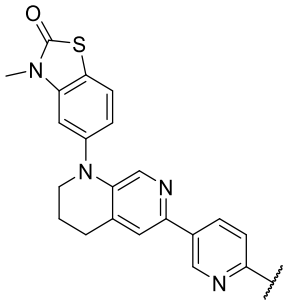
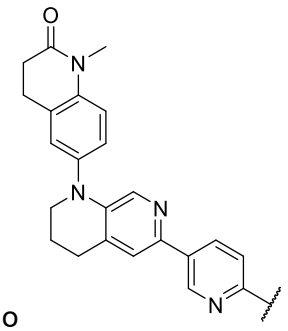

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

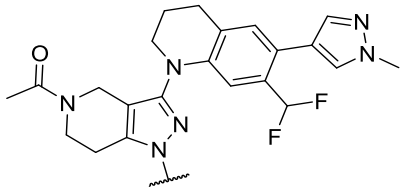
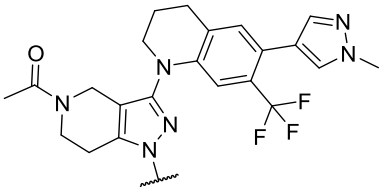
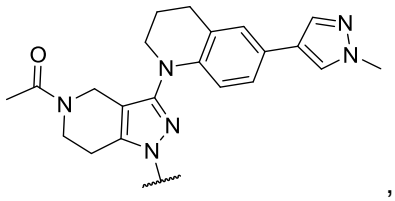
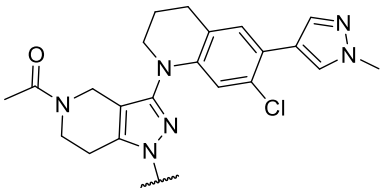
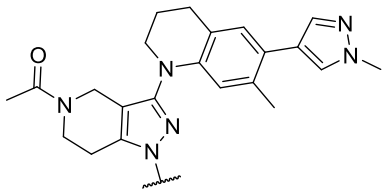
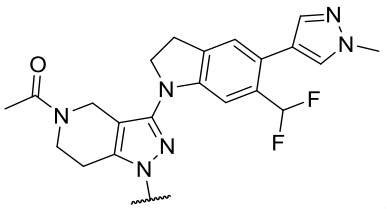
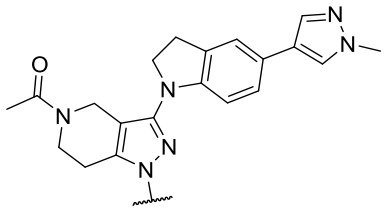
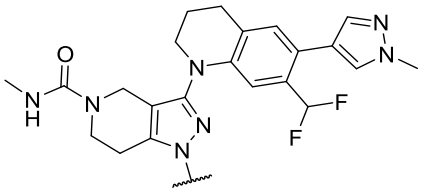
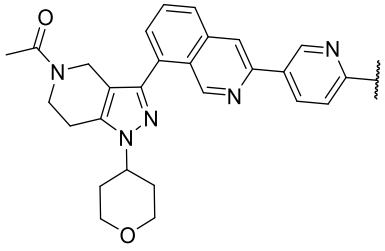
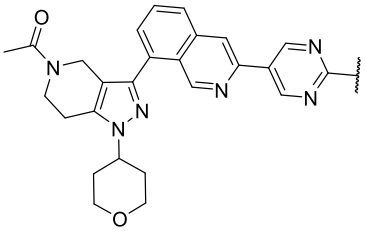

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

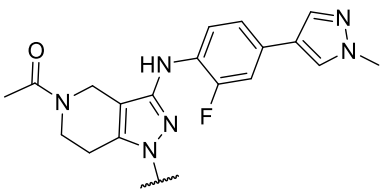
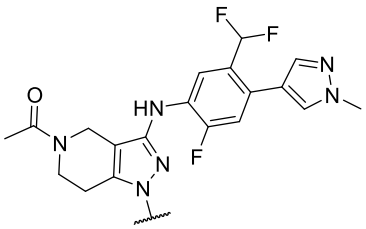
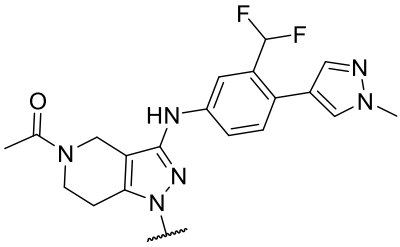
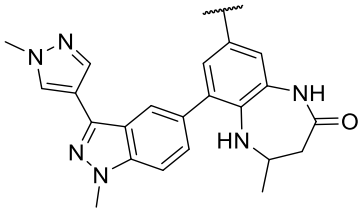
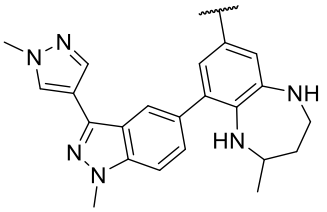
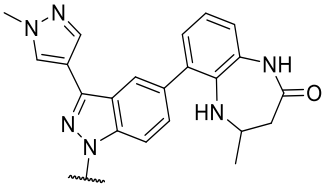
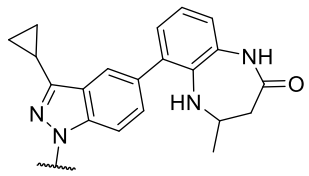
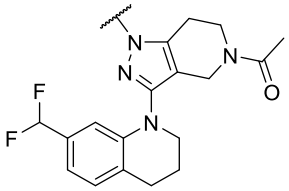
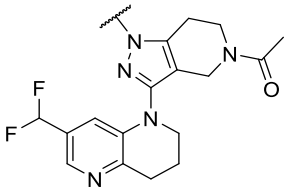
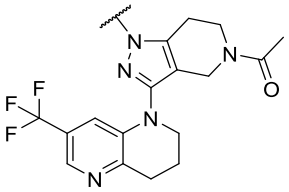
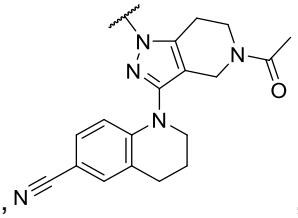
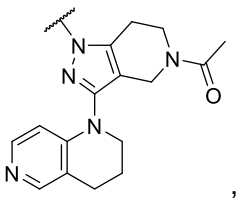
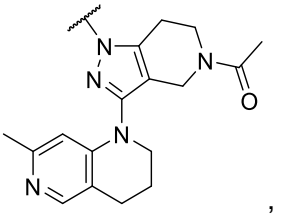
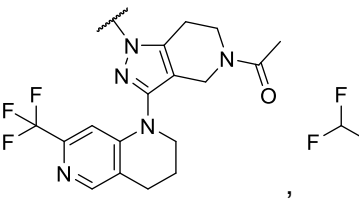
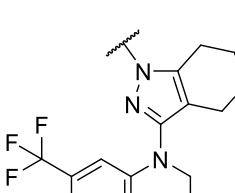
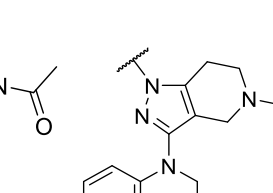
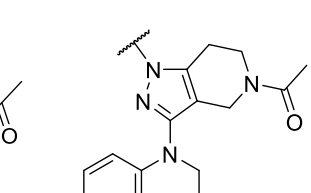
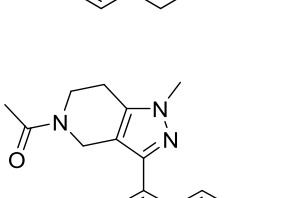
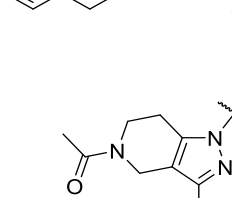
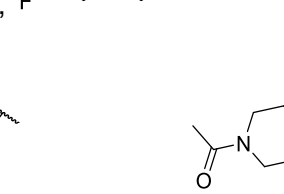
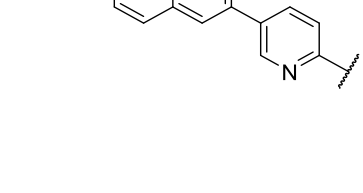
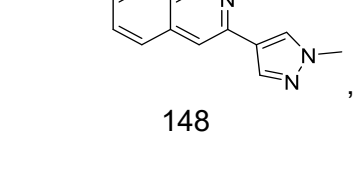
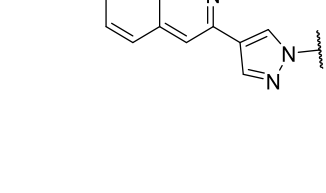
,

,

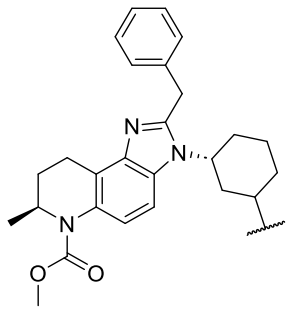
,



, o

.

[00279] Forma de realización 91. El método de acuerdo con cualquiera de las formas de realización 14-89, en donde SB-CBP/p300 tiene una de las siguientes estructuras:

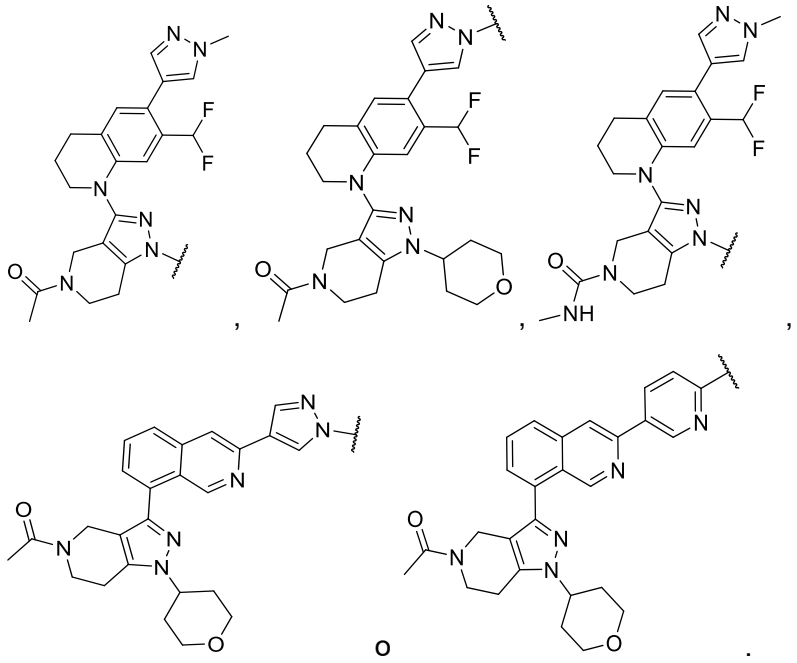

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

, o

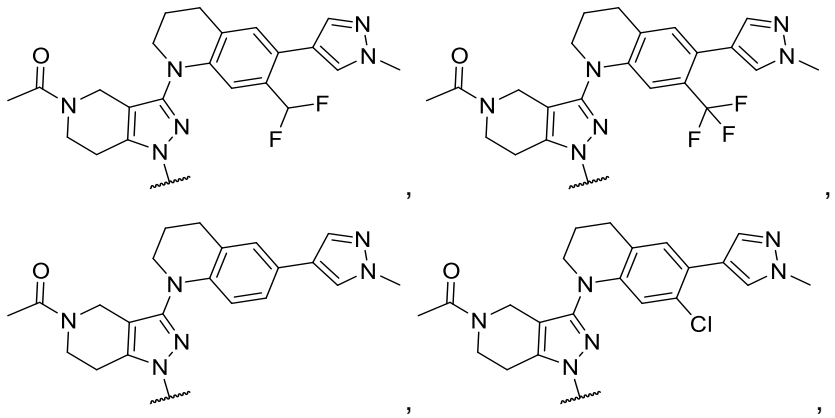


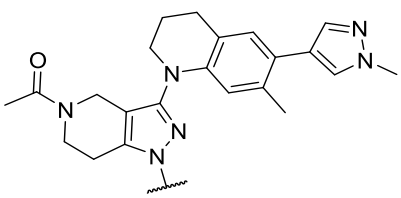
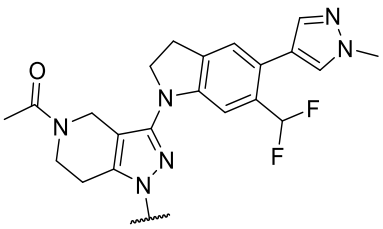
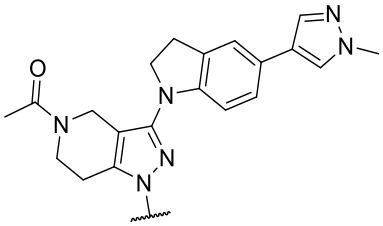
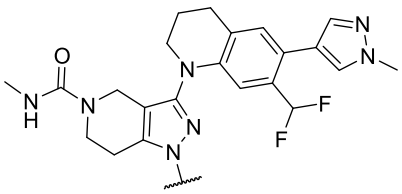
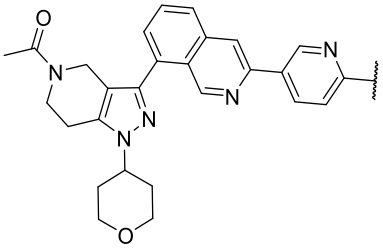
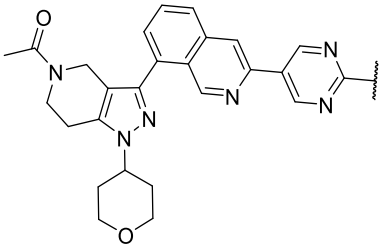
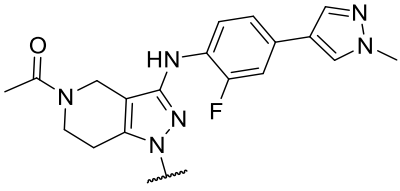
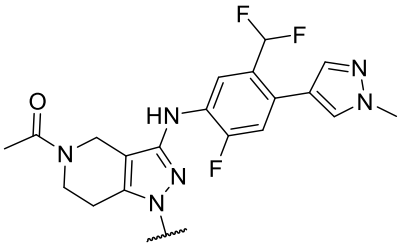
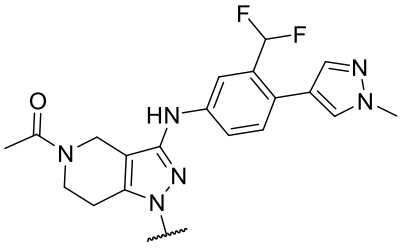
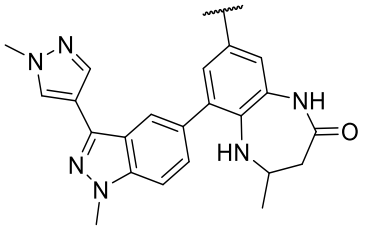
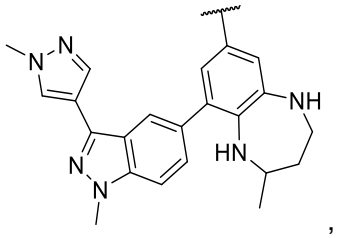
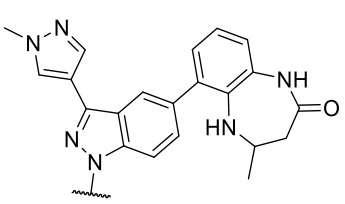
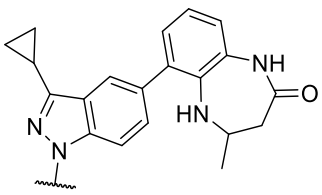
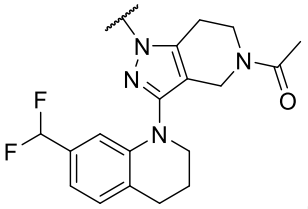
o una sal o solvato farmacéuticamente aceptable de este.

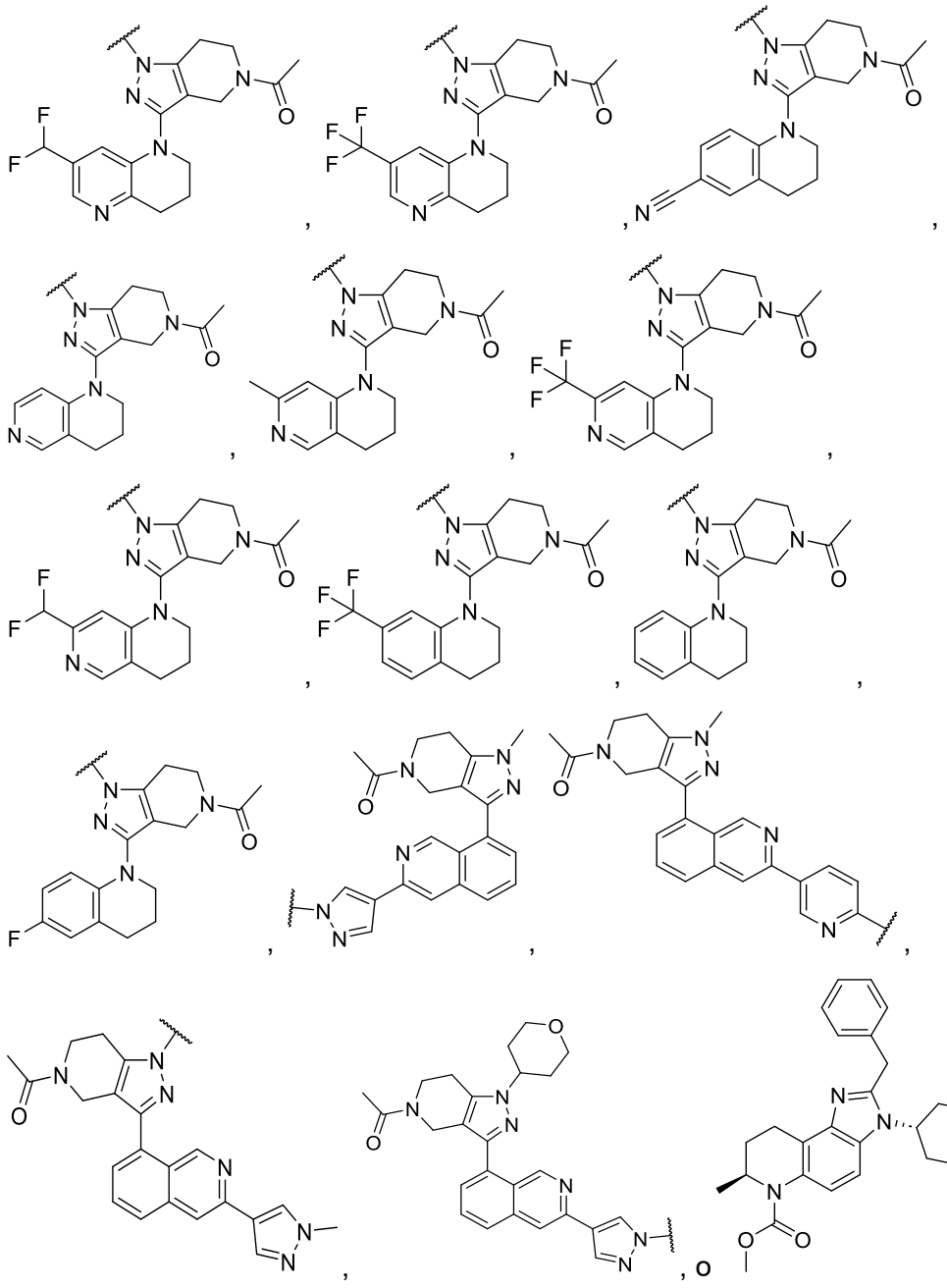
[00280] Forma de realización 92. El compuesto de cualquiera de las formas de realización 14-89, o una sal o solvato farmacéuticamente aceptable de este, en donde SB-CBP/p300 tiene una de las siguientes estructuras:



[00281] Forma de realización 93. El compuesto de cualquiera de las formas de realización 14-89, o una sal o solvato farmacéuticamente aceptable de este, en donde SB-CBP/p300 tiene una de las siguientes estructuras:



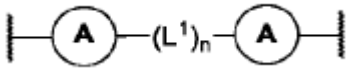

,

,

,

,

,

,

,

,

,

,

,

,

,

,



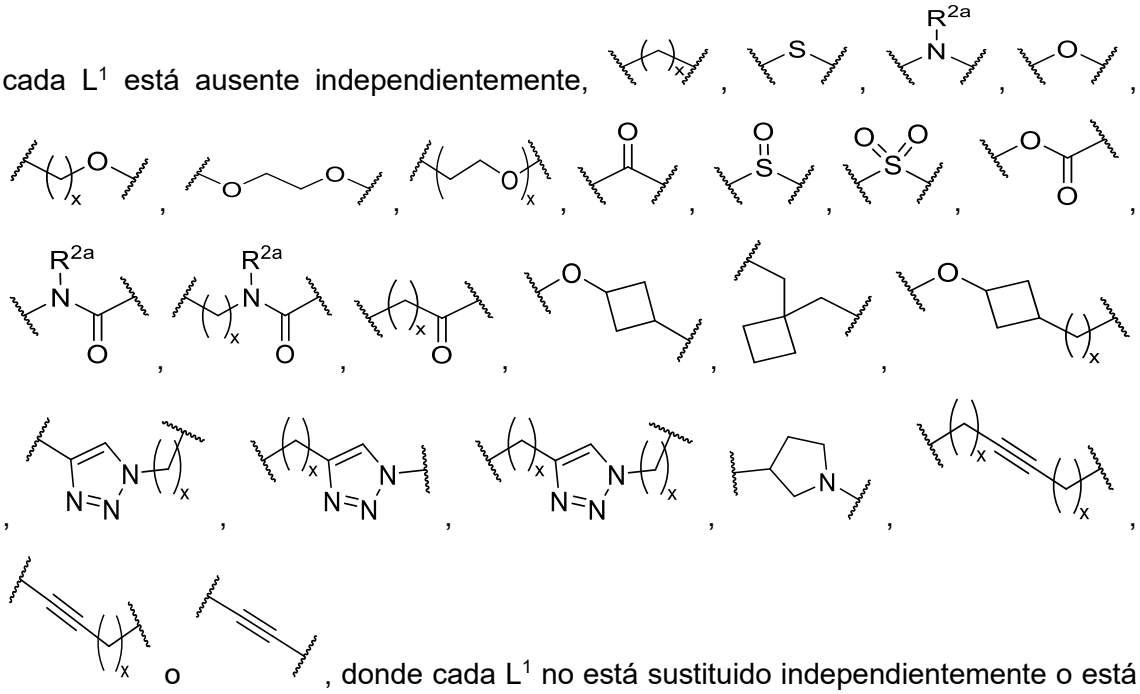
[00282] Forma de realización 94. El compuesto de cualquiera de las formas de realización 1-93, o una sal o solvato farmacéuticamente aceptable de este, en donde L está ausente.

[00283] Forma de realización 95. El compuesto de cualquiera de las formas de realización 1-93, o una sal o solvato farmacéuticamente aceptable de este, donde L comprende C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_{10}cicloalquilo sustituido o no sustituido, heterocicloalquilo de 3 a 10 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, o combinaciones de los

mismos.

[00284] Forma de realización 96. El compuesto de cualquiera de las formas de realización 1-93, o una sal o solvato farmacéuticamente aceptable de este, en donde L está ausente o  , en donde:

cada A está ausente independientemente, cicloalquilo monocíclico sustituido o no sustituido C_3-C_{10}, cicloalquilo bicíclico puenteado sustituido o no sustituido C_3-C_{10}, cicloalquilo bicíclico fusionado sustituido o no sustituido C_3-C_{10}, cicloalquilo espiro bicíclico sustituido o no sustituido C_3-C_{10}, cicloalquilo monocíclico sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo, bicíclico puenteado sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo, bicíclico fusionado sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo, bicíclico espiro sustituido o no sustituido de 3 a 10 miembros heterocicloalquilo,arilo sustituido o no sustituido, o heteroarilo sustituido o no sustituido, donde cada A está independientemente no sustituido o sustituido con x R^{2b};

cada L^1 está ausente independientemente,  , donde cada L^1 no está sustituido independientemente o está sustituido con x R^{2b};

n es 2, 3, 4, 5 o 6;

Cada n es independientemente 0, 1, 3, 4, 5, 6 o 7 (preferentemente, 0 o 1);

cada R^{2a} es independientemente hidrógeno o alquilo C_1-C_6sustituido o no sustituido; y

cada R^{2b} es independientemente hidrógeno, halógeno, alquil C_1-C_6 sustituido o no sustituido, fluoroalquilo C_1-C_6 sustituido o no sustituido, heteroalquilo C_1-C_6 sustituido o

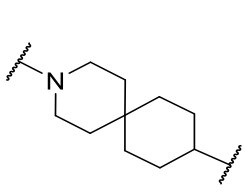
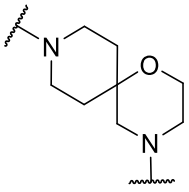
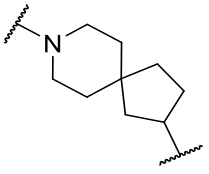
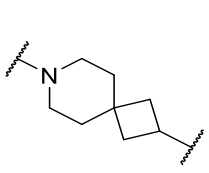
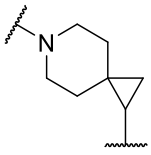
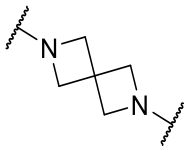
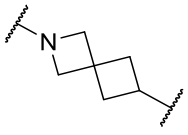
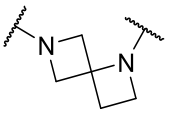
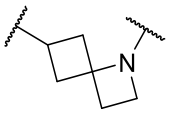
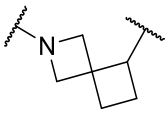
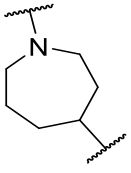
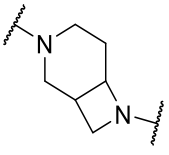
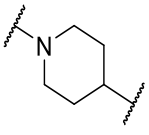
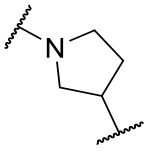
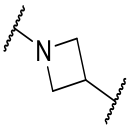
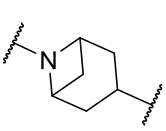
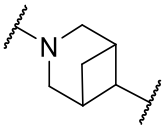
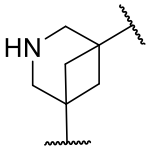
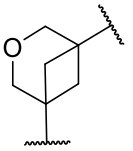
no sustituido, cicloalquilo C_3-C_8 sustituido o no sustituido, heterocicloalquilo de 3 a 8 miembros sustituido o no sustituido, arilo sustituido o no sustituido, heteroarilo sustituido o no sustituido, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)N(R^b)_2$, -$OC(=O)OR^a$, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2N(R^b)_2$, -$N(R^b)_2$, -$NR^bC(=O)N(R^b)_2$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^a$, -$NR^bS(=O)_2R^a$, -$C(=O)R^b$, -$C(=O)OR^b$, o -$C(=O)N(R^b)$;

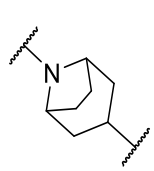
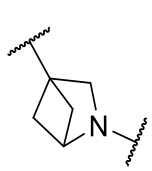
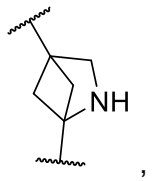
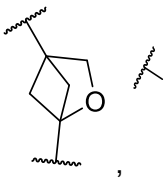
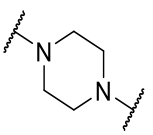
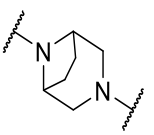
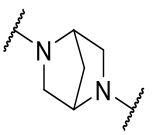
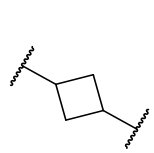
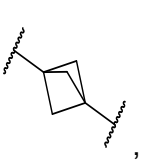
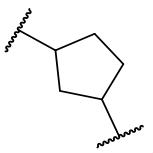
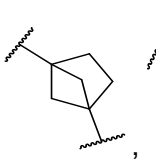
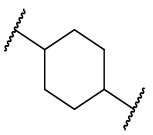
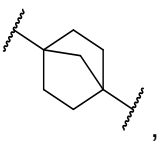
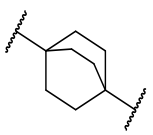
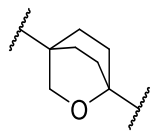
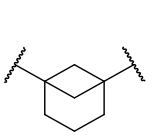
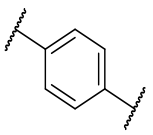
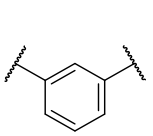
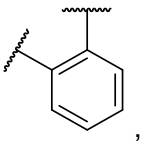
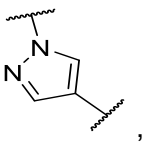
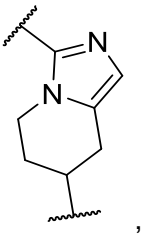
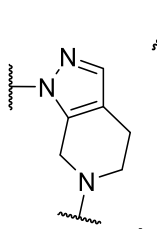
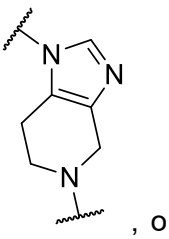
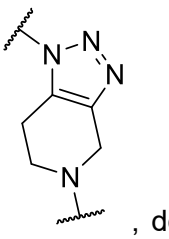
Cada R^a es independientemente sustituido o no sustituido C_1-C_6alquilo, sustituido o no sustituido C_1-C_6fluoroalquilo, sustituido o no sustituido C_1-C_6heteroalquilo, sustituido o no sustituido C_3-C_8cicloalquilo, sustituido o no sustituido monocíclico de 3 a 8 miembros heterocicloalquilo, sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

cada R^b es independientemente hidrógeno, C_1-C_6alquilo sustituido o no sustituido, C_1-C_6fluoroalquilo sustituido o no sustituido, C_1-C_6heteroalquilo sustituido o no sustituido, C_3-C_8cicloalquilo sustituido o no sustituido, monocíclico de 3 a 8 miembros heterocicloalquilo sustituido o no sustituido, arilo sustituido o no sustituido, o heteroarilo monocíclico sustituido o no sustituido;

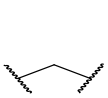
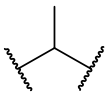
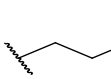
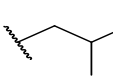
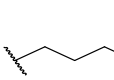
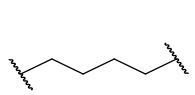
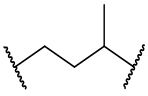
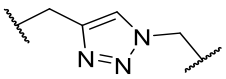
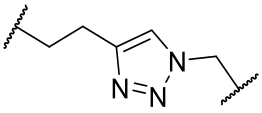
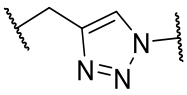
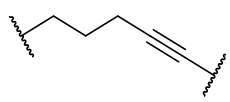
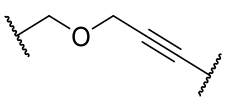
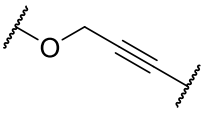
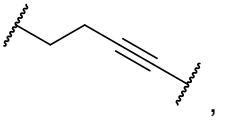
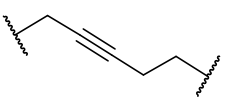
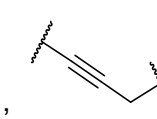
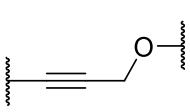
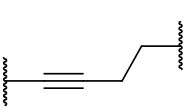
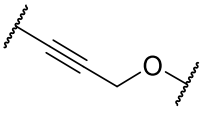
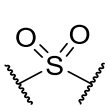
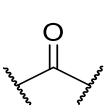
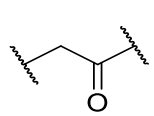
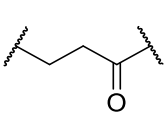
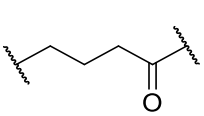
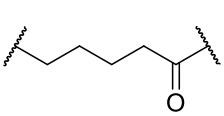
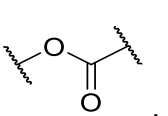
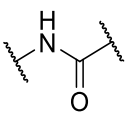
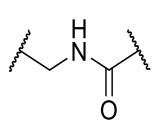
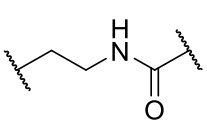
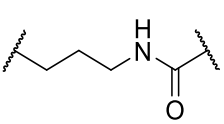
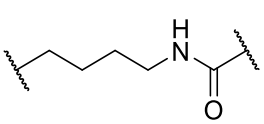
o dos R^b en el mismo átomo de N se toman junto con el átomo de N al que están unidos para formar un heterociclo que contiene N, sustituido o no sustituido.

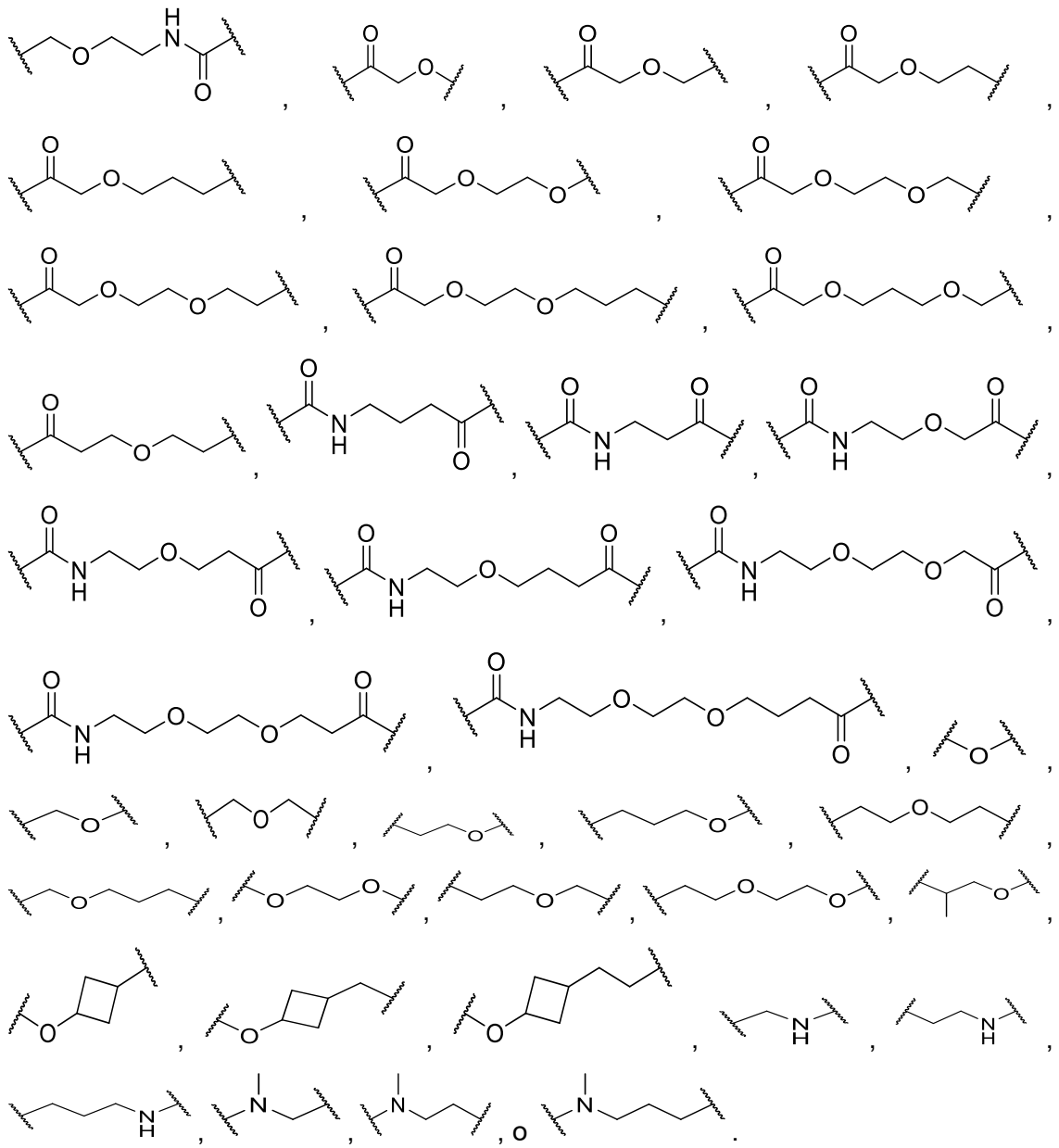
[00285] Forma de realización 97. El compuesto de la forma de realización 96, o una sal o solvato farmacéuticamente aceptable de este, en donde:

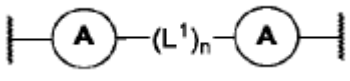
cada A está ausente independientemente,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

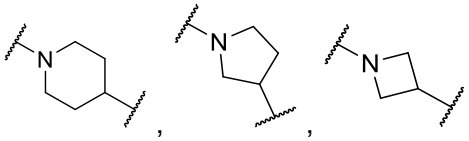

























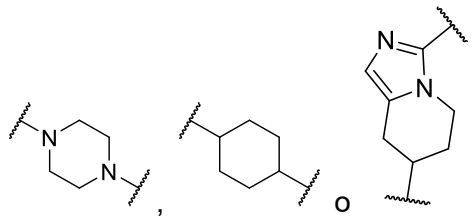
, , o , donde cada A no está sustituido o está sustituido independientemente por x R^{2b};

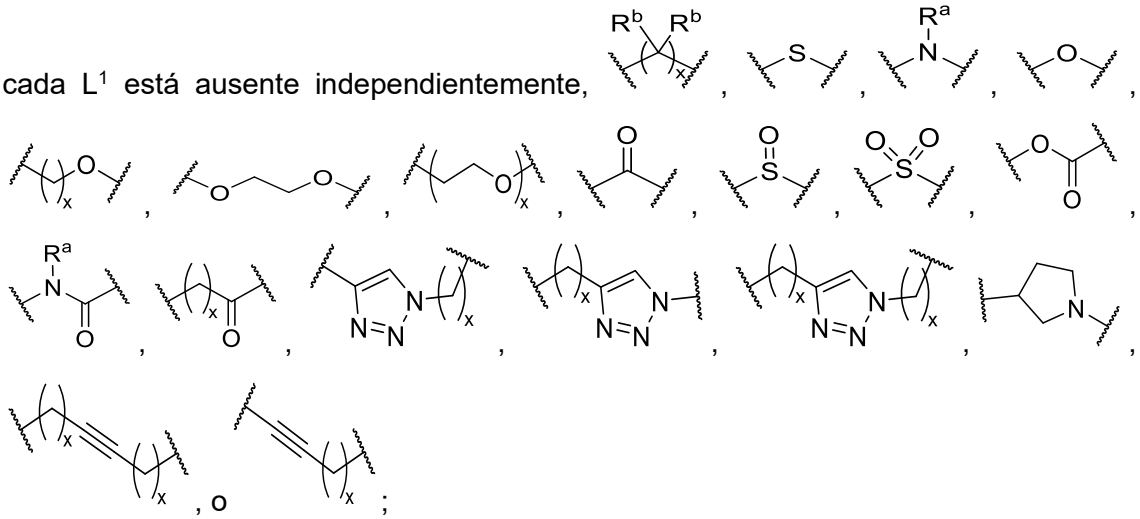
$(L^1)_n$ está ausente, 

































[00286] Forma de realización 98. El compuesto de cualquiera de las formas de realización 1-93, o una sal o solvato farmacéuticamente aceptable de este, en donde L está ausente o  en donde:

cada A está ausente de forma independiente, 



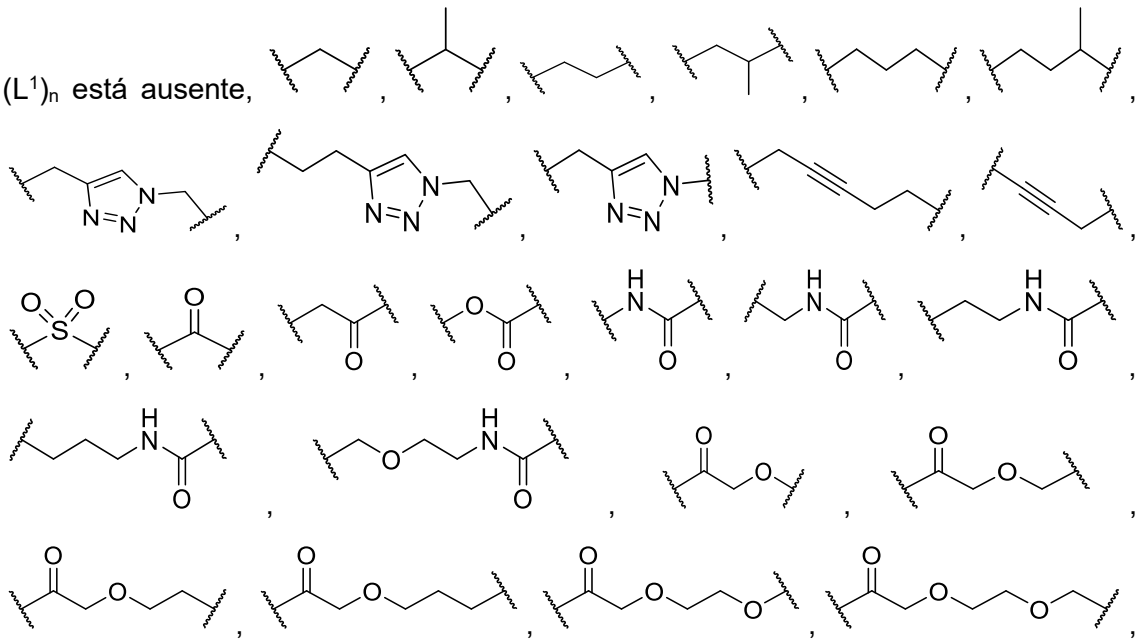
cada L^1 está ausente independientemente, 

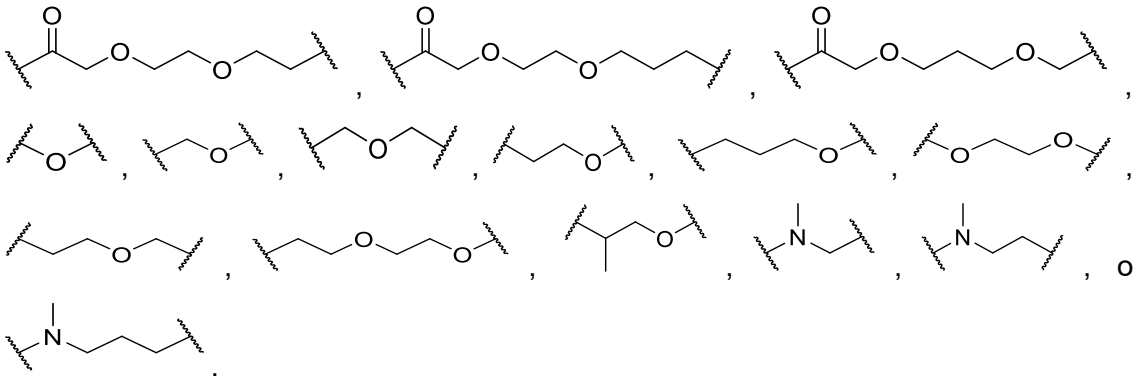
n es 1, 2 o 3; cada x es independientemente 1, 2, 3, 4, 5 o 6;

cada R^a es independientemente: hidrógeno; o alquilo C_{1-6};

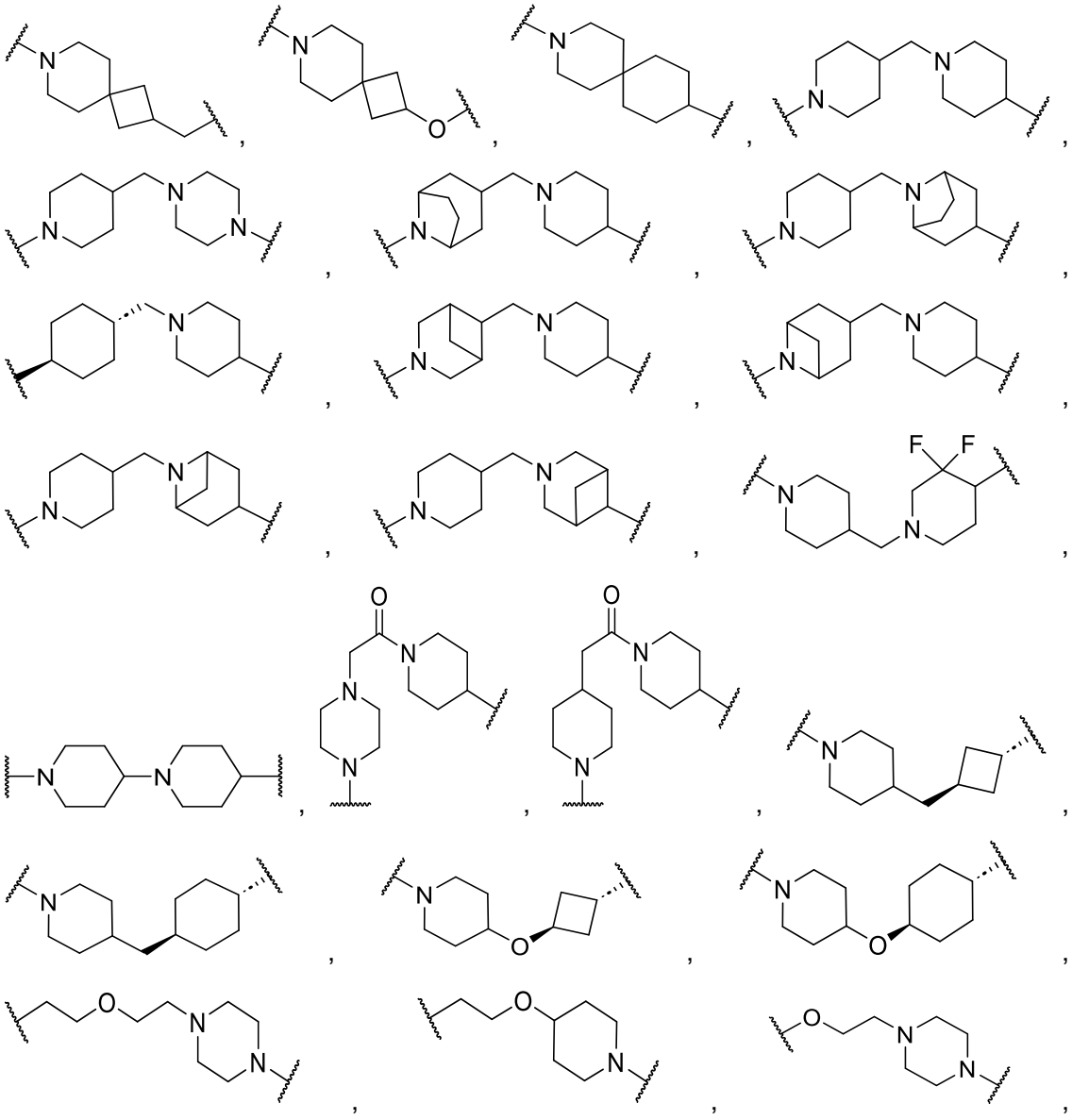
Cada R^b es independientemente hidrógeno, halógeno o alquilo C_1-C_6 sustituido o no sustituido.

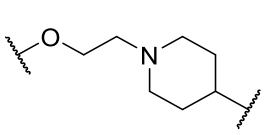
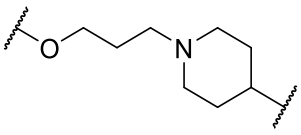
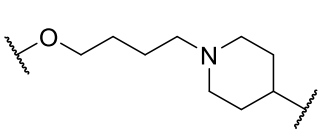
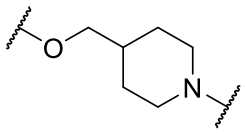
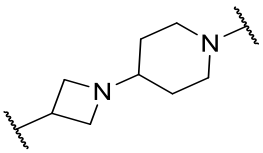
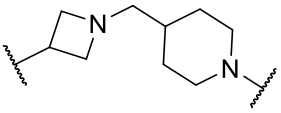
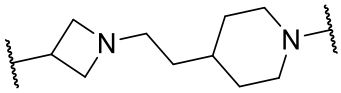
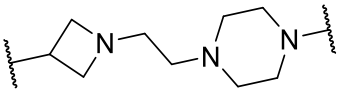
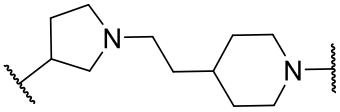
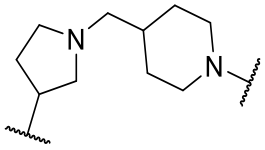
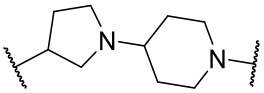
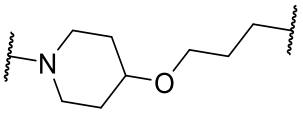
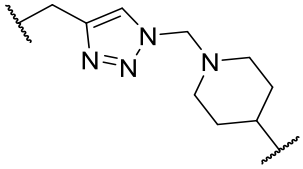
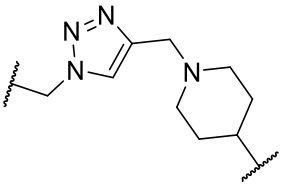
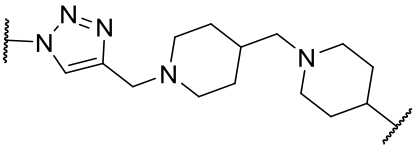
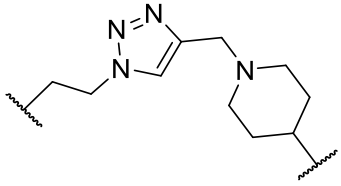
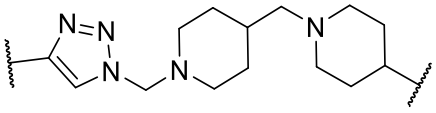
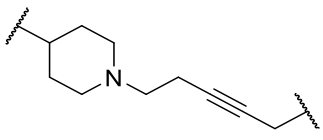
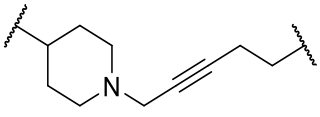
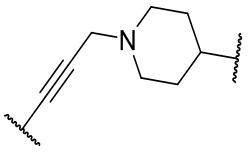
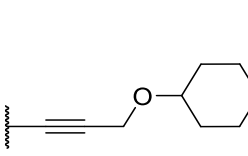
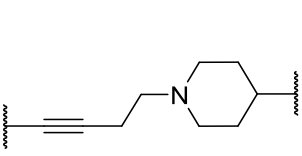
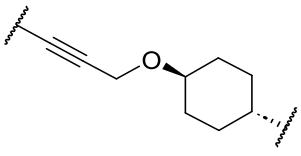
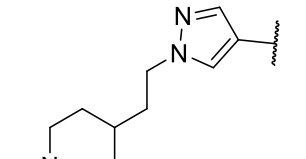
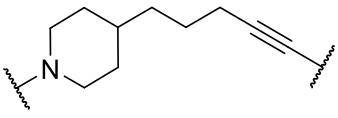
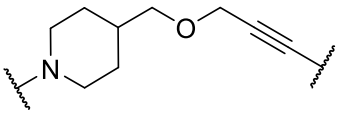
[00287] Forma de realización 99. El compuesto de cualquiera de las formas de realización 96-98, o una sal o solvato farmacéuticamente aceptable de este, en donde:

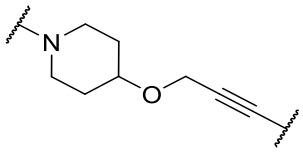
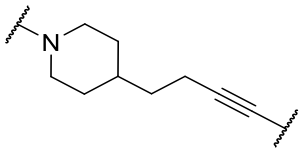
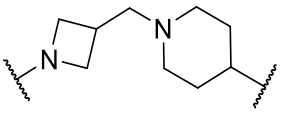
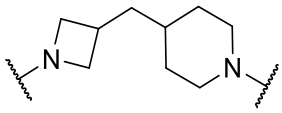
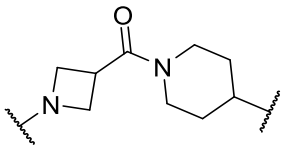
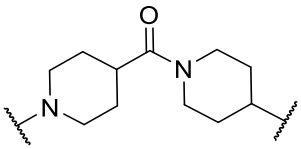
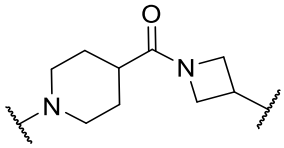
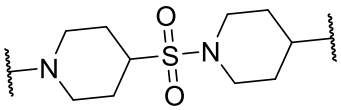
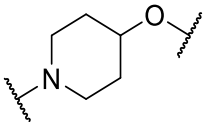
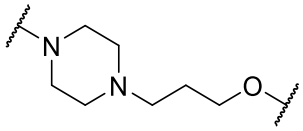
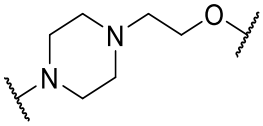
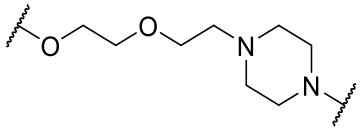
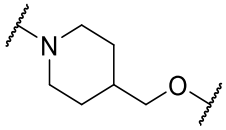
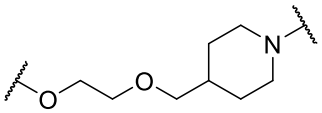
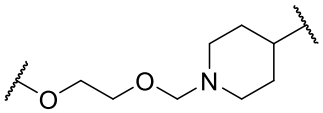
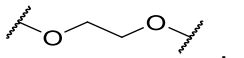
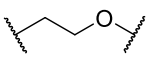
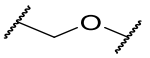
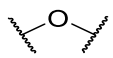
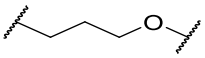
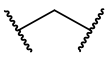
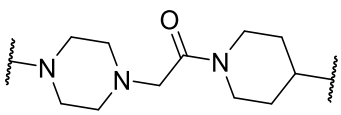
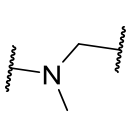
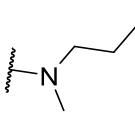
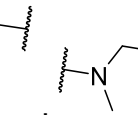
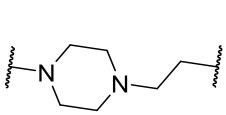
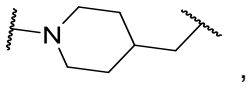
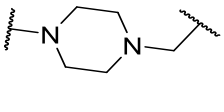
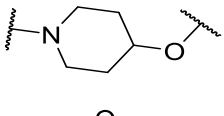
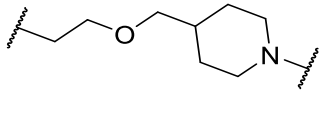
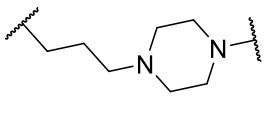
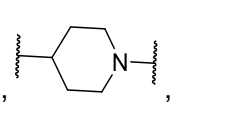
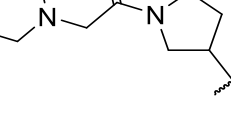
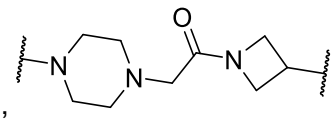
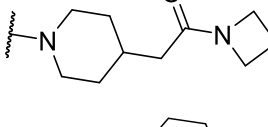
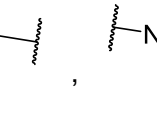
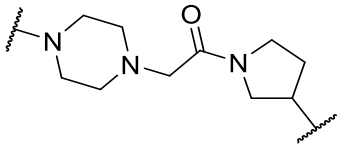
$(L^1)_n$ está ausente, 

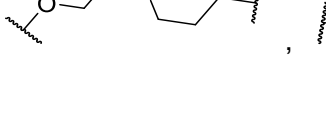
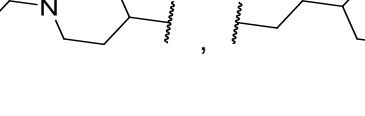
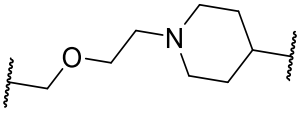


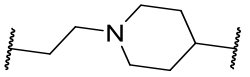
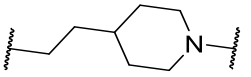
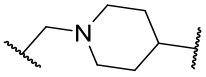
[00288] Forma de realización 100. El compuesto de cualquiera de las formas de realización 1-99, o una sal o solvato farmacéuticamente aceptable de este, en donde L tiene una de las siguientes estructuras:

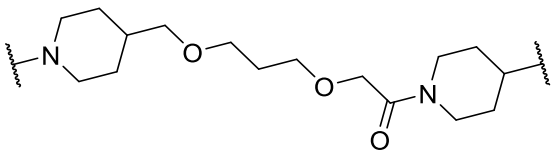
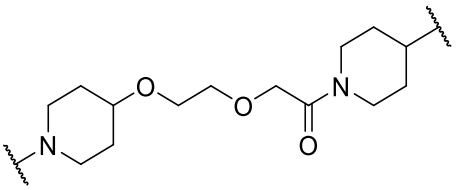
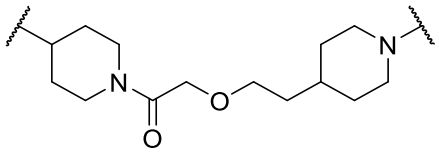
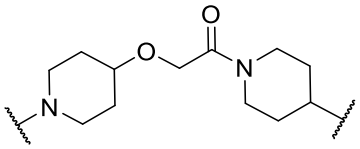
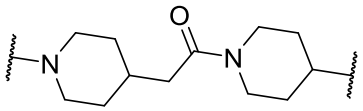
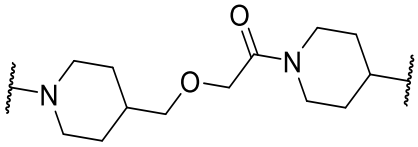
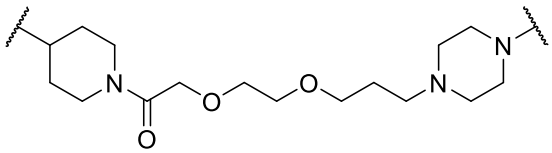
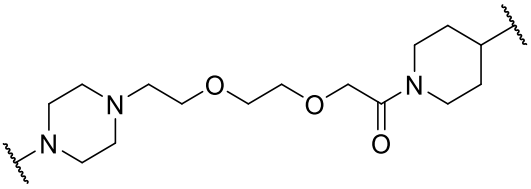
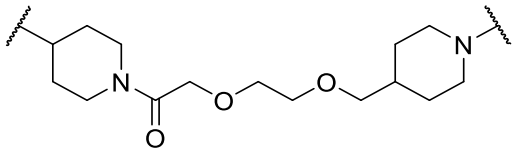
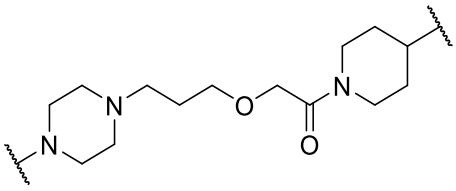
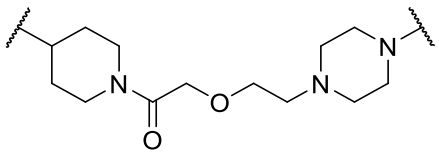
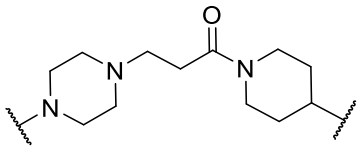
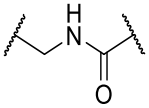
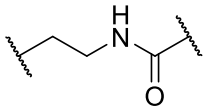
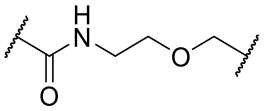
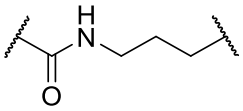
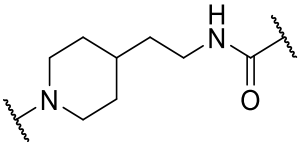
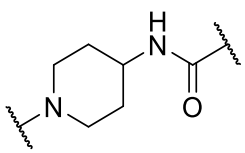
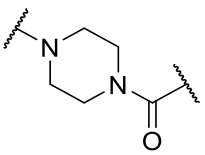
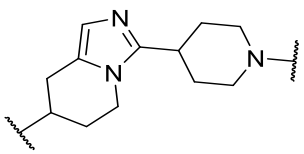
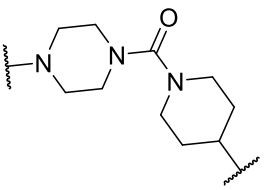
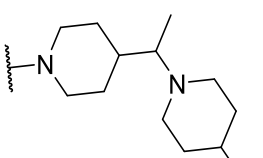
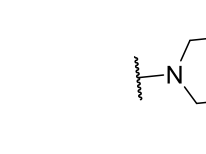
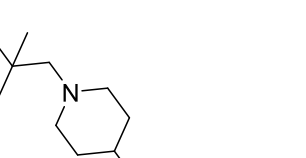
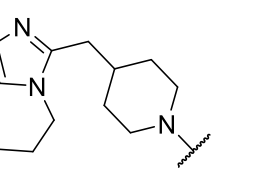



,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

.

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

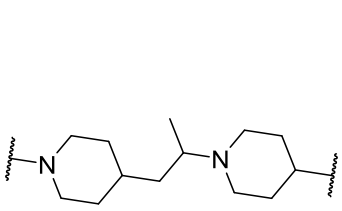
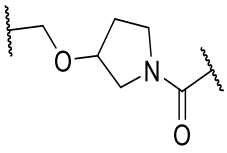
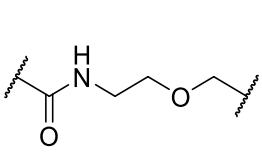
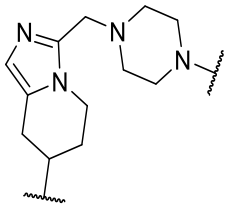
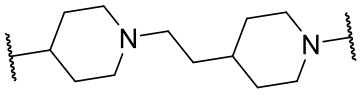
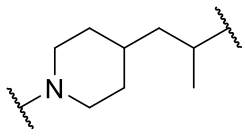
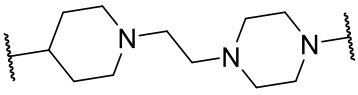
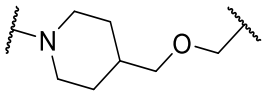
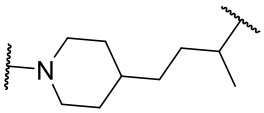
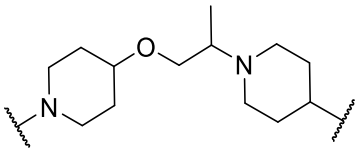
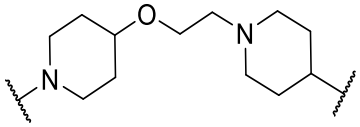
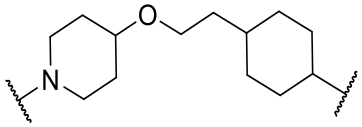
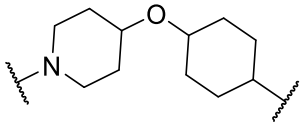
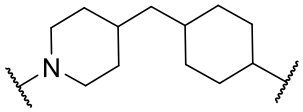
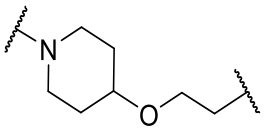
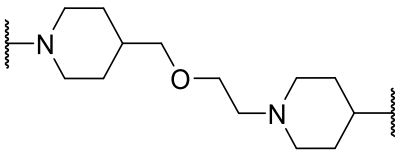
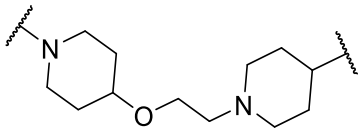
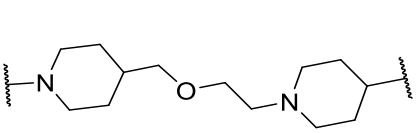
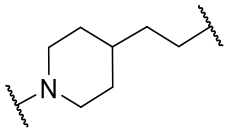
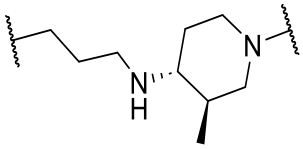
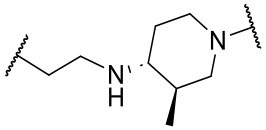
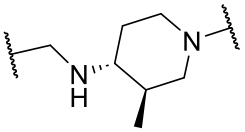
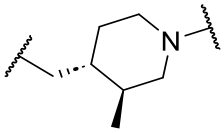
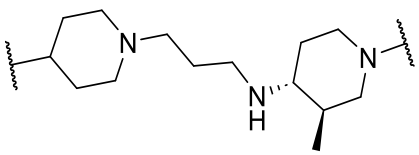
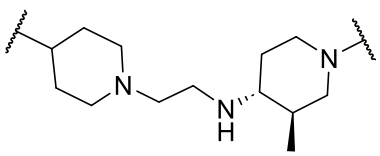
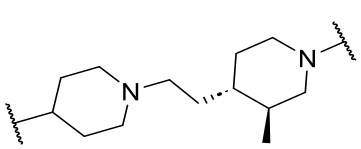
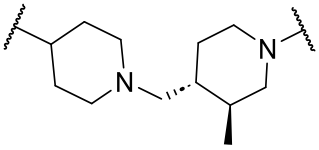
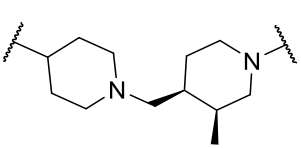
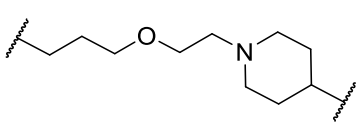
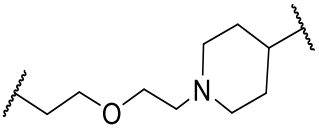
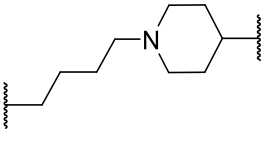
,

,

,

,

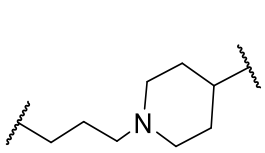
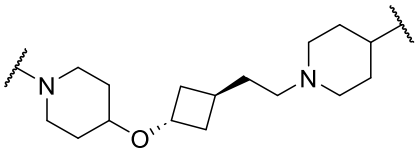
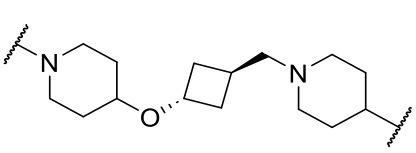
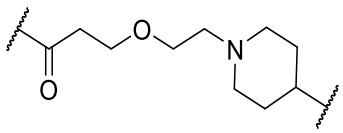
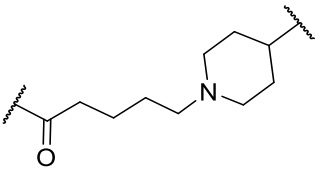
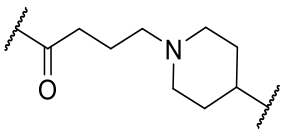
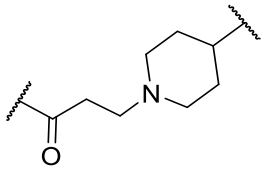
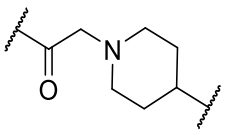
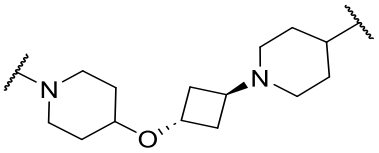
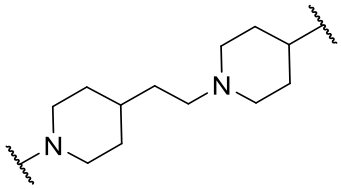
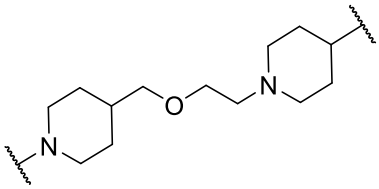
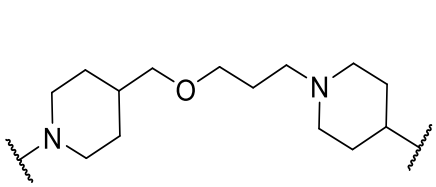
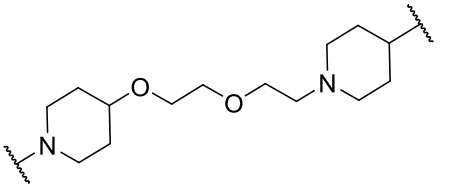
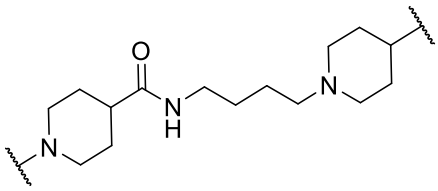
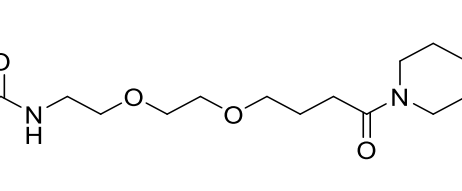
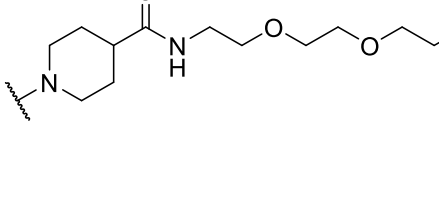
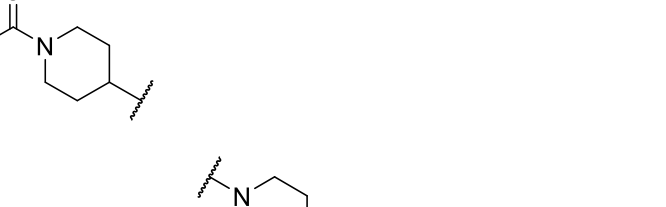
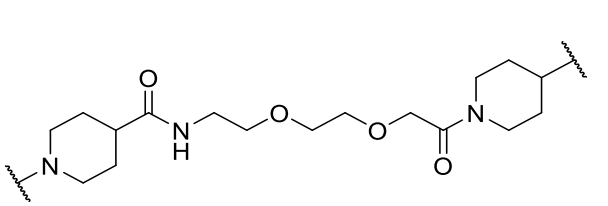
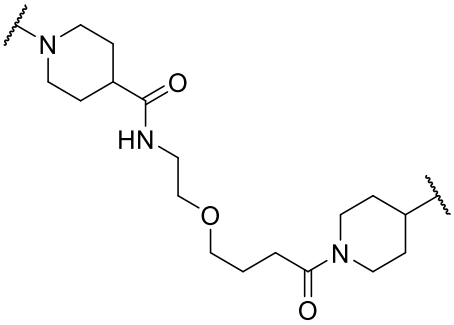

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

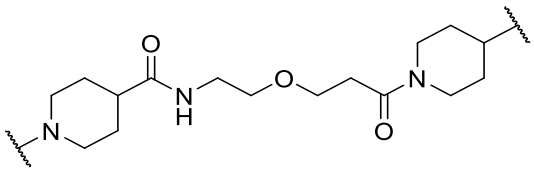
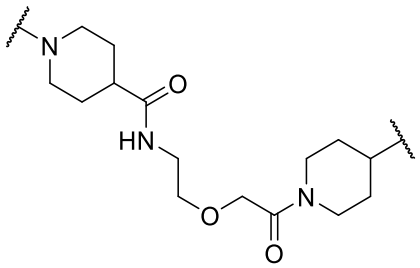
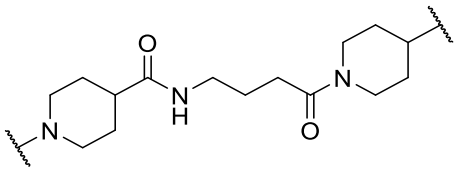
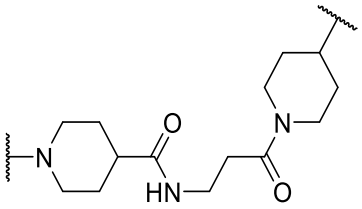
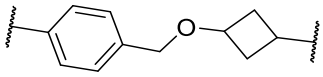
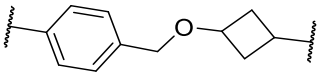
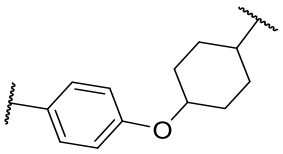
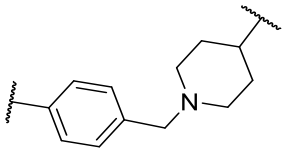
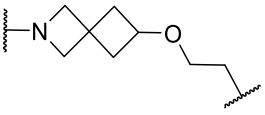
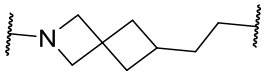
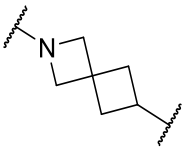
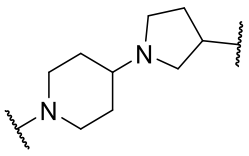
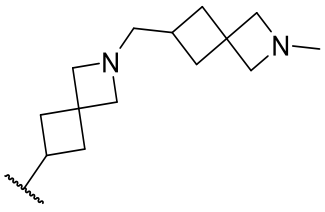
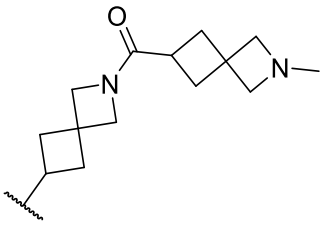
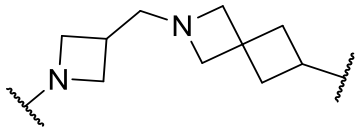
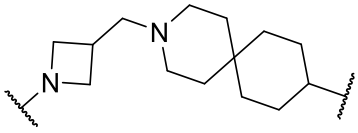
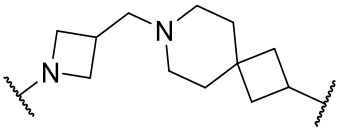
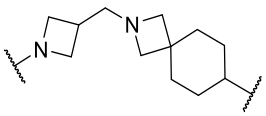
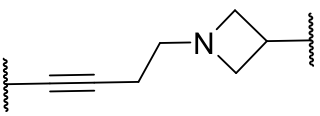
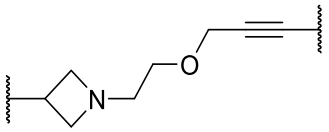
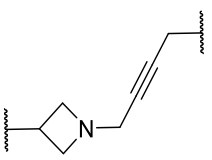
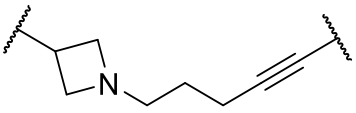
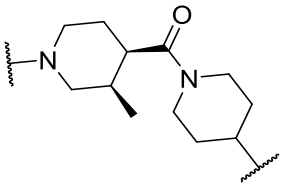
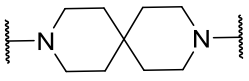
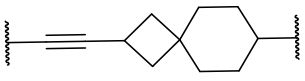
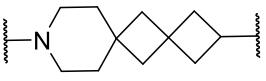
,

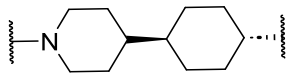
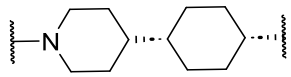
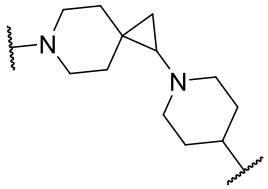
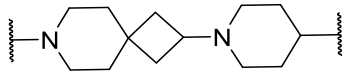
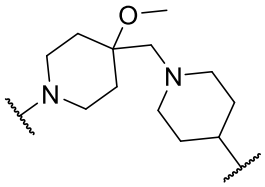
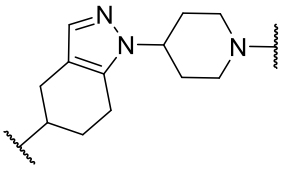
,

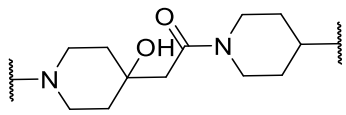
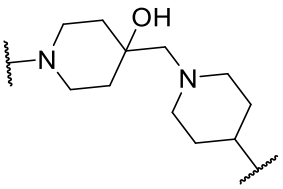
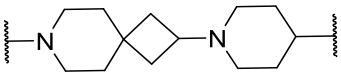
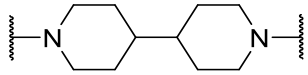
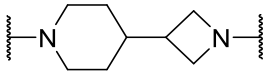
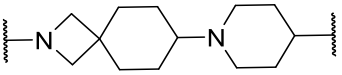
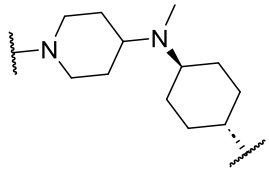
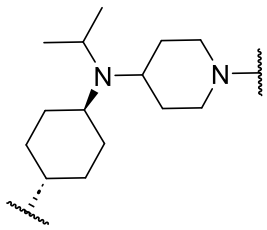
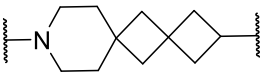
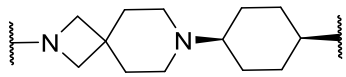
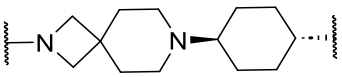
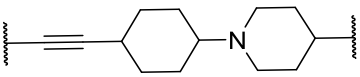
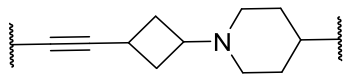
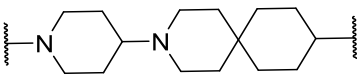
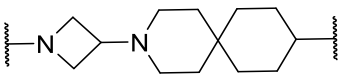
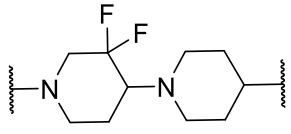
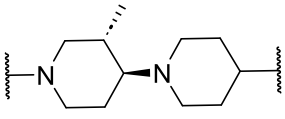
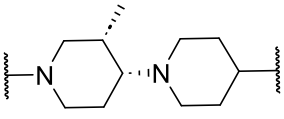
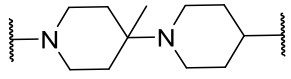
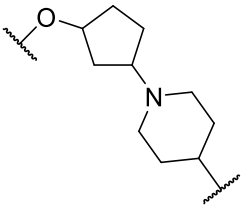
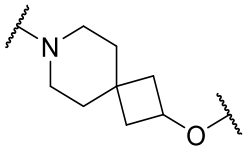
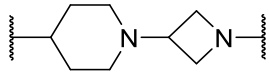
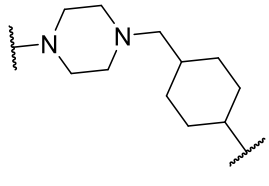
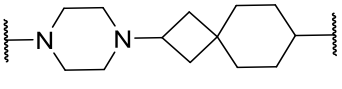
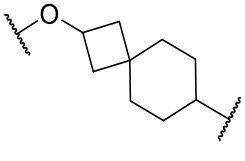

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

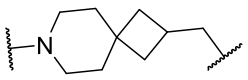
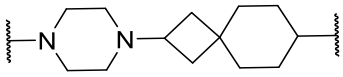
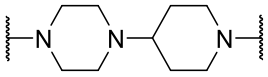
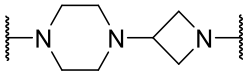
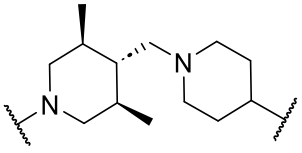
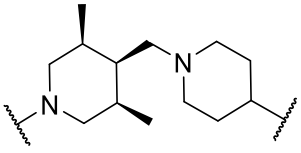

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

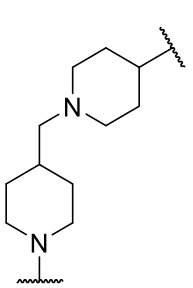
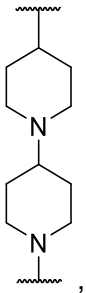
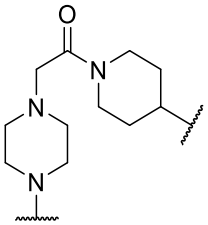
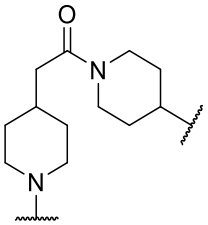
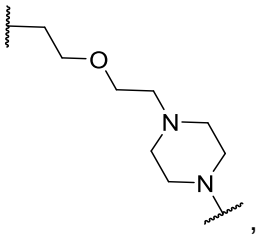
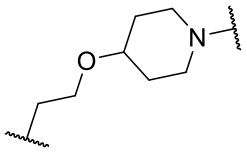
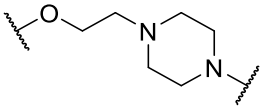
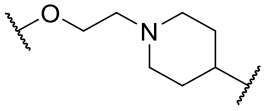
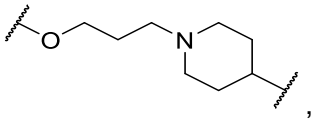
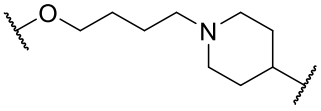
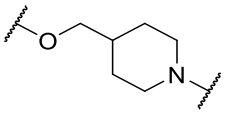
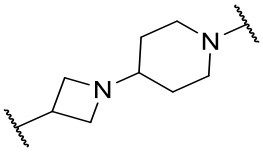
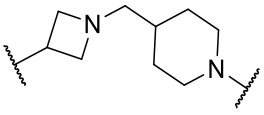
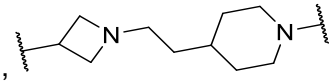
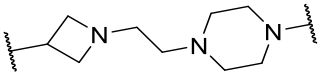
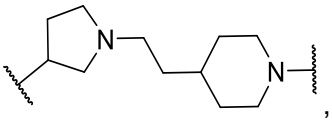
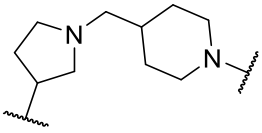
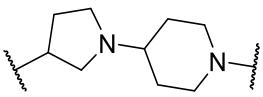
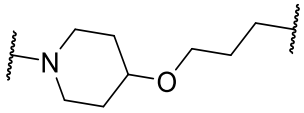
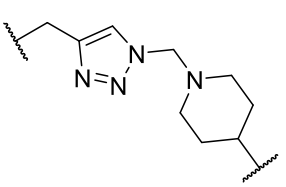
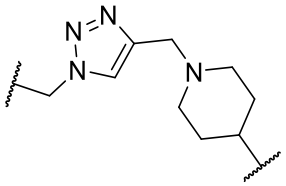
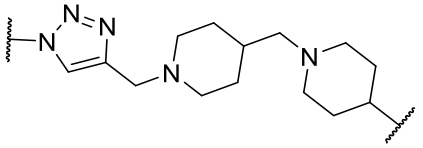

,

,

,

,

,

,

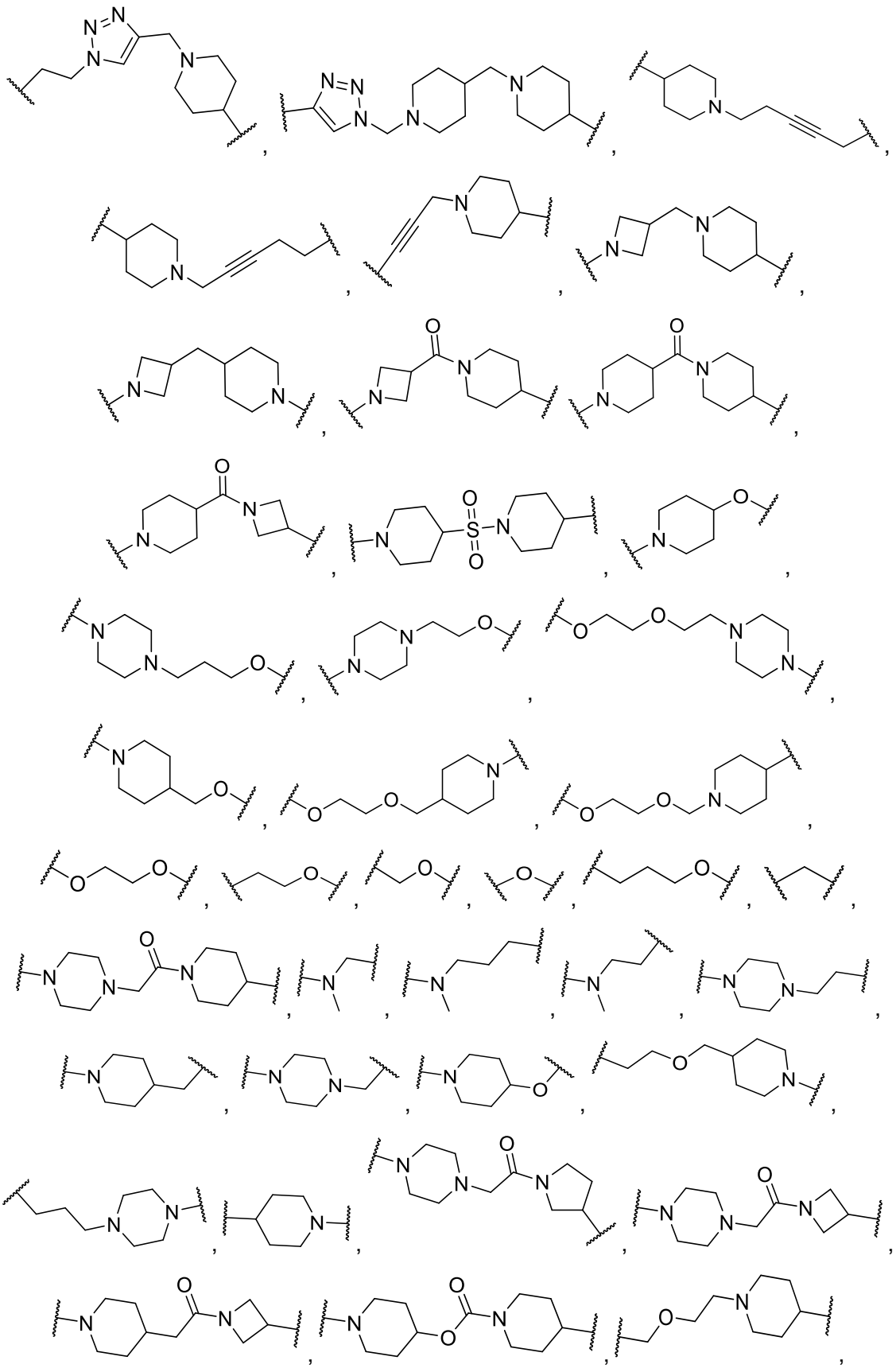

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

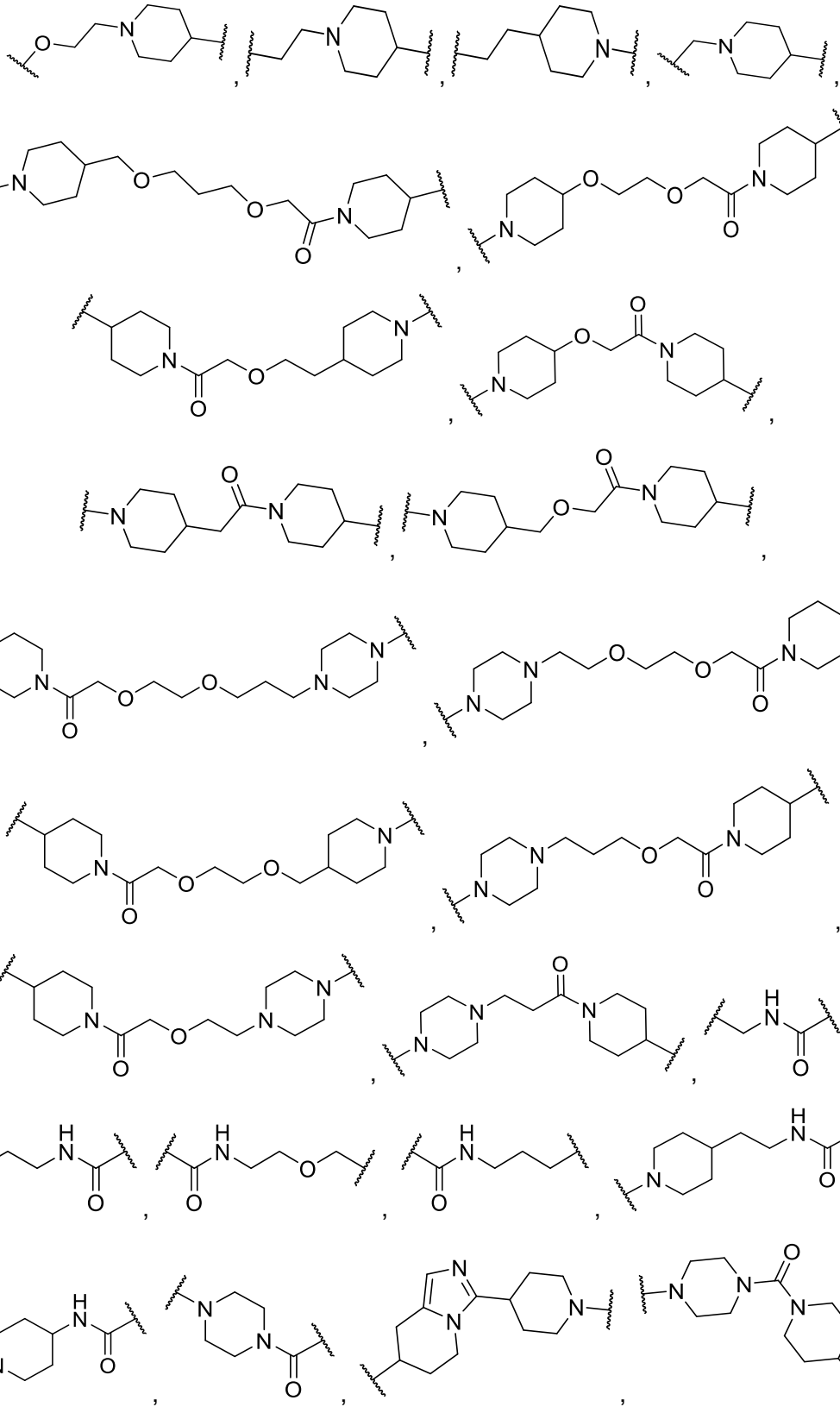

,

,

,

,

, o

,

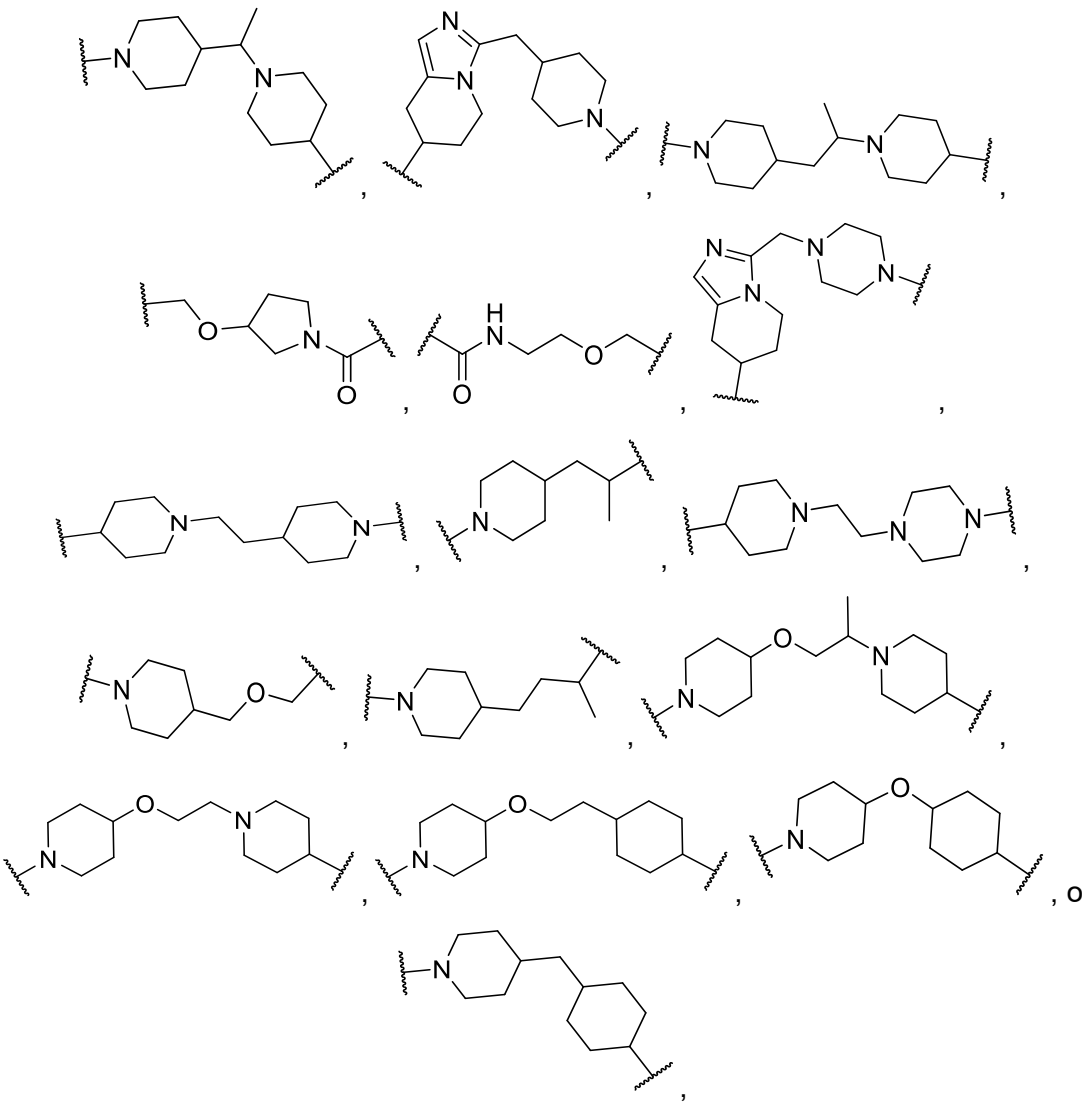
o una sal o solvato farmacéuticamente aceptable de este.

[00289] Forma de realización 101. El compuesto de cualquiera de las formas de realización 1-99, o una sal o solvato farmacéuticamente aceptable de este, en donde L tiene una de las siguientes estructuras:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,







o una sal o solvato farmacéuticamente aceptable de este.

[00290] Forma de realización 102. los compuestos de acuerdo con la Tabla 1, o una sal de este farmacéuticamente aceptable.

[00291] Forma de realización 103. Un complejo ternario estable que comprende:

a. una o más proteínas dependientes de la enfermedad (PDE);

b. Receptor de andrógenos (AR); y

c. compuesto inhibidor condicional heterobifuncional de cualquiera de las formas de realización 1-105;

donde DDP y AR están presentes en una célula de interés (COI) y la abundancia relativa de AR en la COI es mayor que la abundancia relativa de DDP en la COI.

[00292] Forma de realización 104. El complejo ternario estable del ejemplo 103, en el que DDP es la proteína ATM (Ataxia-telangiectasia mutada), la proteína ATR (Ataxia telangiectasia y Rad3 relacionada), la quinasa Aurora A (AurkA), AurkB, la proteína

quinasa relacionada con el ciclo de división celular 7 (CDC7), la quinasa de punto de control 1 (CHK1), CHK2, la quinasa dependiente de ciclina 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, la ADN metiltransferasa 1 (DNMT1), la exportina 1 (XPO1), la histona deacetilasa 1 (HDAC1), HDAC2, HDAC3, el miembro 11 de la familia de la kinesina (KIF11), la quinasa de la proteína quinasa activada por mitógeno 1 (MEK1), MEK2, Myc, la proteína 8 regulada negativamente durante el desarrollo expresada en células precursoras neuronales (NEDD8), SMARCA2/4, Proteína de unión a CREB (CBP)/p300, proteína 5 que contiene repeticiones WD (WDR5), factor 1 asociado a DDB1 y CUL4 (DCAF1), fosfatidilinositol-3 quinasa (PI3K), proteína arginina metiltransferasa 5 (PRMT5), subunidad 1 del factor de empalme 3b (SF3B1), WEE1, subunidades del proteasoma 20S, coactivador 1 del receptor de esteroides (SRC1), SRC2 o SRC3.

[00293] Forma de realización 105. El complejo ternario estable del ejemplo 103, en el que DDP es Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), fosfatidilinositol-3 kinase (PI3K) o WEE1.

[00294] Forma de realización 106. El complejo ternario estable del ejemplo 103, en el que el DDP es la proteína de unión a CREB (CBP)/p300.

[00295] Forma de realización 107. Un complejo ternario estable que comprende:

a. CBP/p300;

b. Receptor de andrógenos (AR); y

c. compuesto inhibidor condicional heterobifuncional de cualquiera de las formas de realización 1-105;

donde CBP/p300 y DP están presentes en una célula de interés (COI) y la abundancia relativa de DP en la COI es mayor que la abundancia relativa de CBP/p300 en la COI.

[00296] Forma de realización 108. Un método para inhibir selectivamente la actividad de una proteína dependiente de la enfermedad (DDP) en una célula de interés (COI) de un mamífero que comprende administrar un compuesto heterobifuncional de cualquiera de las formas de realización 1-102, o una sal o solvato farmacéuticamente aceptable de este, donde la COI expresa el receptor de andrógenos (AR).

[00297] Forma de realización 109. El método del ejemplo 108, en el que el compuesto heterobifuncional de cualquiera de los ejemplos 1-102, o una sal o solvato farmacéuticamente aceptable de este, inhibe la actividad del DDP en el COI pero no inhibe la actividad del DDP en las células que expresan el DDP y no expresan el AR.

[00298] Forma de realización 110. El método de realización 108, en el que el AR está sobreexpresado, hiperactivo o ambos sobreexpresados e hiperactivos en el COI.

[00299] Forma de realización 111. El método de cualquiera de las formas de realización 108-110, donde DDP es Ataxia-telangiectasia mutada (ATM), Ataxia telangiectasia y proteína relacionada con Rad3 (ATR), Aurora quinasa A (AurkA), AurkB, proteína quinasa relacionada con el ciclo de división celular 7 (CDC7), quinasa de punto de control 1 (CHK1), CHK2, quinasa dependiente de ciclina 1 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK9, ADN metiltransferasa 1 (DNMT1), Exportina 1 (XPO1), histona deacetilasa 1 (HDAC1), HDAC2, HDAC3, miembro 11 de la familia de la kinesina (KIF11), proteína quinasa activada por mitógeno quinasa 1 (MEK1), MEK2, Myc, proteína 8 regulada negativamente durante el desarrollo expresada en células precursoras neuronales (NEDD8), SMARCA2/4, proteína de unión a CREB (CBP)/p300, proteína 5 que contiene repeticiones WD (WDR5), factor 1 asociado a DDB1 y CUL4 (DCAF1), fosfatidilinositol-3 quinasa (PI3K), proteína arginina metiltransferasa 5 (PRMT5), subunidad 1 del factor de empalme 3b (SF3B1), WEE1, subunidades del proteasoma 20S, coactivador 1 del receptor de esteroides (SRC1), SRC2 o SRC3.

[00300] Forma de realización 112. El método de cualquiera de las formas de realización 108-111, donde DDP es Aurora Kinase A (AurkA), Checkpoint kinase 1 (CHK1), CHK2, CDK4, CDK6, Myc, SMARCA2/4, CREB-binding protein (CBP)/p300, WD repeat-containing protein 5 (WDR5), DDB1- and CUL4-associated factor 1 (DCAF1), phosphodilinositol-3 kinase (PI3K) o WEE1.

[00301] Forma de realización 113. El método de acuerdo con una cualquiera de las formas de realización 108-111, en donde el gen DDP es un gen de antígeno de leucocitos humanos (CBP).

[00302] Forma de realización 114. Un método para tratar el cáncer en un mamífero que comprende administrar al mamífero un compuesto heterobifuncional de cualquiera de las formas de realización 1-102.

[00303] Forma de realización 115. Un método para aumentar la función del proteosoma en un sujeto que comprende administrar a dicho sujeto una cantidad eficaz de un compuesto de cualquiera de las formas de realización 1 a 102, o una sal, solvato, clatrato o profármaco de este farmacéuticamente aceptable.

[00304] Forma de realización 116. El procedimiento del Forma de realización 115, en el que el cáncer es un cáncer de páncreas.

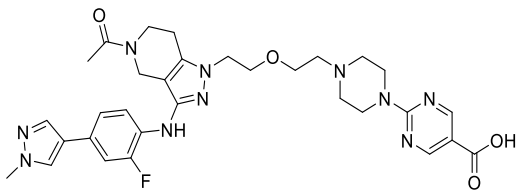
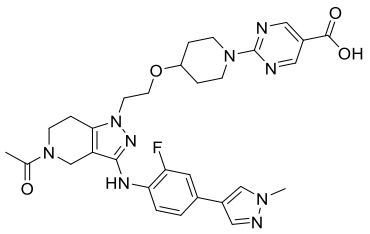
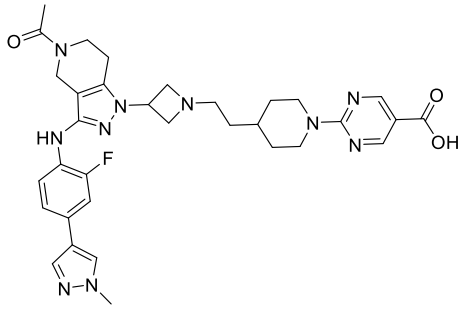
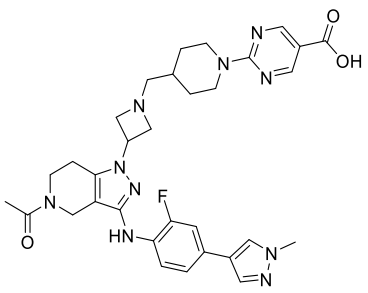
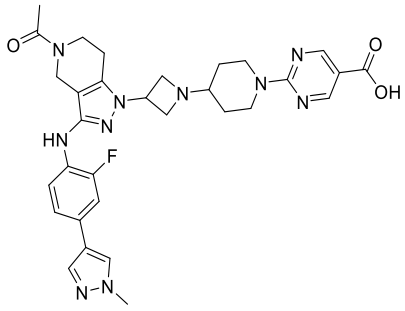
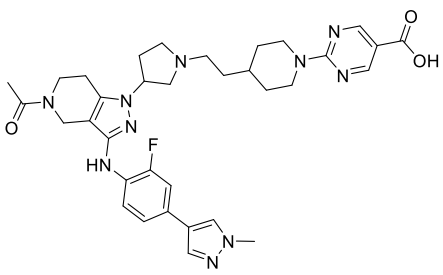
[00305] Forma de realización 117. El procedimiento del Forma de realización 115, en el que el cáncer es un cáncer esofágico.

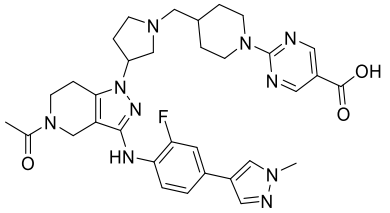
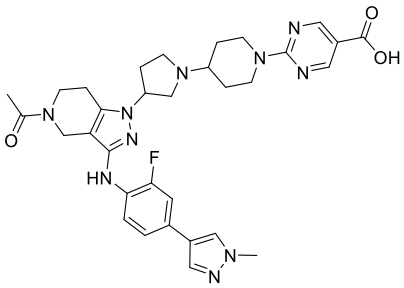
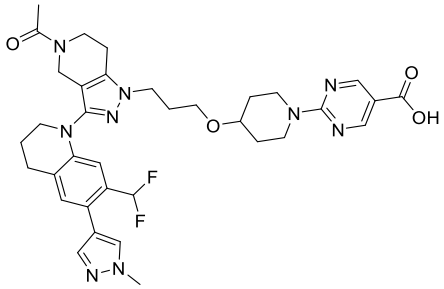
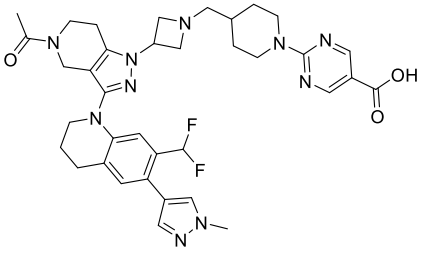
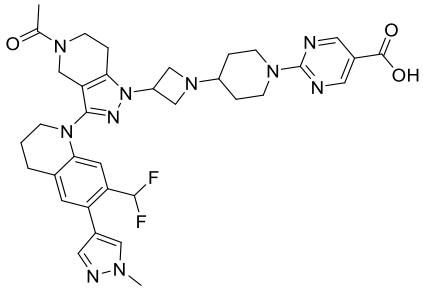
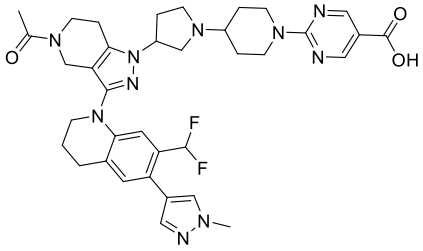
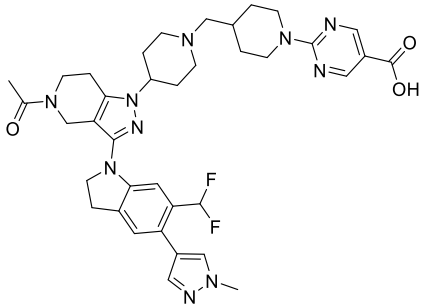
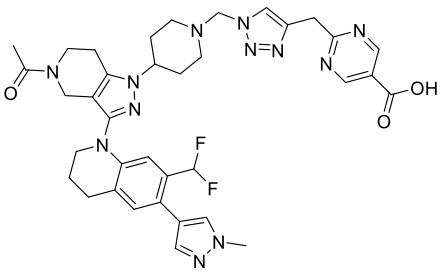
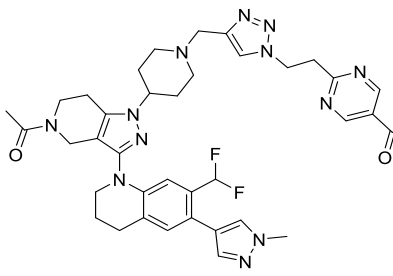
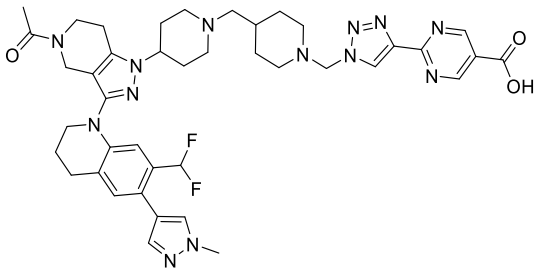
[00306] Forma de realización 118. Un método para tratar una enfermedad o afección dependiente del receptor de andrógenos o mediada por el receptor de andrógenos en mamíferos que comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto según cualquiera de las formas de realización 1-102, o una sal o solvato farmacéuticamente aceptable de este.

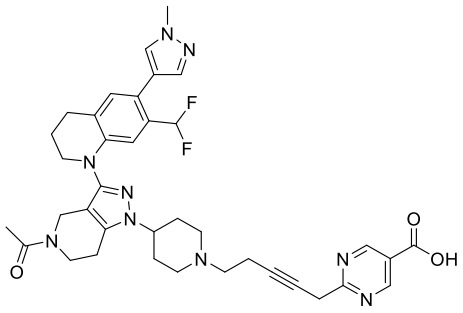
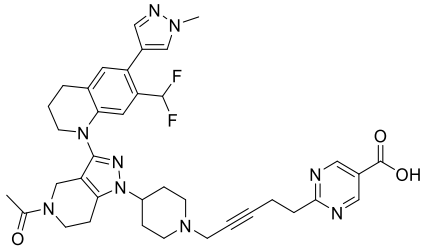
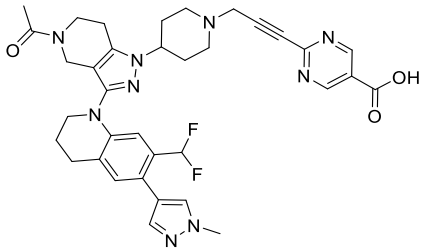
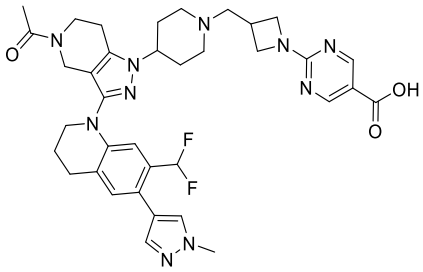
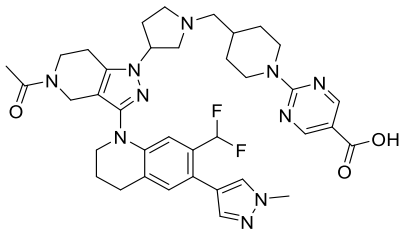
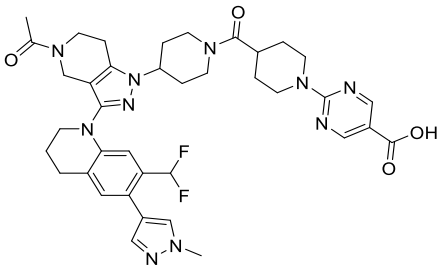
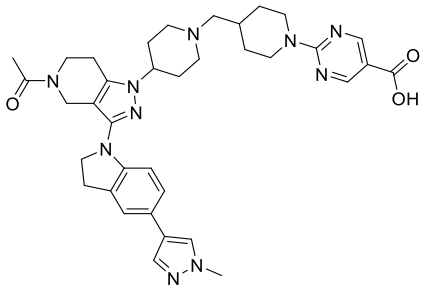
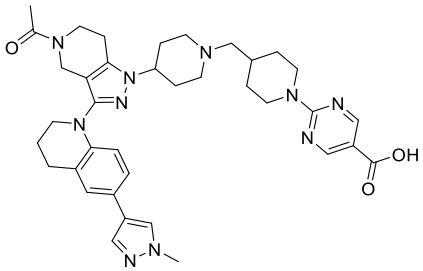
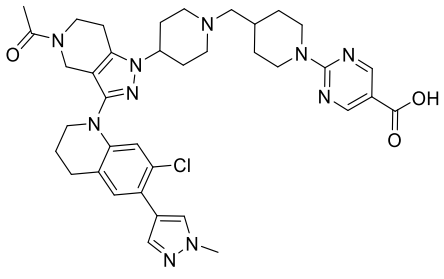
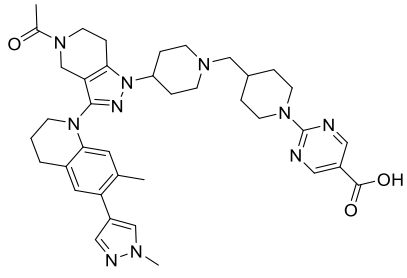
[00307] Forma de realización 119. El método de realización 118, en el que se selecciona una enfermedad o condición dependiente del receptor de andrógenos o mediada por el receptor de andrógenos entre la hiperplasia prostática benigna, el hirsutismo, los adenomas y las neoplasias de la próstata, las células tumorales benignas o malignas que contienen el receptor de andrógenos, el cáncer de próstata, el cáncer de mama, el cáncer de endometrio y el cáncer de útero.

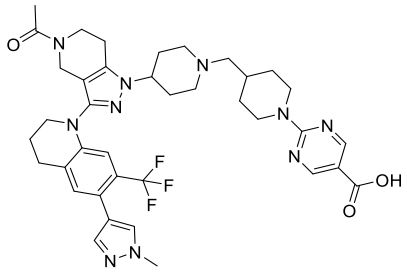
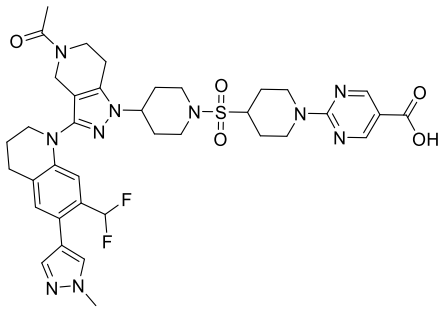
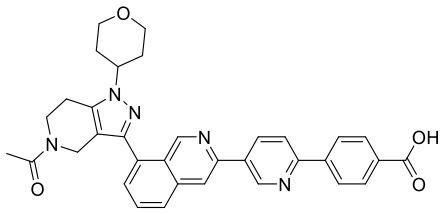
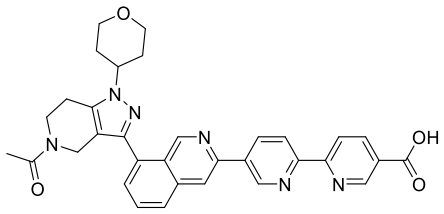
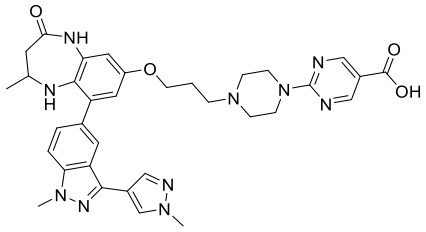
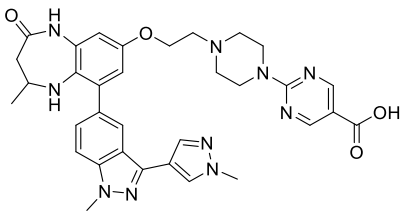
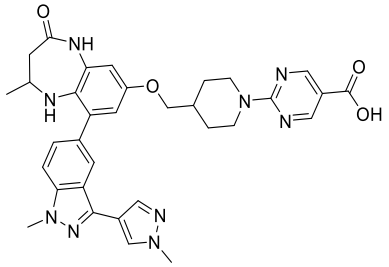
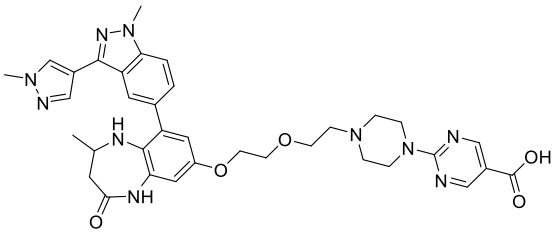
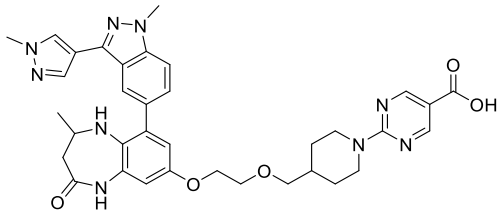
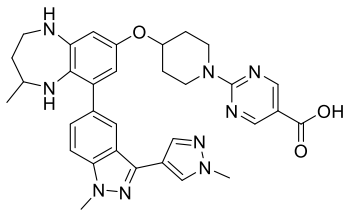
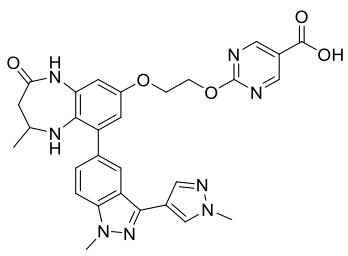
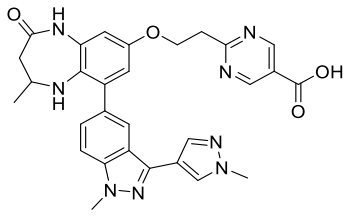
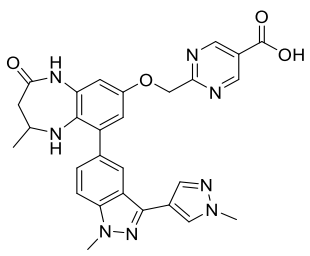
[00308] Forma de realización 120. Una composición farmacéutica que comprende un compuesto de cualquiera de las formas de realización 1-102, o una sal o solvato farmacéuticamente aceptable de este, y un excipiente farmacéuticamente aceptable.

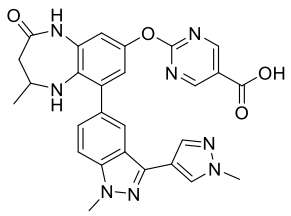
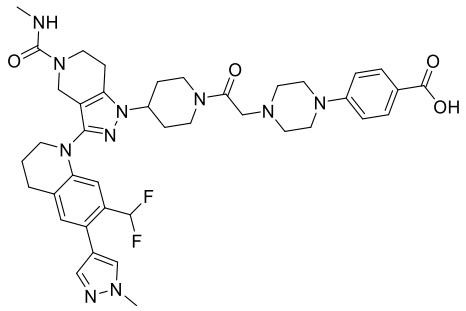
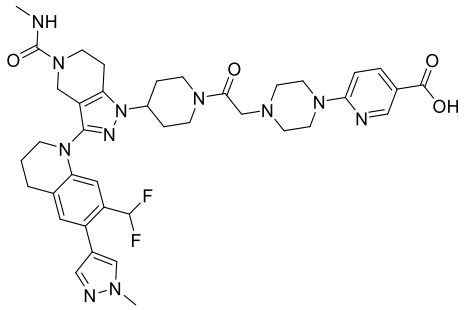
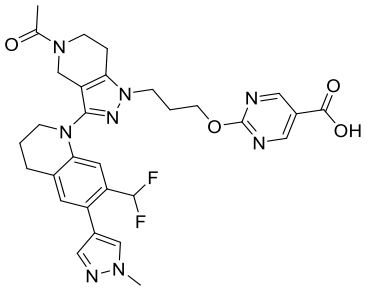
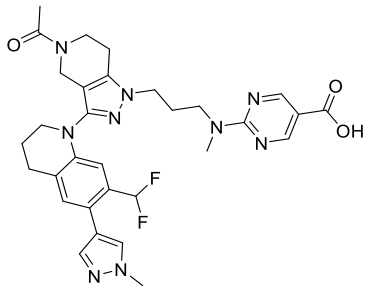
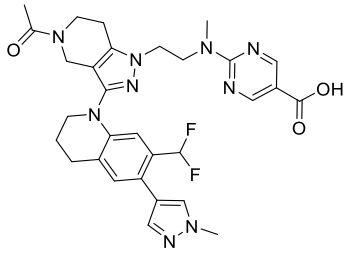
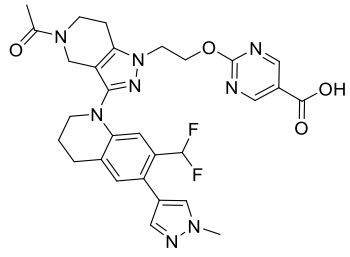
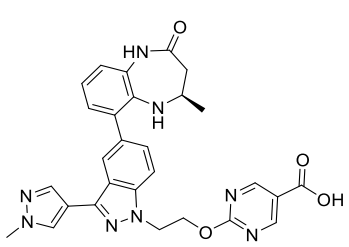
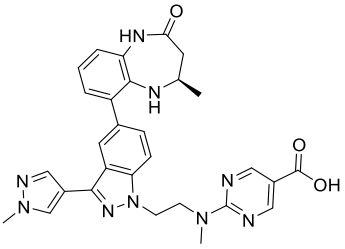
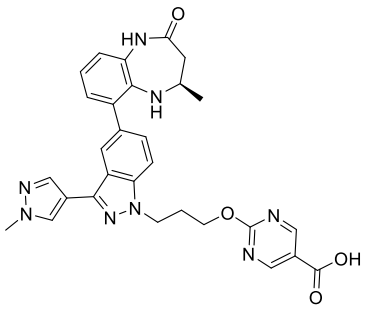
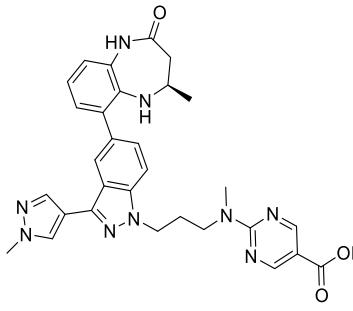
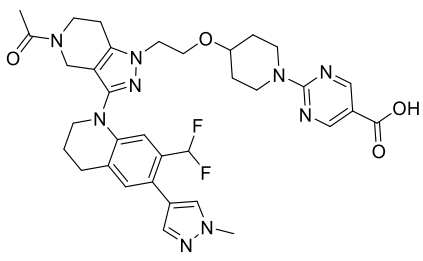
[00309] Forma de realización 121. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:

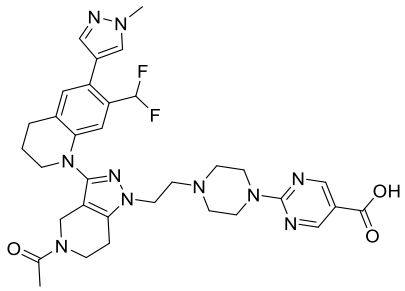
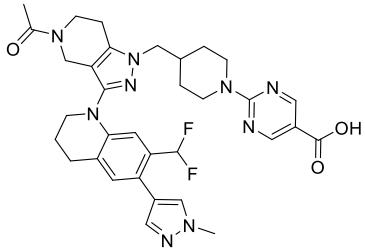
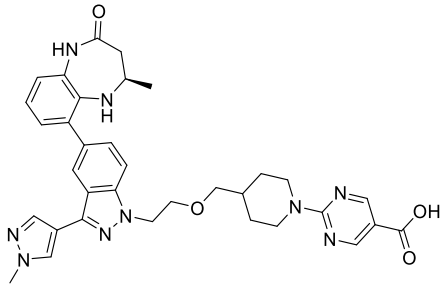
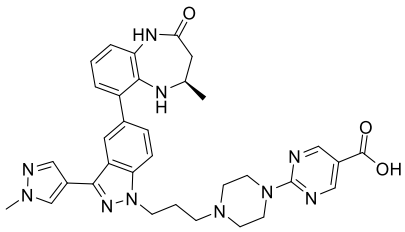
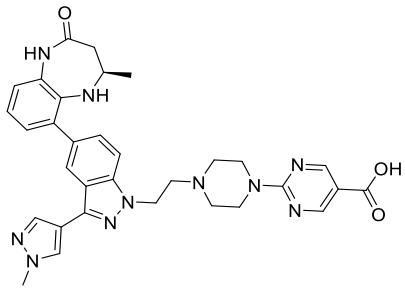
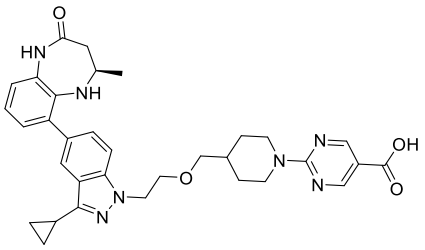
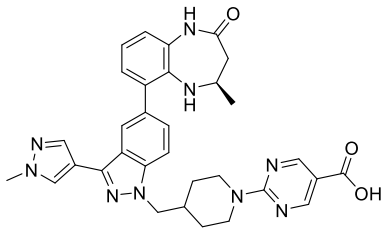
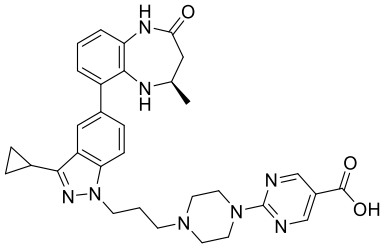
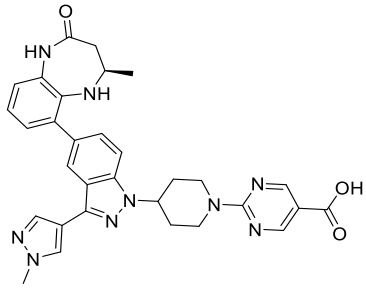
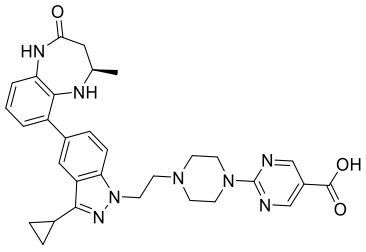
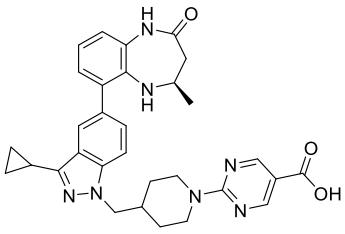
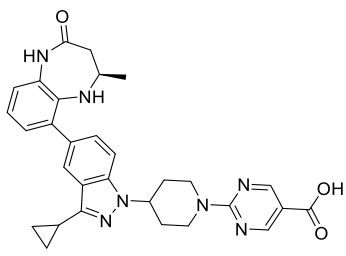
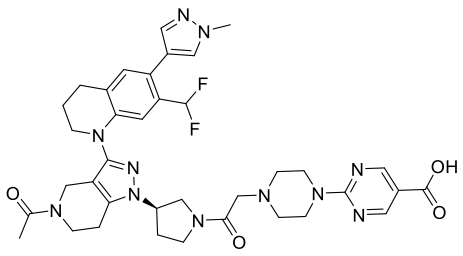

,

,

,

,

,

,

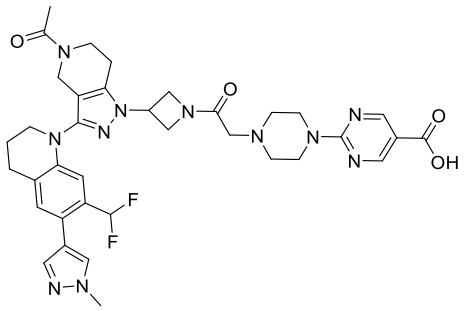
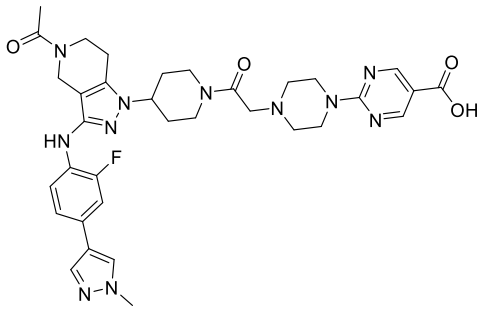
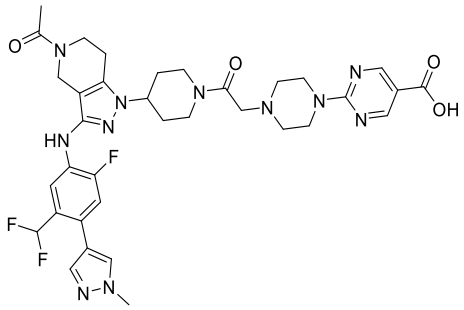
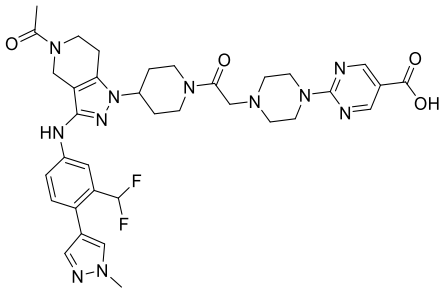
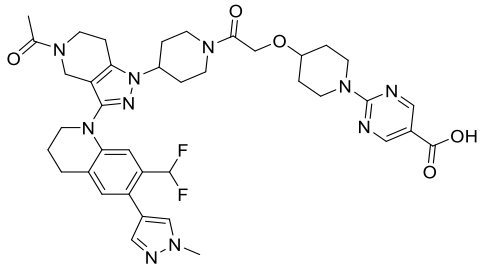
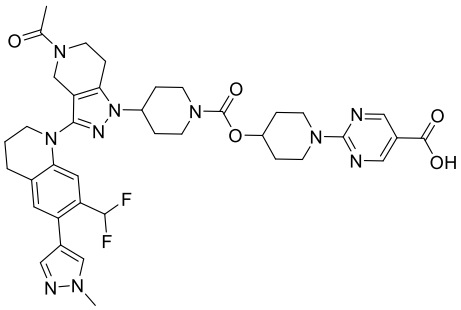
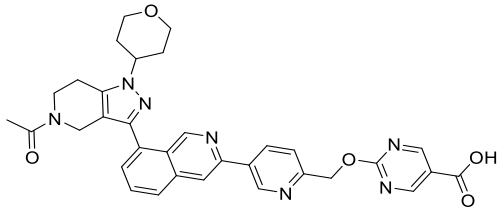
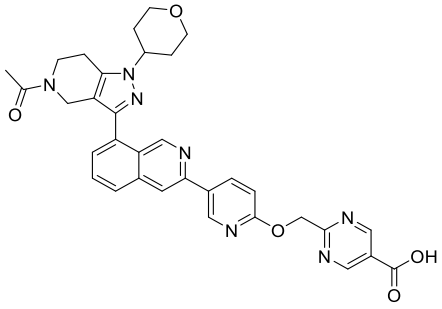
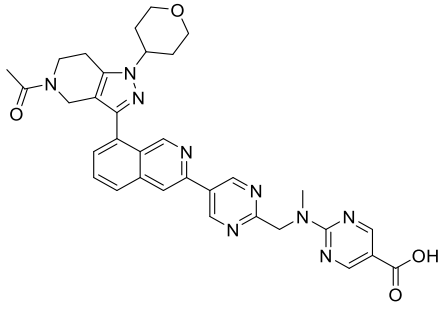
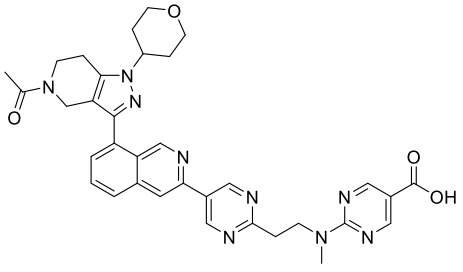

,

,

,

,

,

,

,

,

,


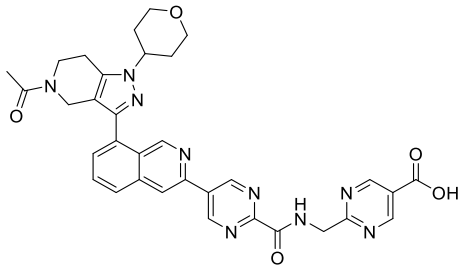
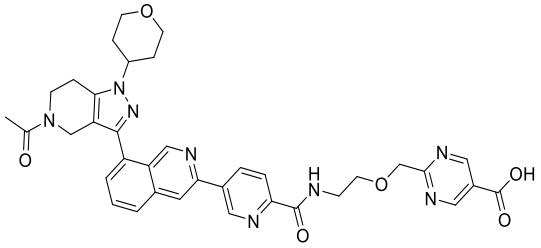
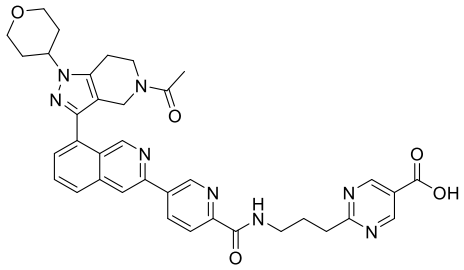
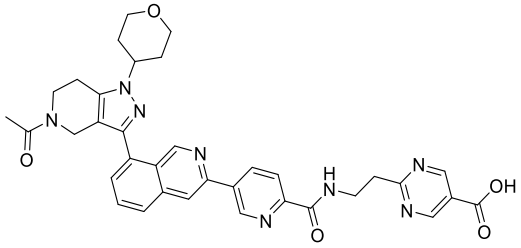
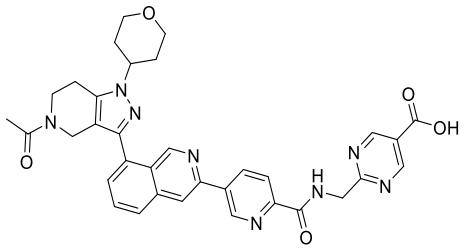
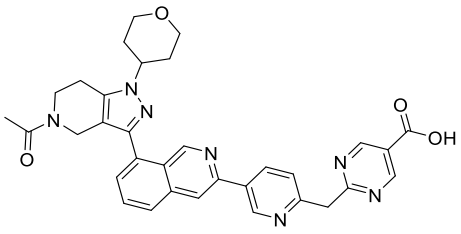
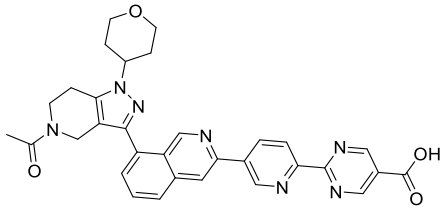
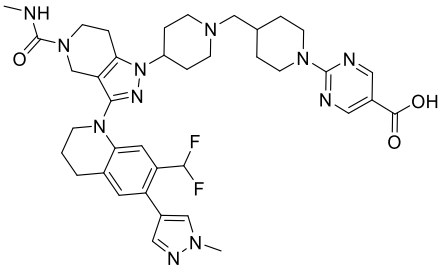
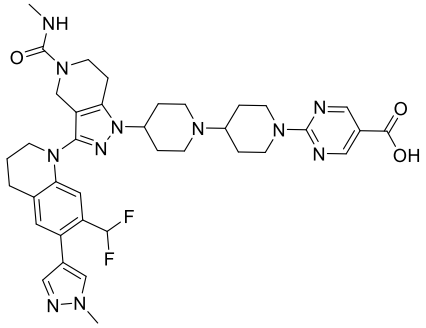
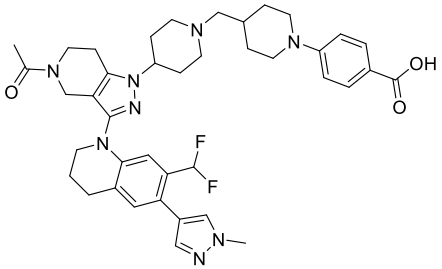
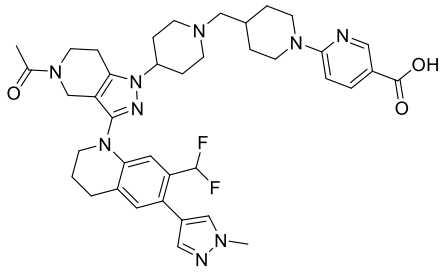
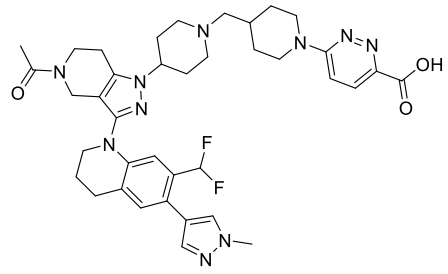

,

,

,

,

,

,

,

,

,

,

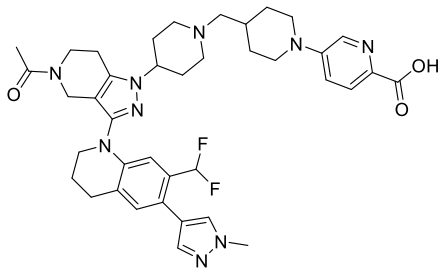
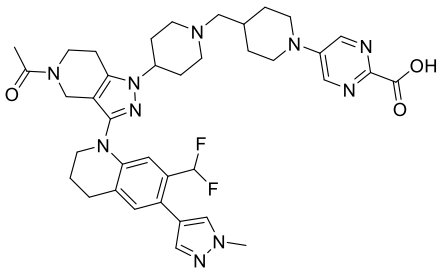
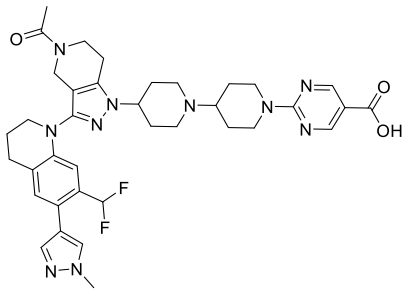
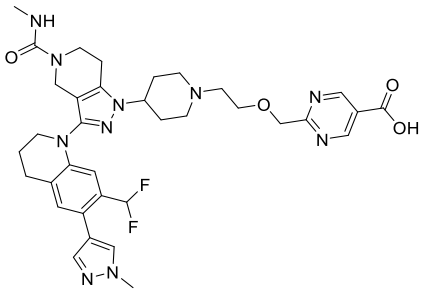
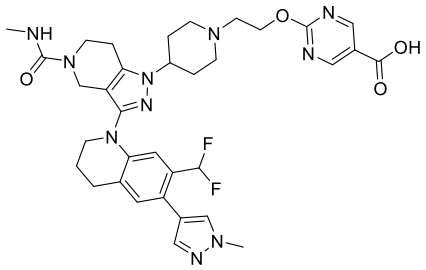
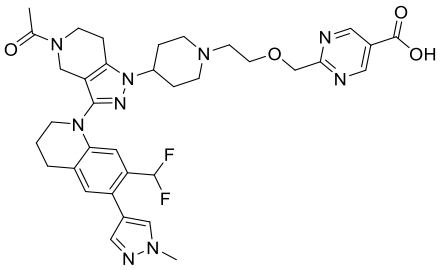
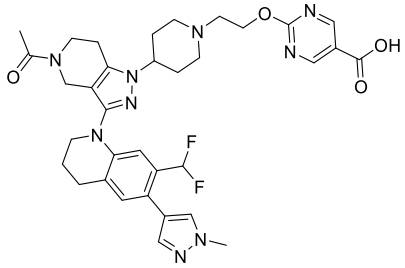
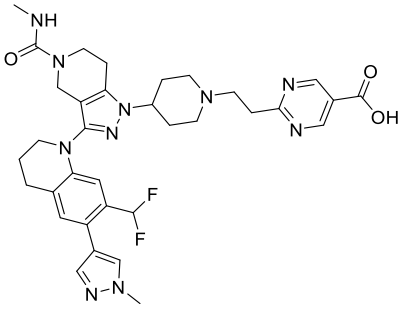
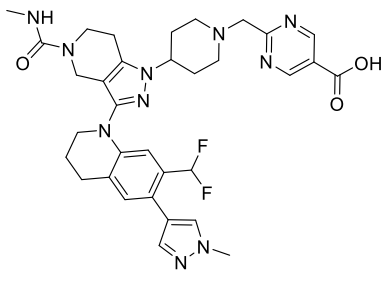

,

,

,

,

,

,

,

,

,

,

,

,

,

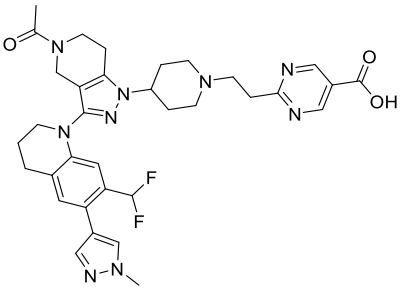

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

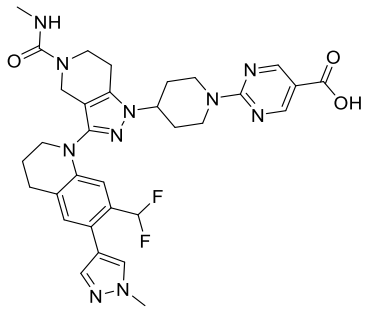
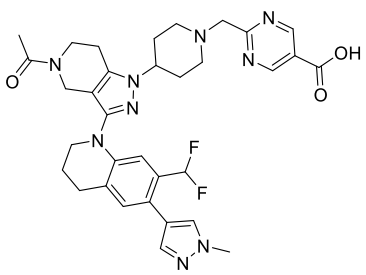
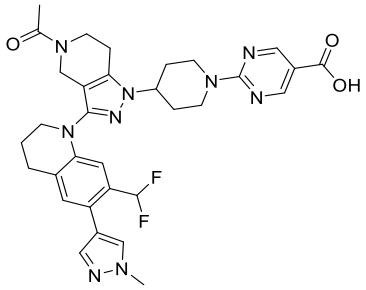
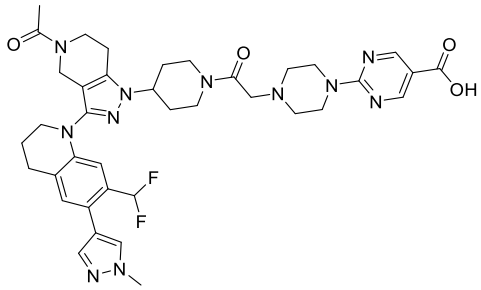
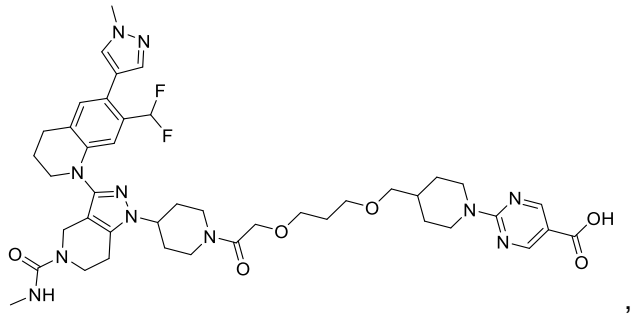
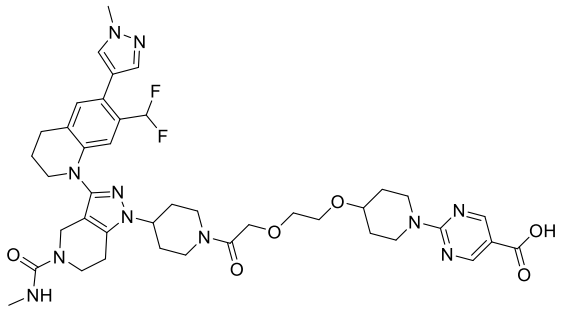
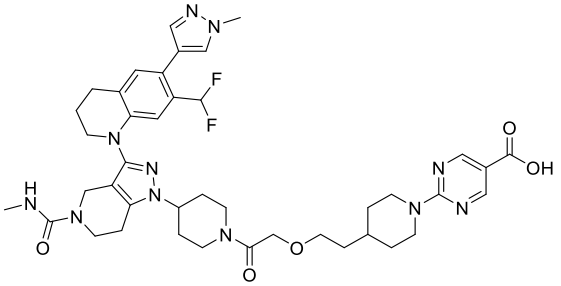
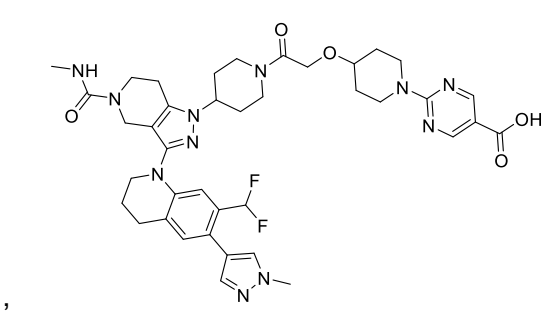
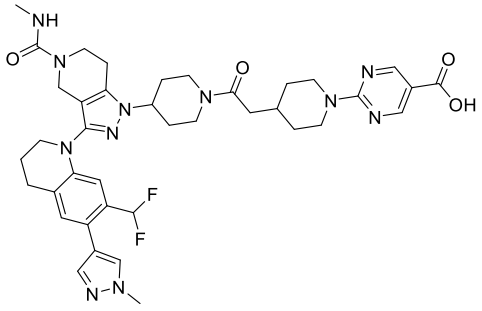
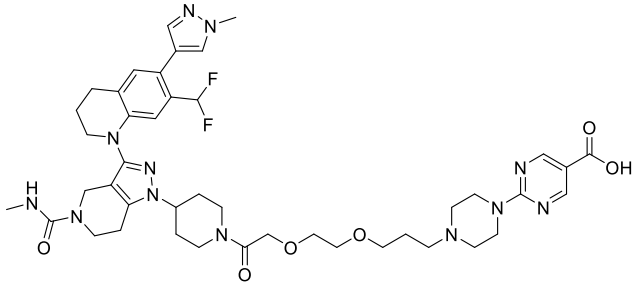

,

,

,

,

,

,

,

,

,

,

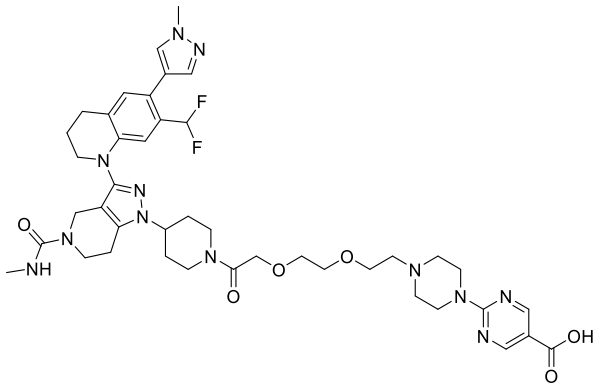
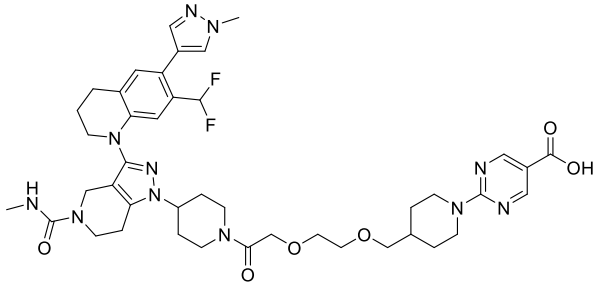
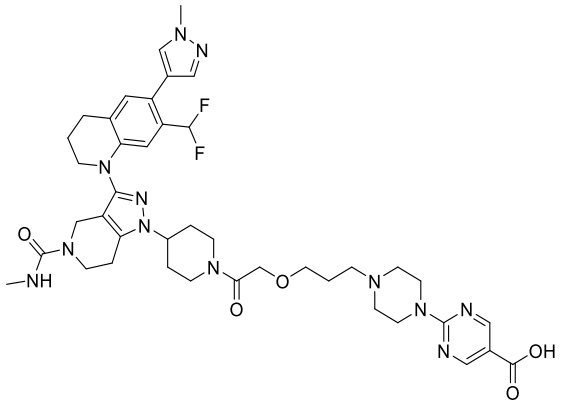
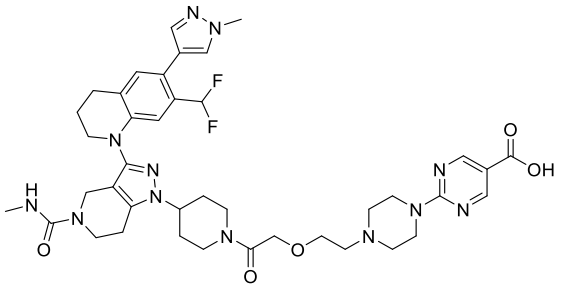
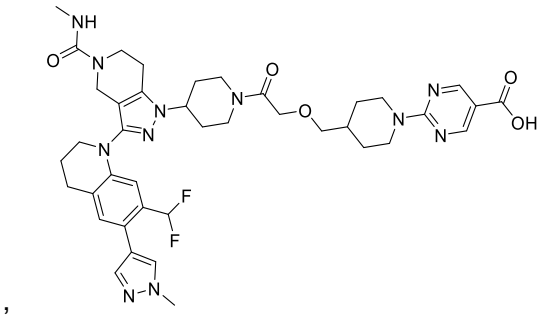
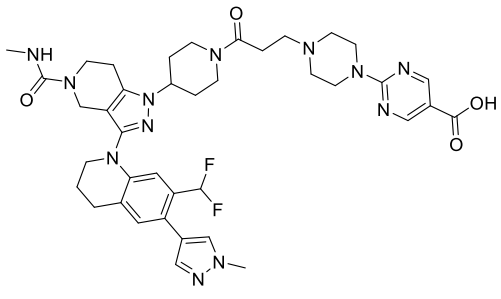

,

,

,

,

,

,

,

,

,

,

,

,

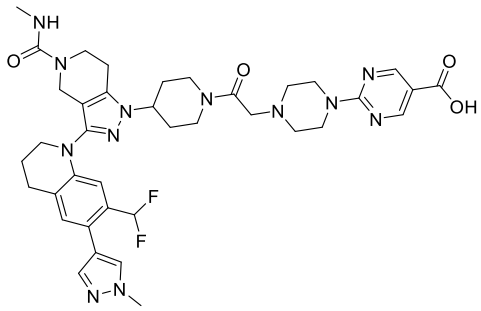
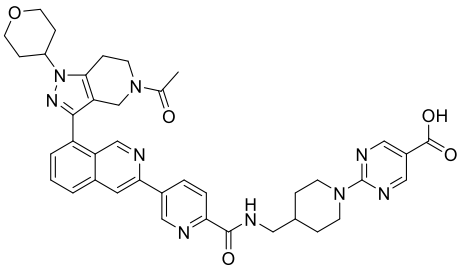
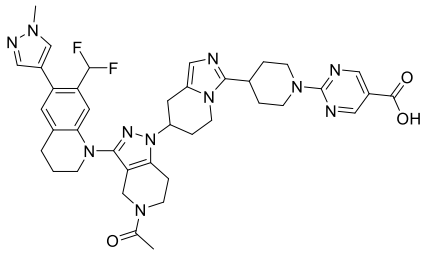
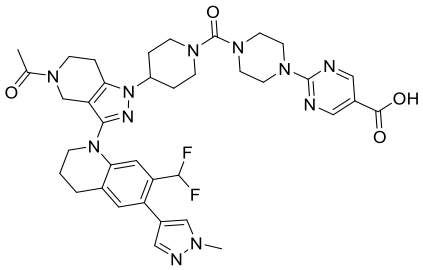
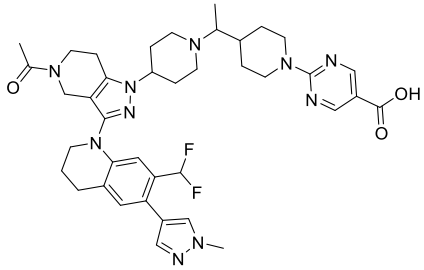
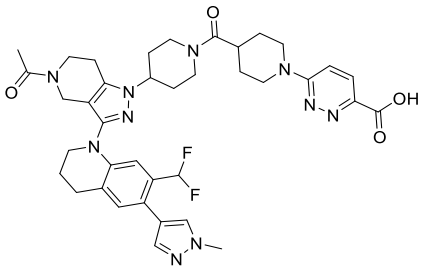
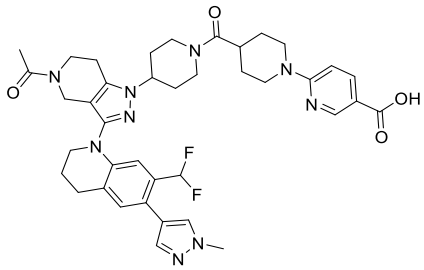
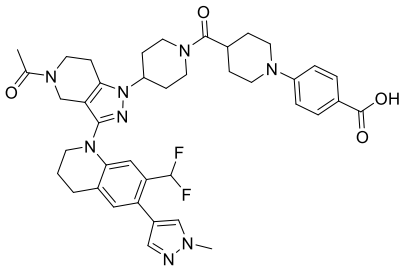
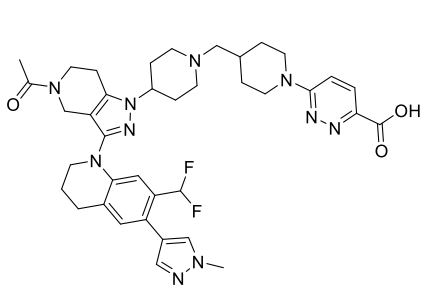
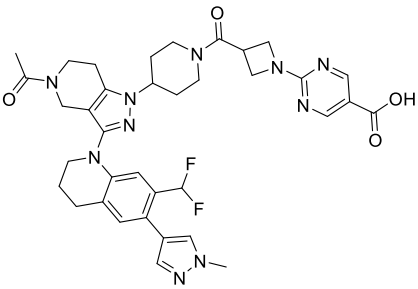

,

,

,

,

,

,

,

,

,

,

,

,

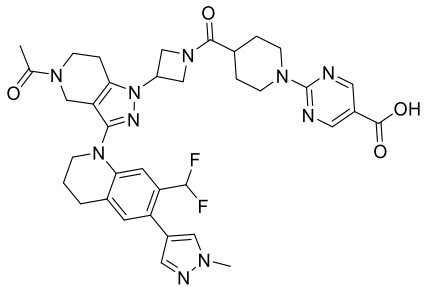
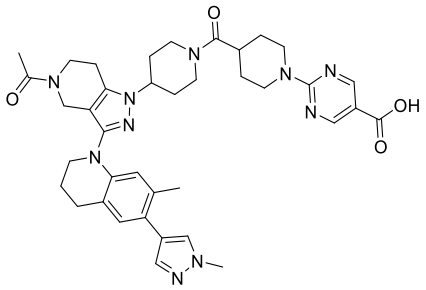
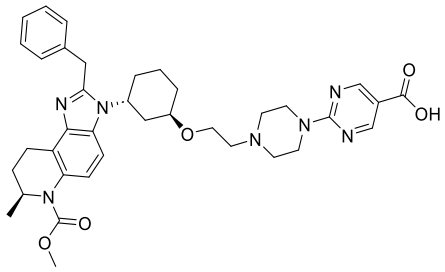
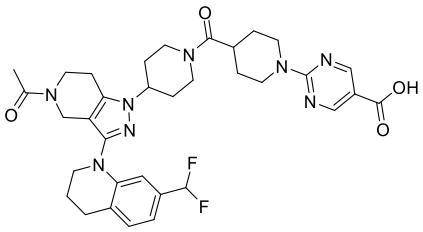
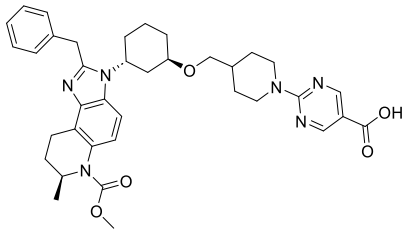
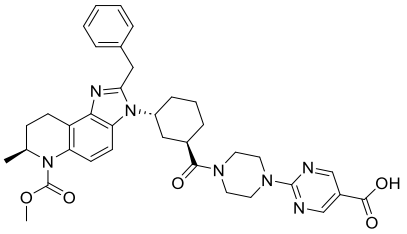
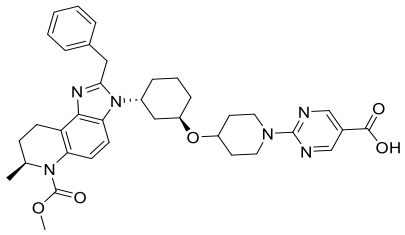
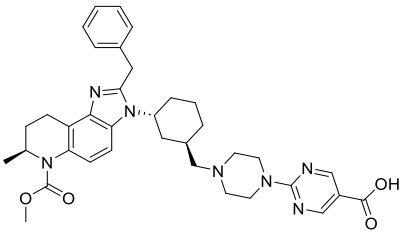
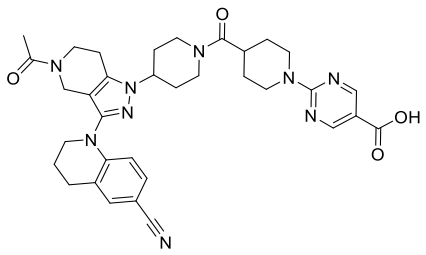
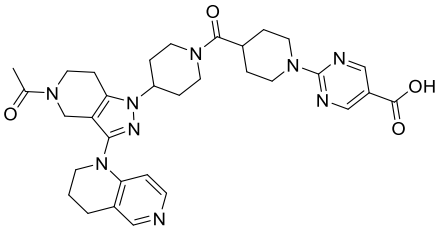
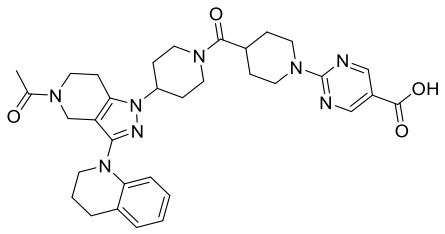
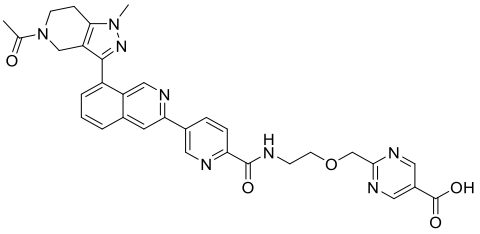

,

,

,

,

,

,

,

,

,



,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

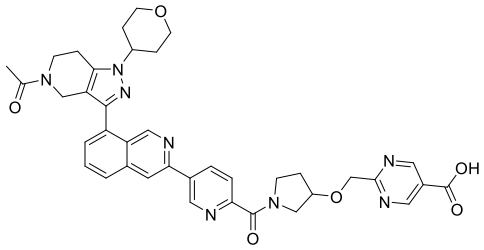
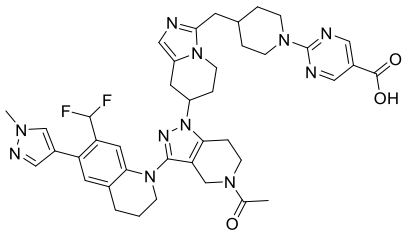
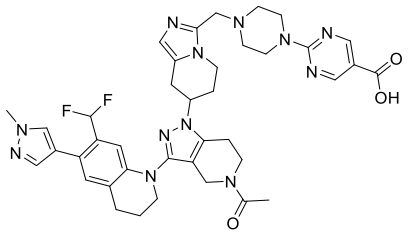
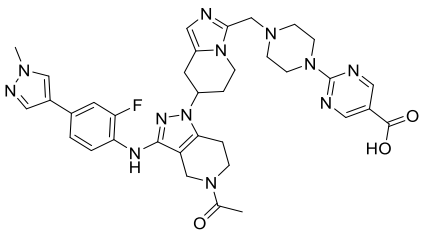
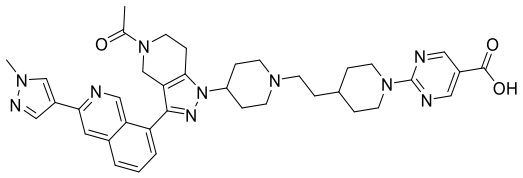
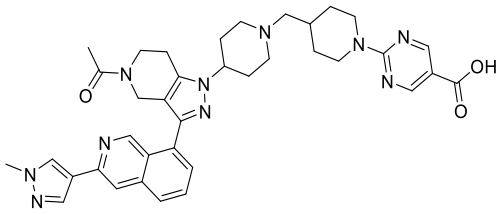
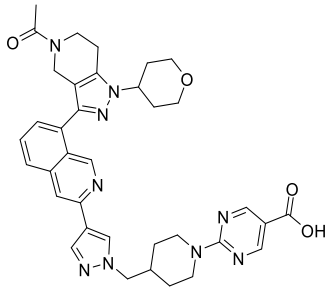
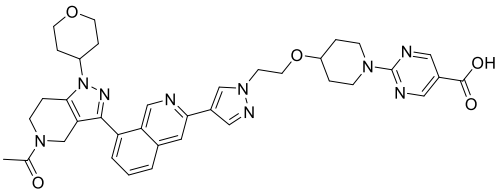
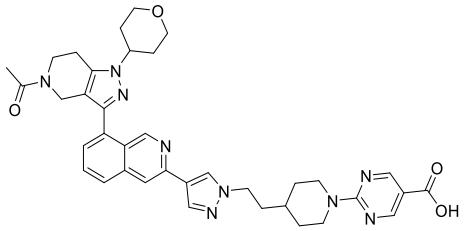
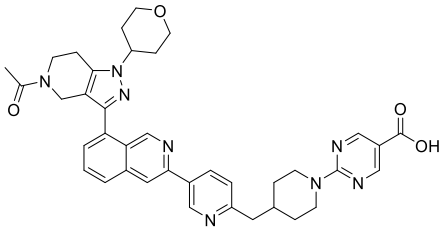
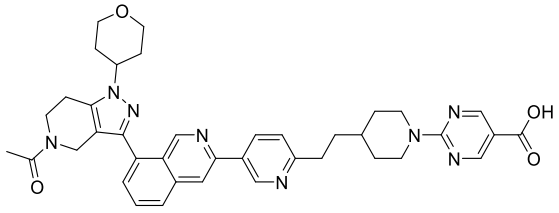
,

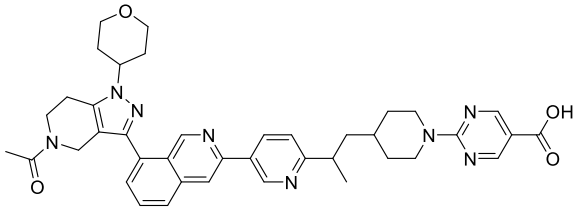
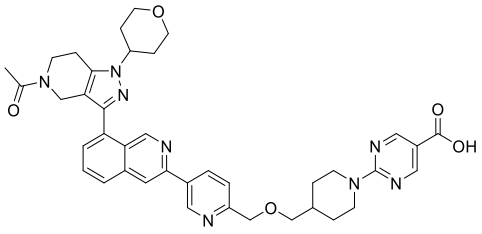
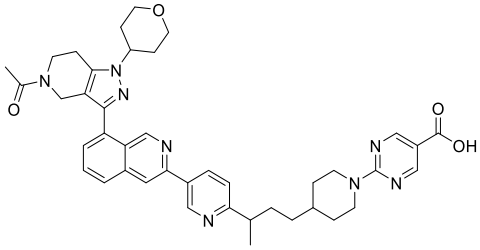
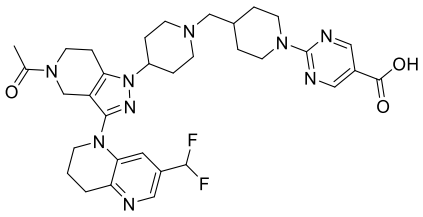
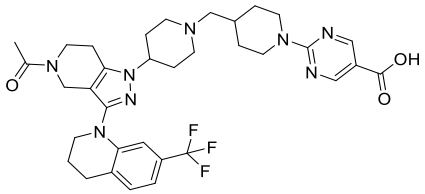
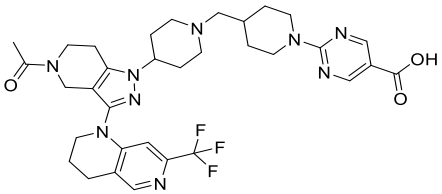
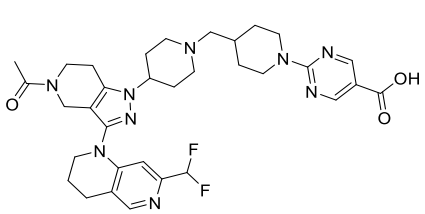
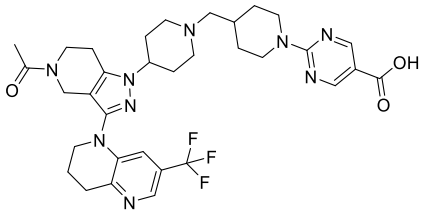
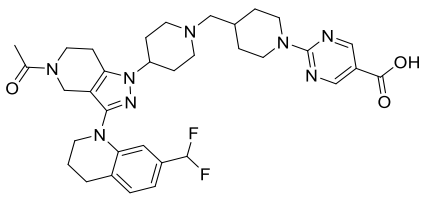
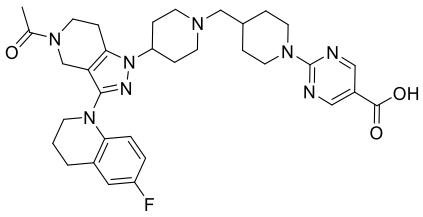
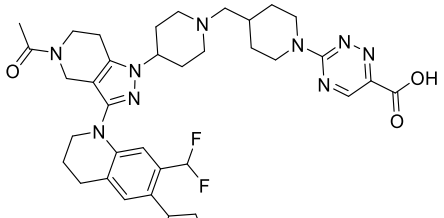
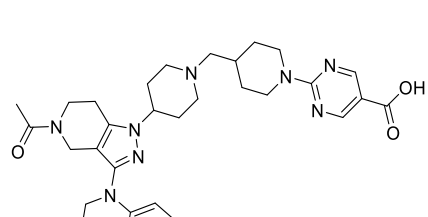
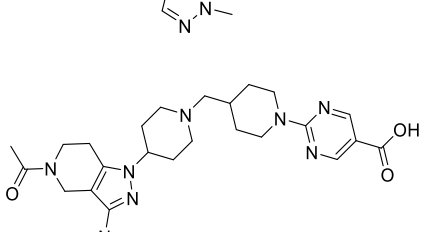
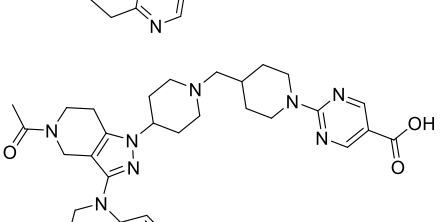
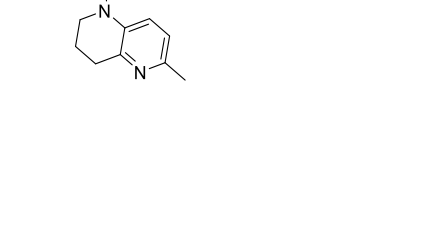
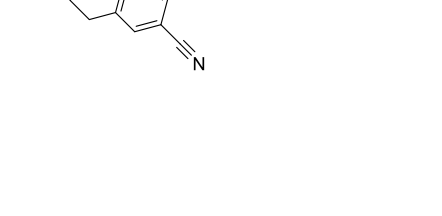
,

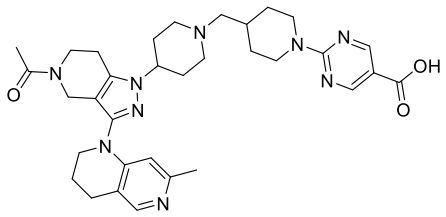
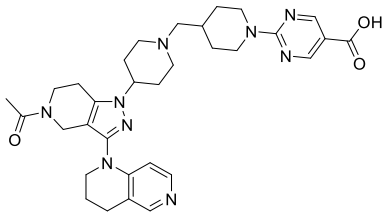
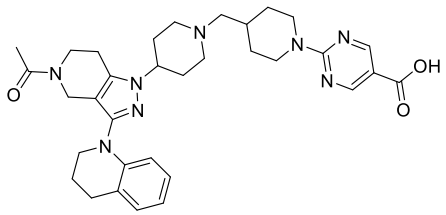
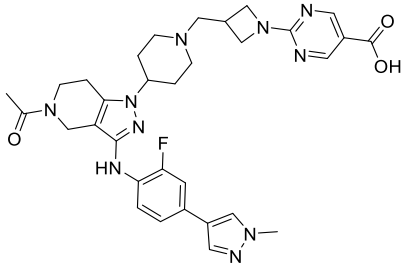
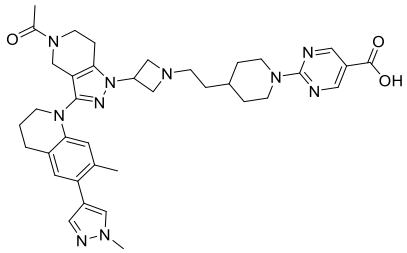
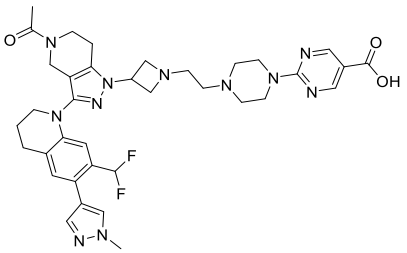
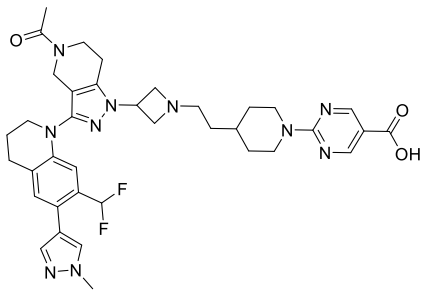
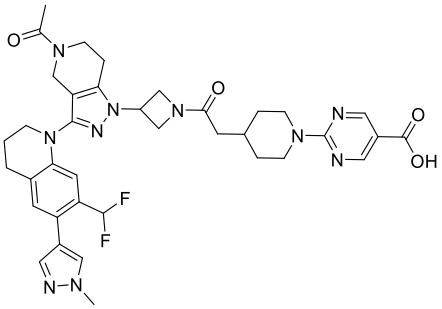
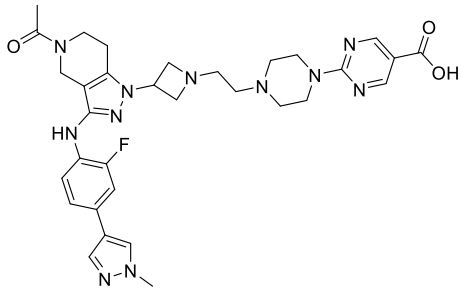
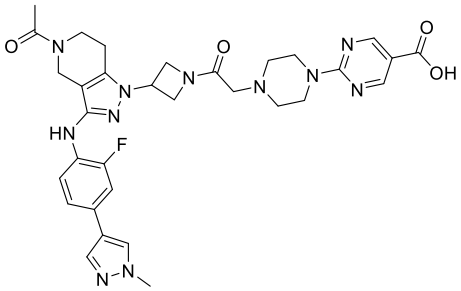
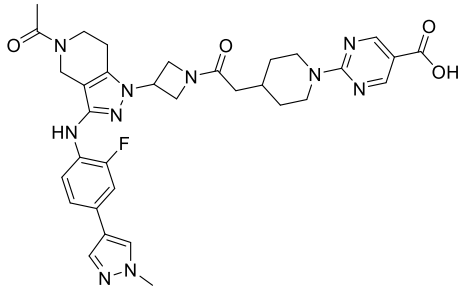
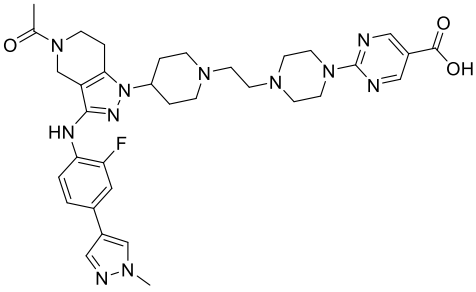

,

,

,

,

,

,

,

,

,

,

,

,

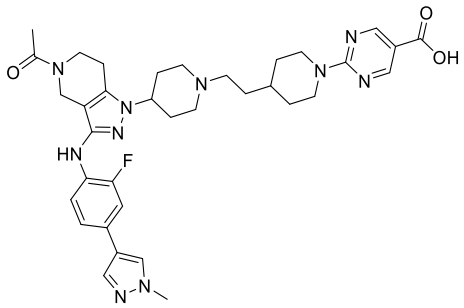
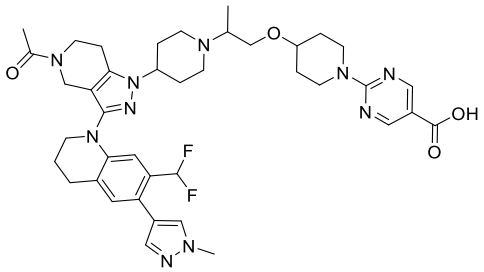
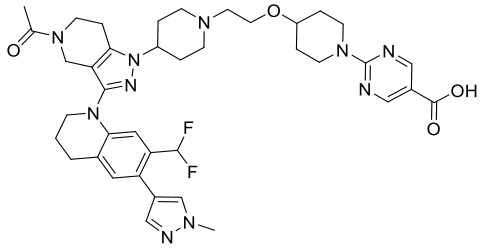
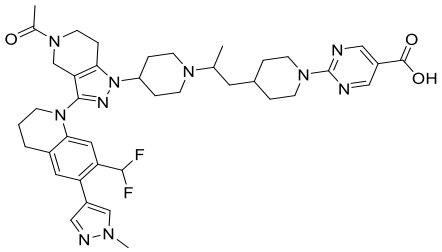
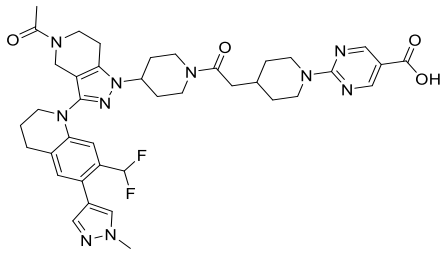
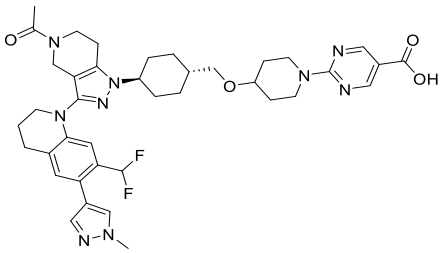
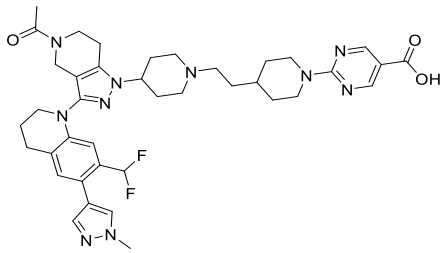
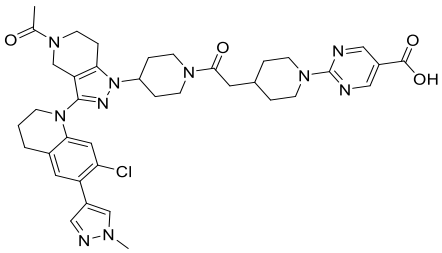
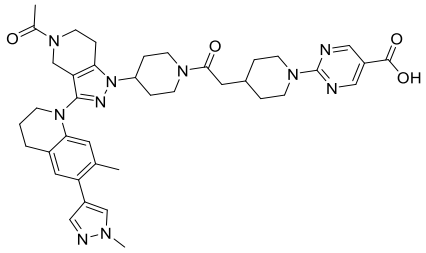
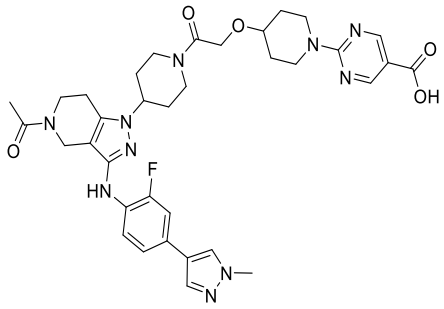
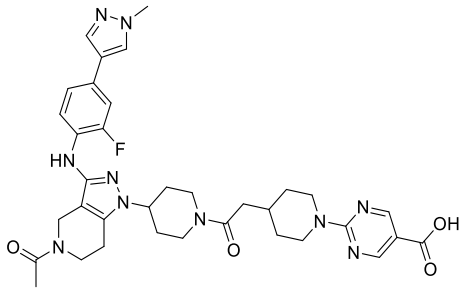
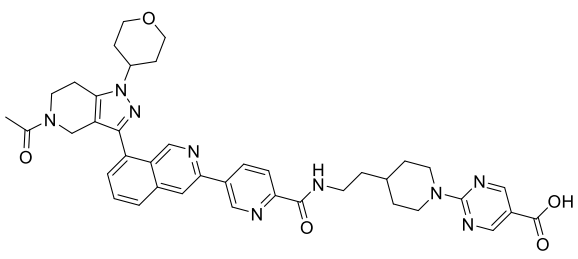
,

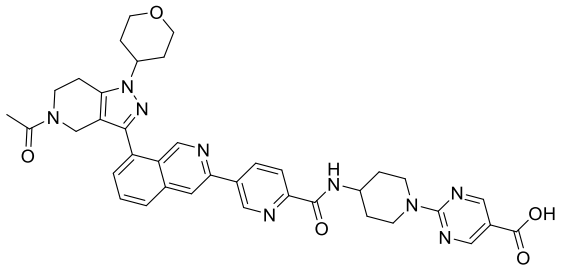
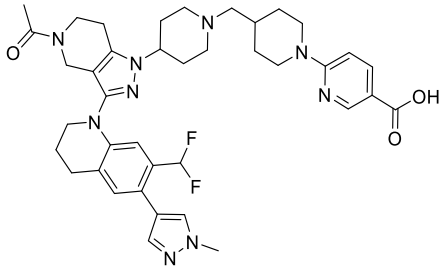
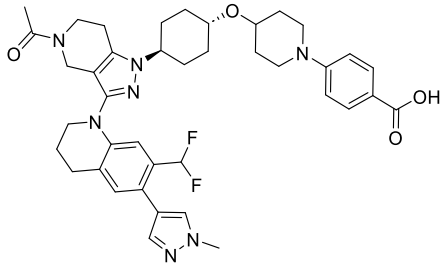
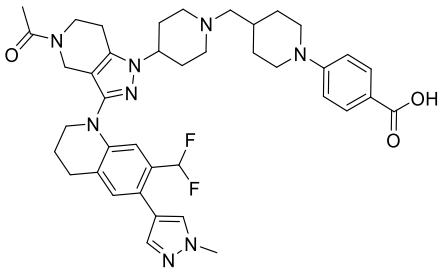
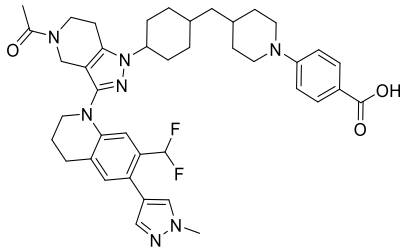
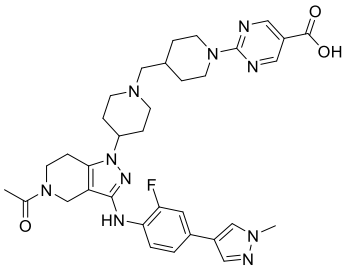
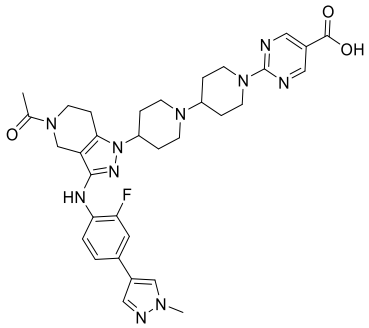
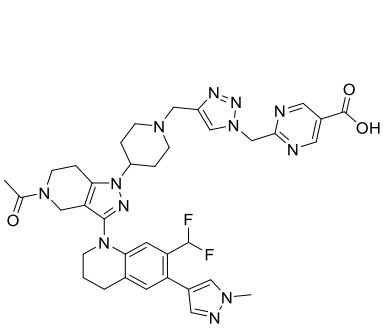
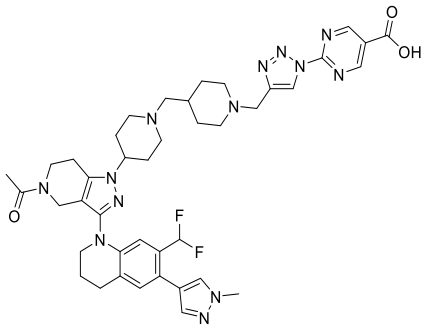
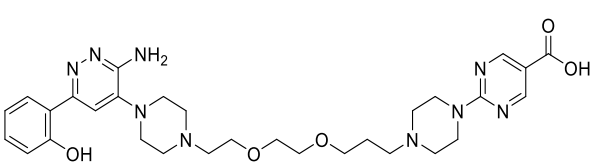
,

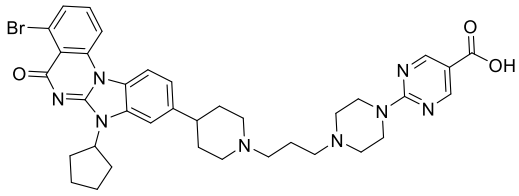
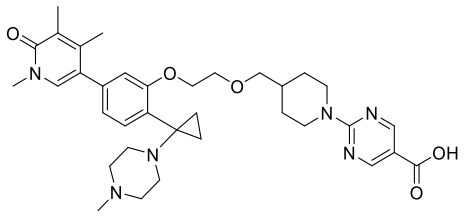
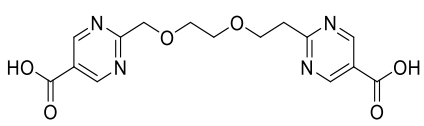
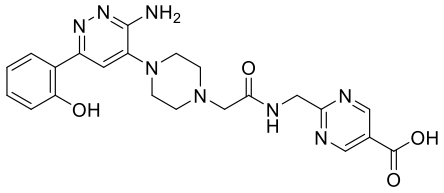
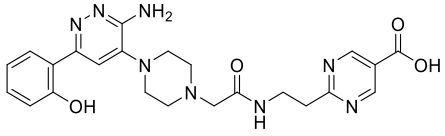
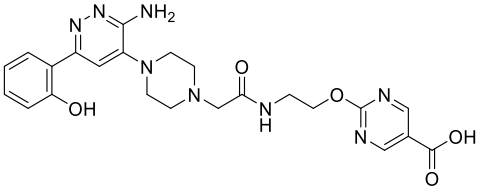
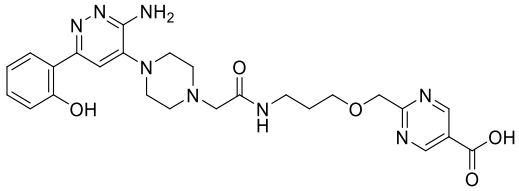
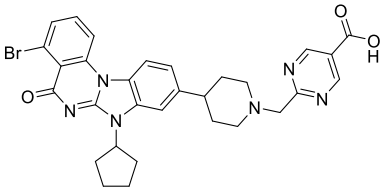
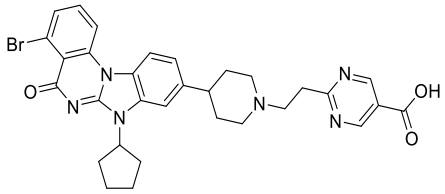
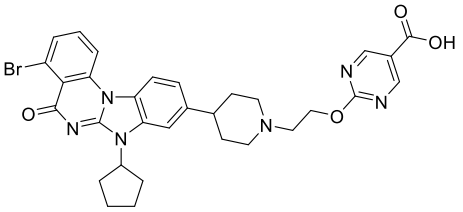
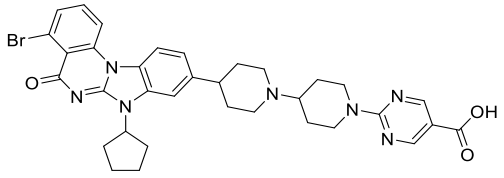
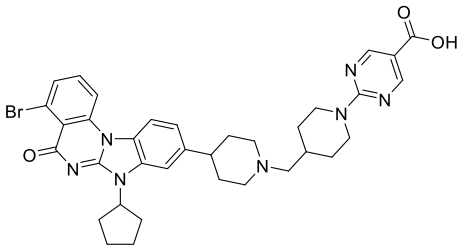
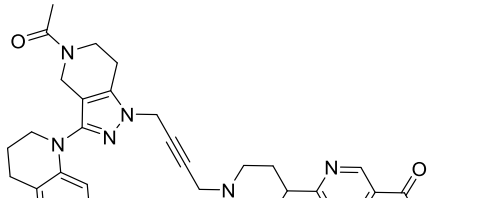

,

,

,

,

,

,

,

,

,

,



,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

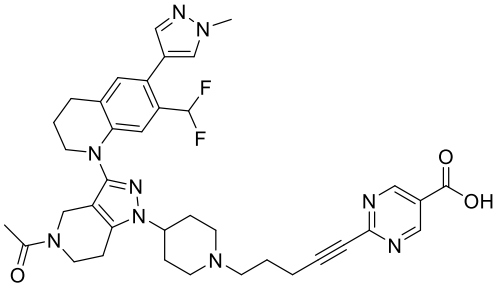

,

,

,

,

,

,

,

,

,

,

,

,

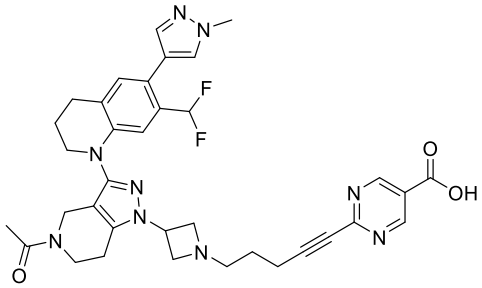
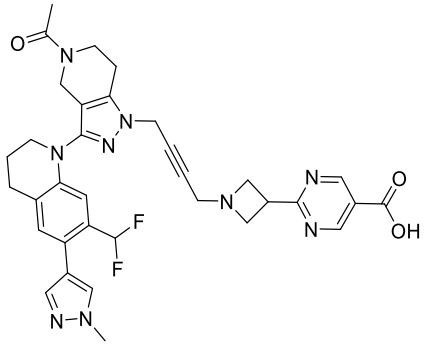
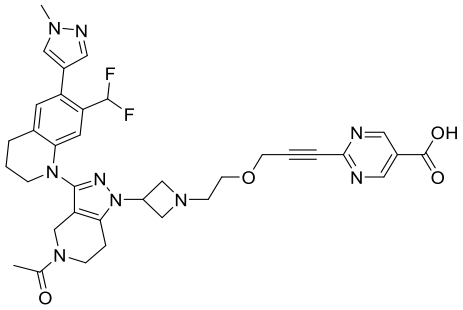
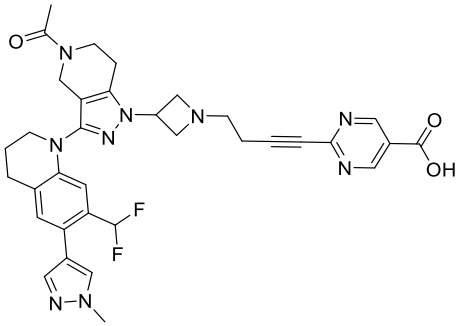
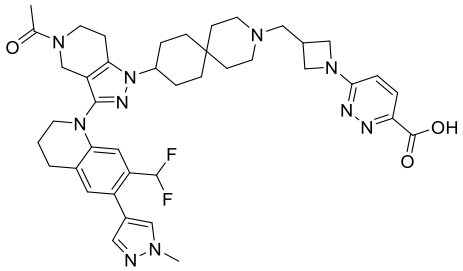
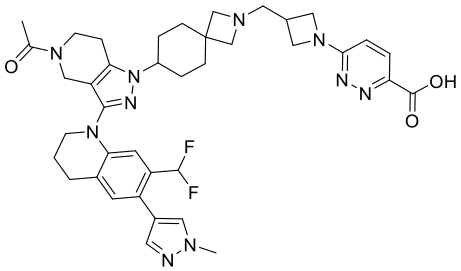
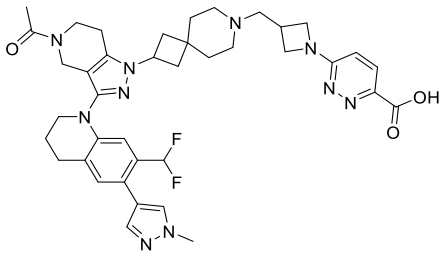
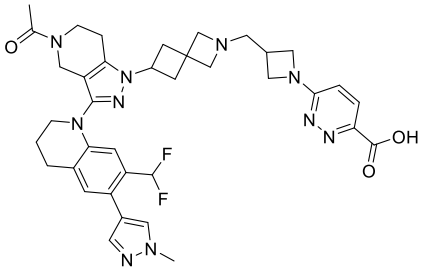
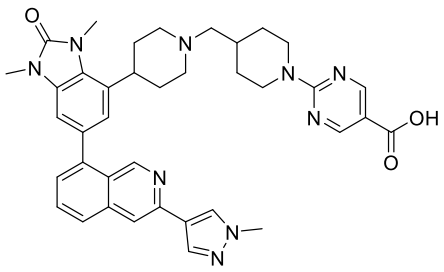
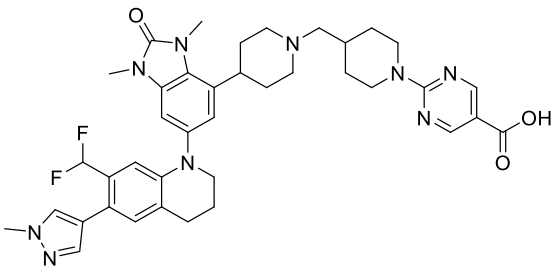

,

,

,

,

,

,

,

,

,

,

,

,

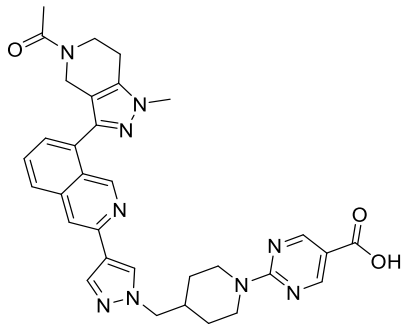
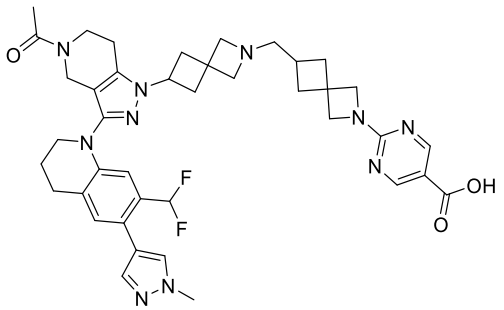
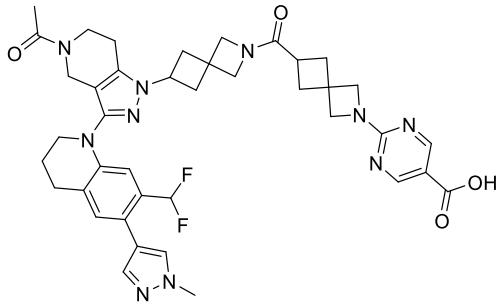
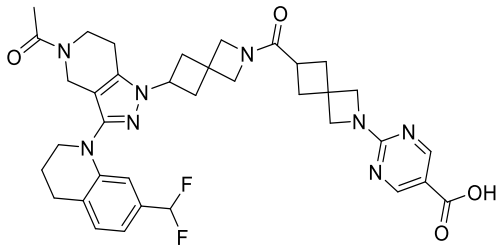
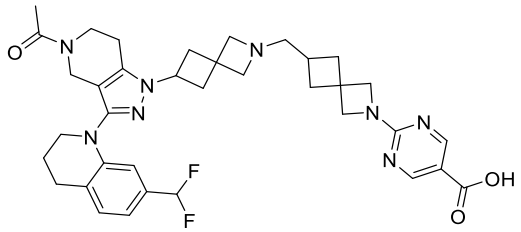
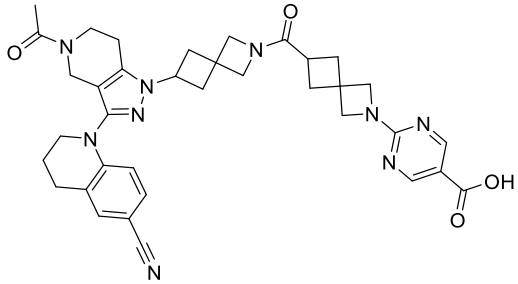
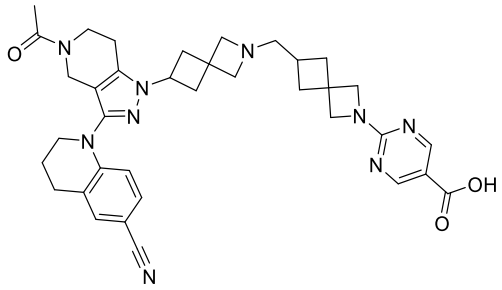
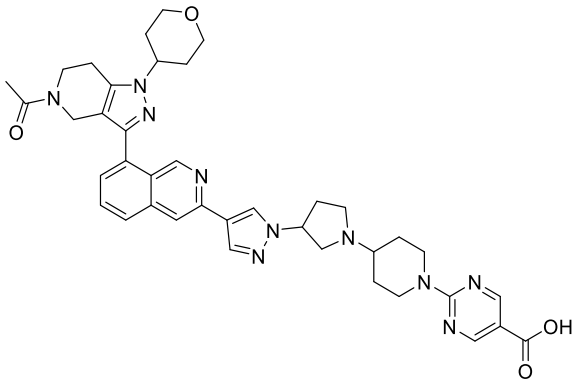
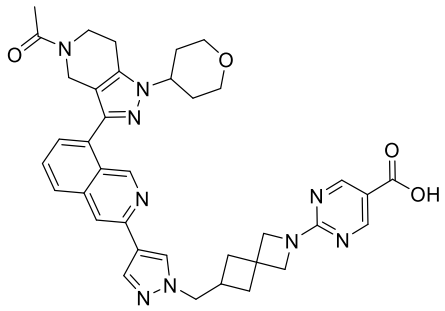
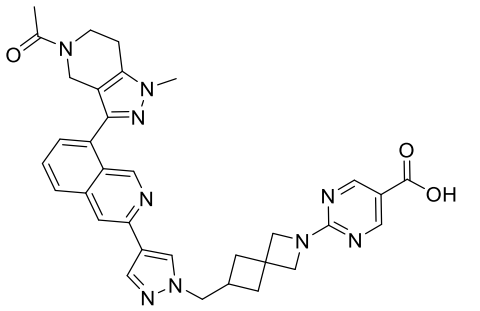

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

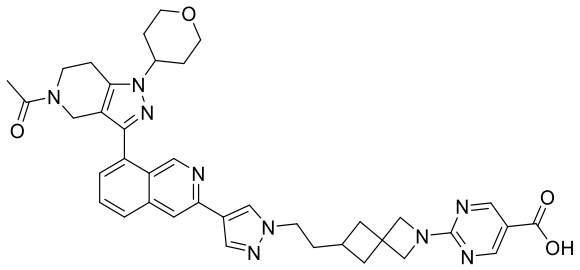
,

,

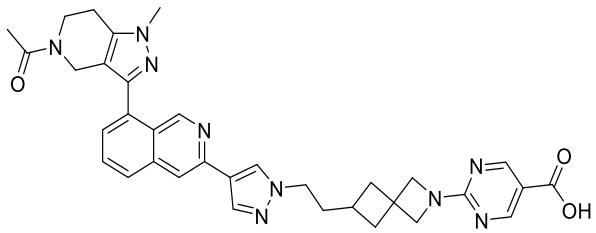

,

,

,

,

,

,

,

,

,

,

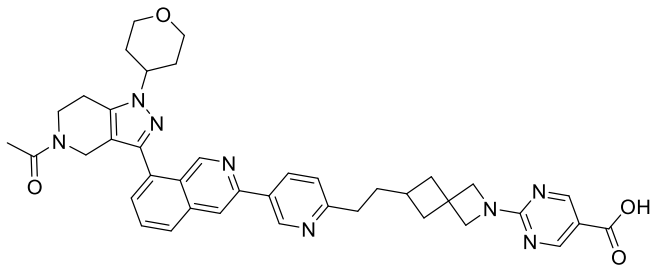

,

,

,

,

,

,

,

,

,

,

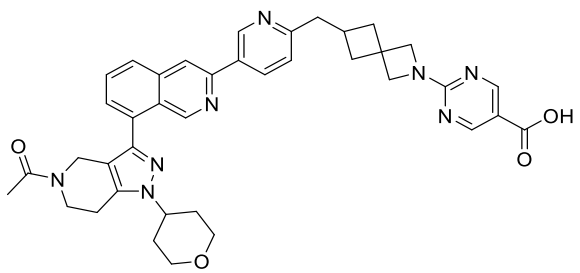
,

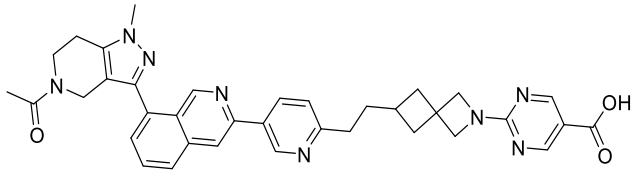
,

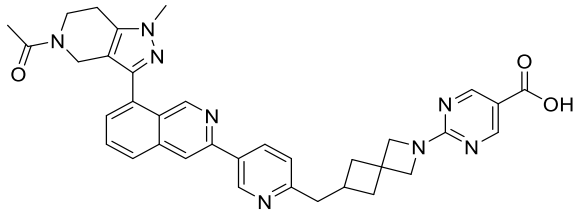

,

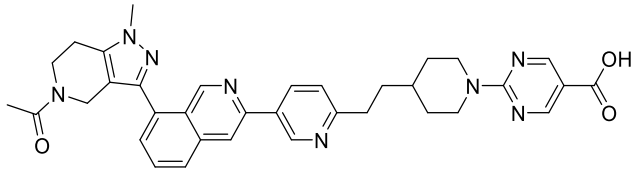

,

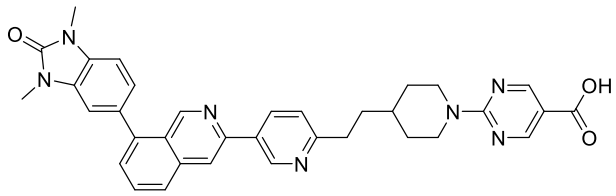

,

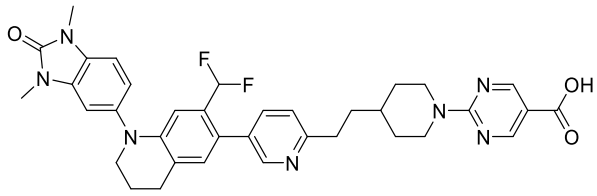

,

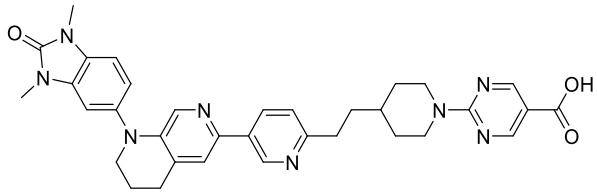

,

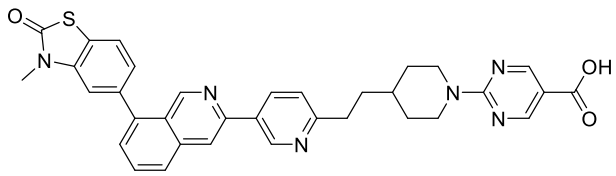

,

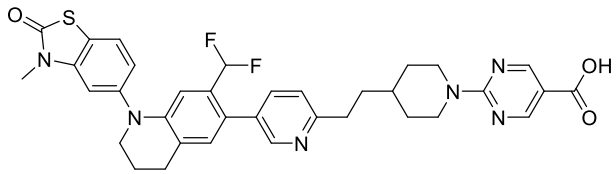

,

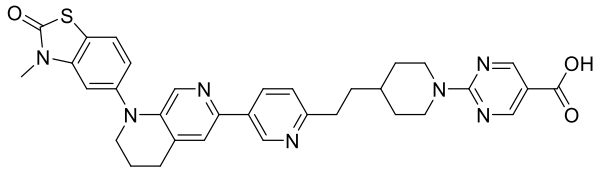

,

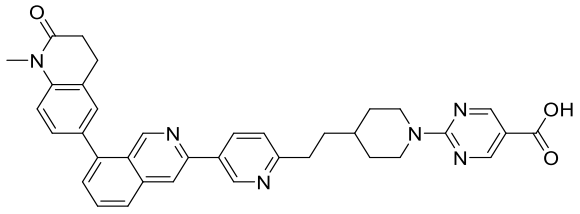

,

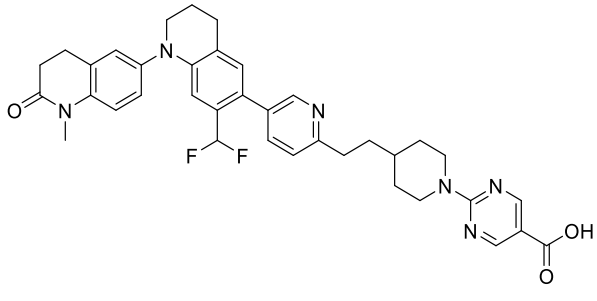

,

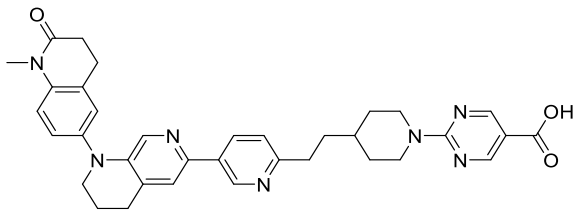
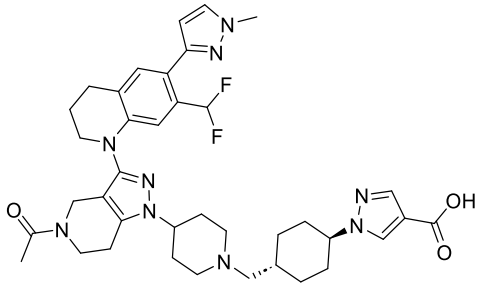
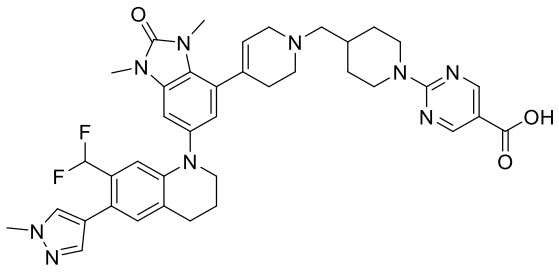
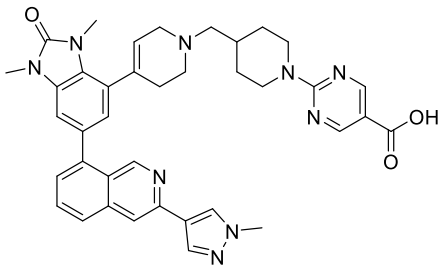
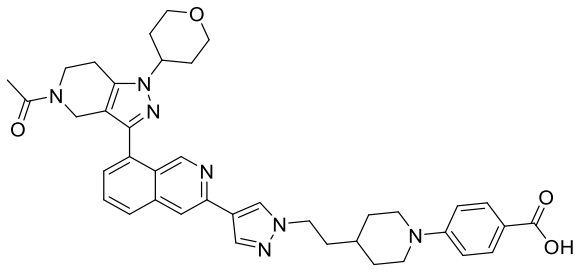
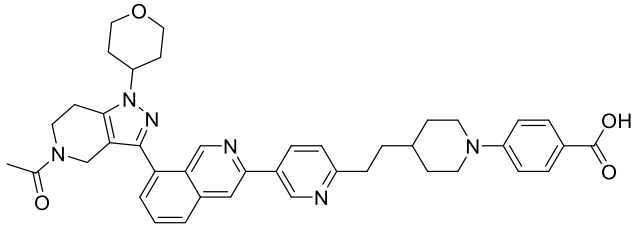
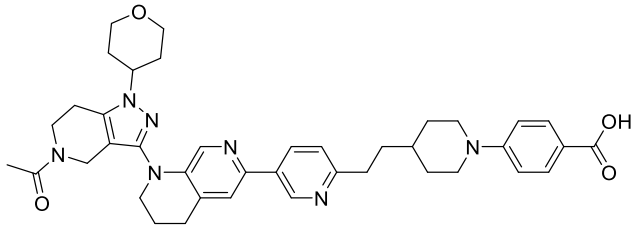
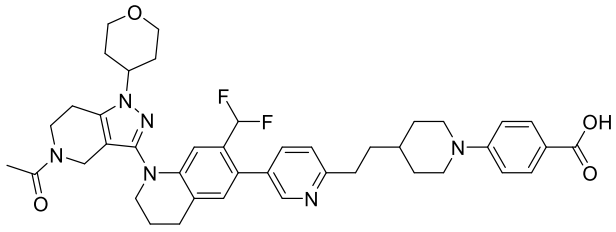

,

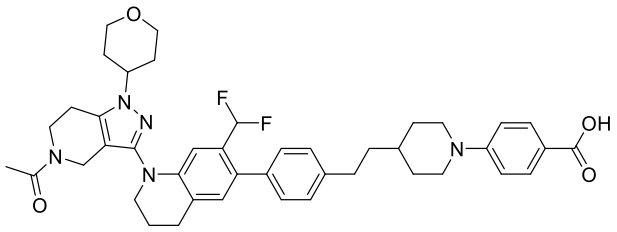
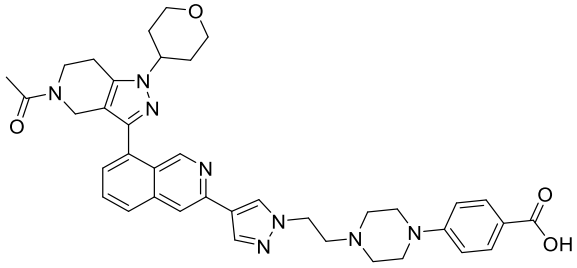
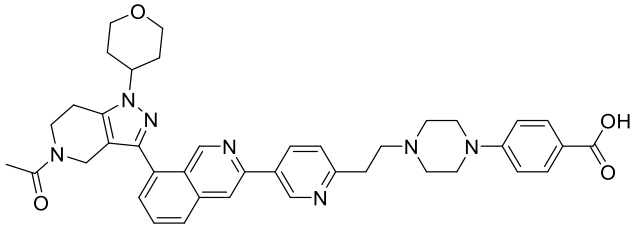
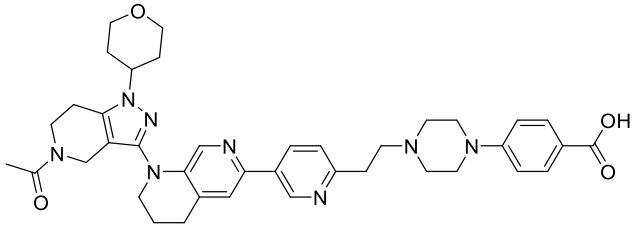
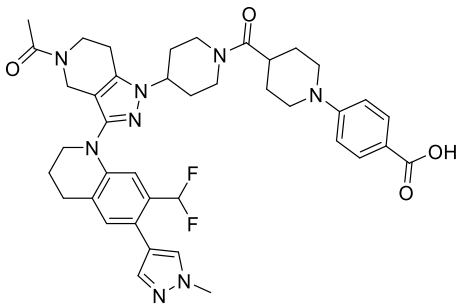
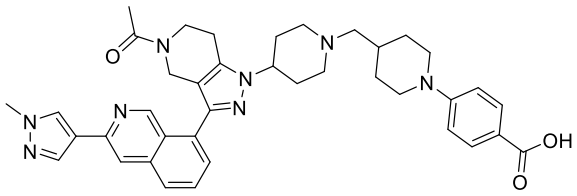
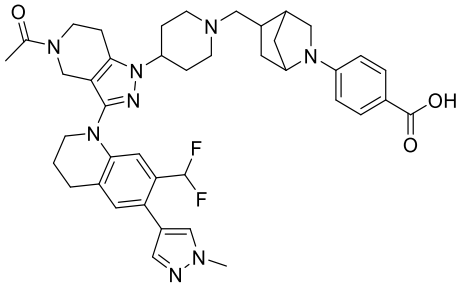
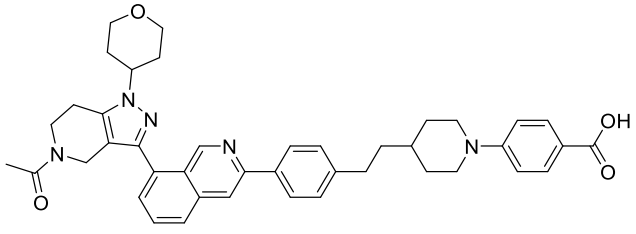

,

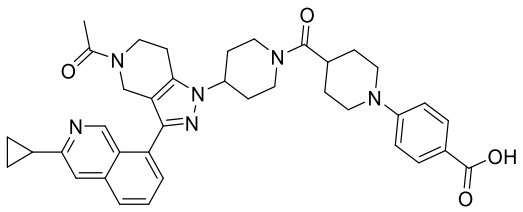
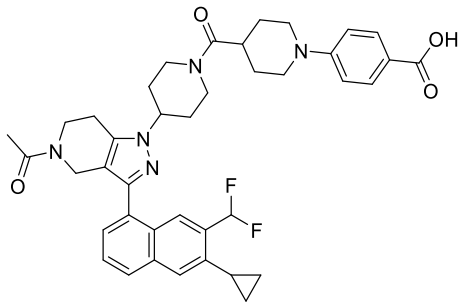
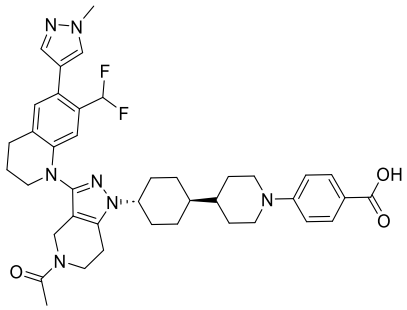
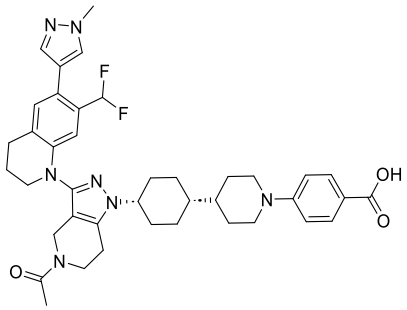
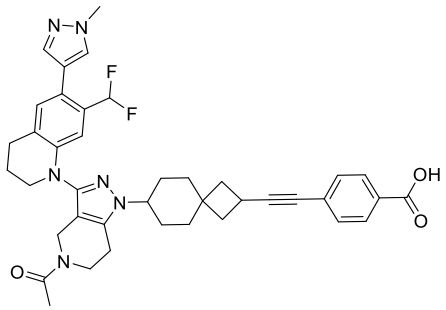
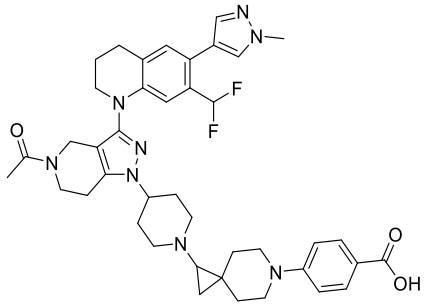
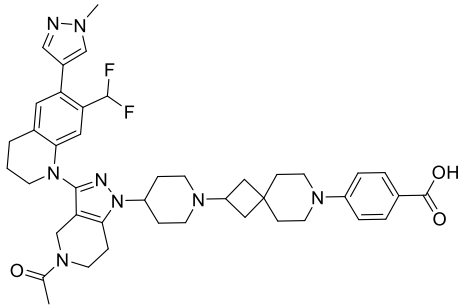
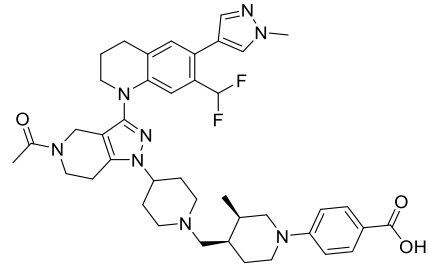
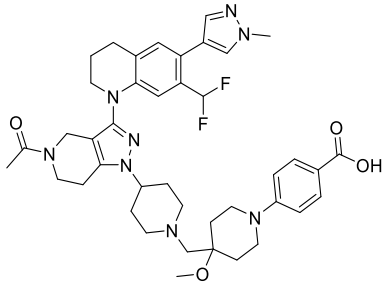
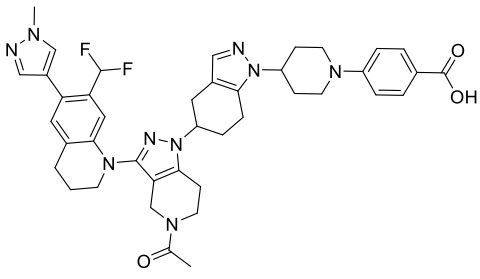

,

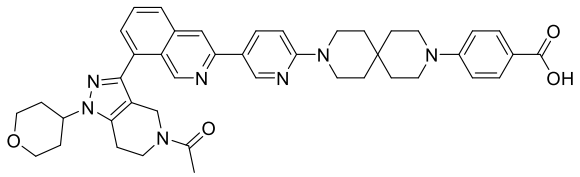
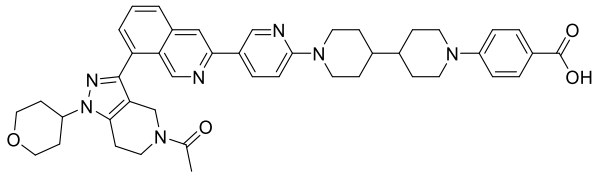
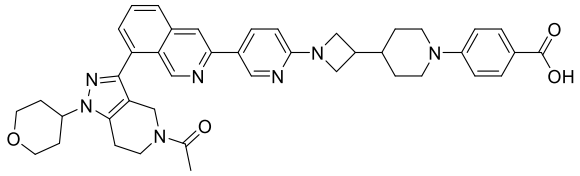
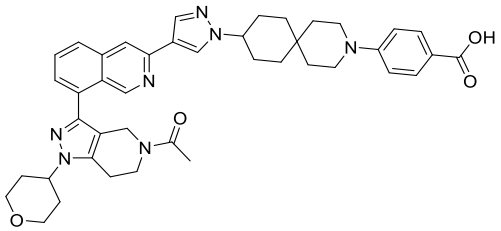
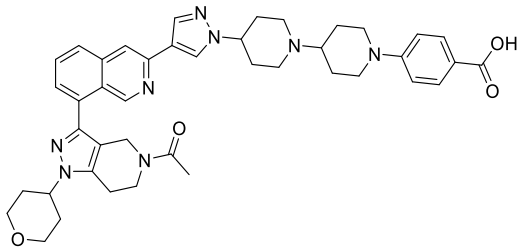
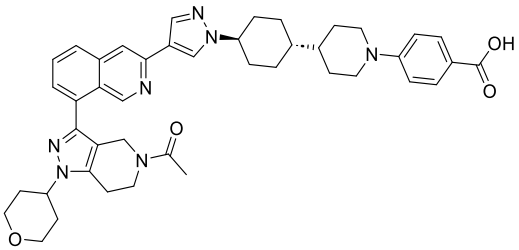
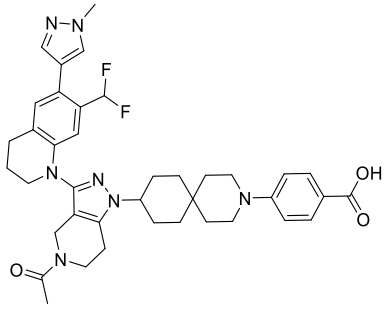
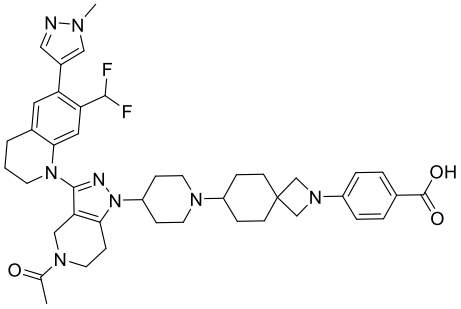
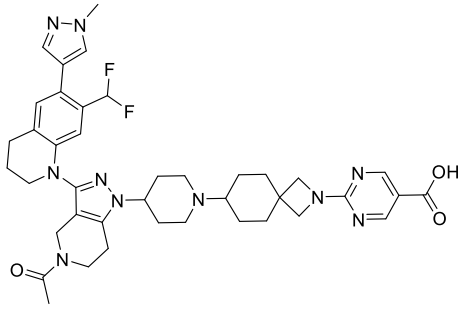
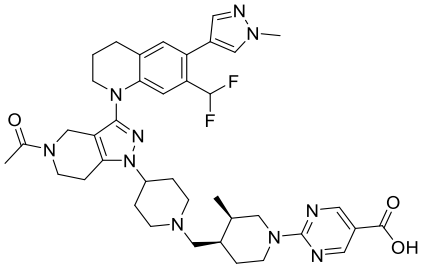

,

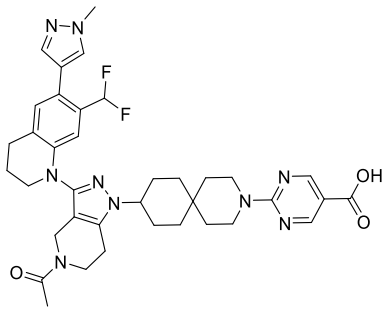
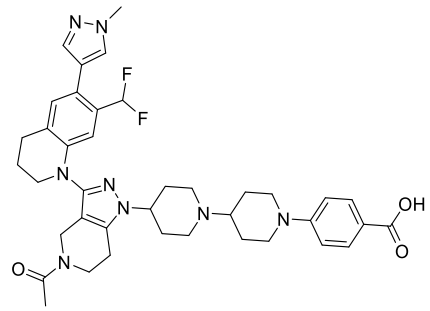
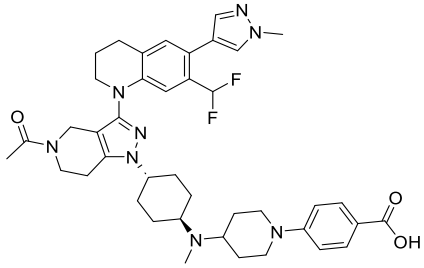
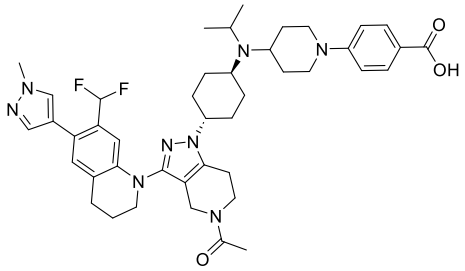
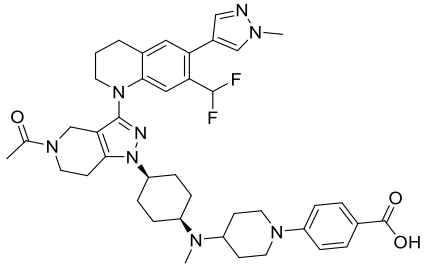
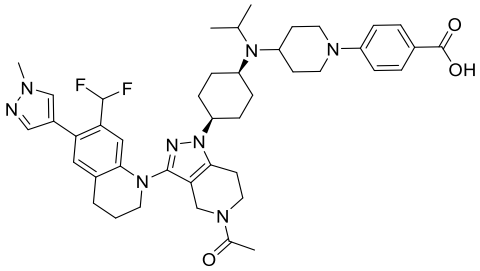
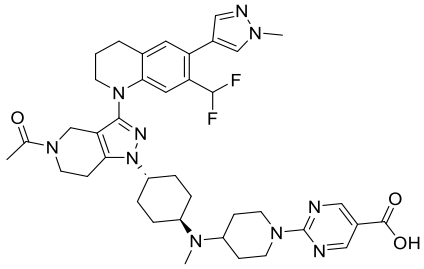
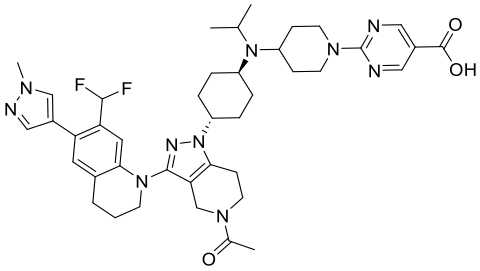
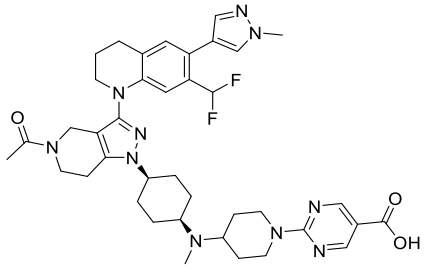
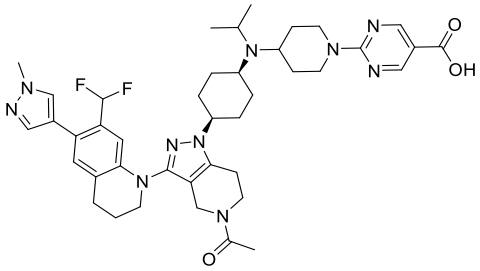

,

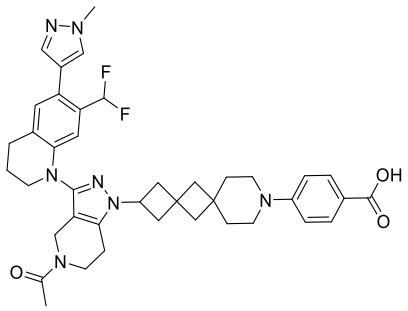
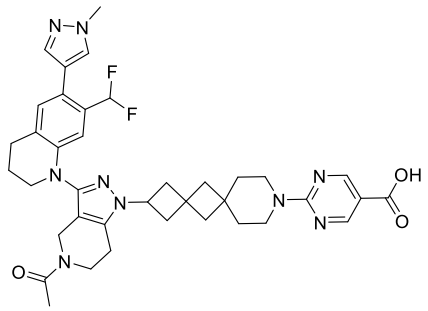
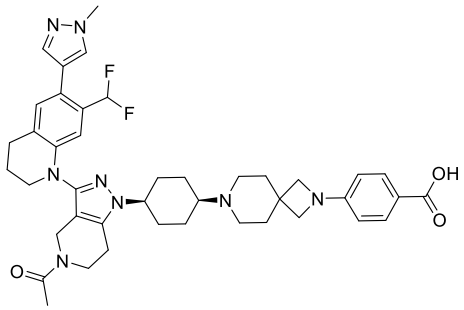
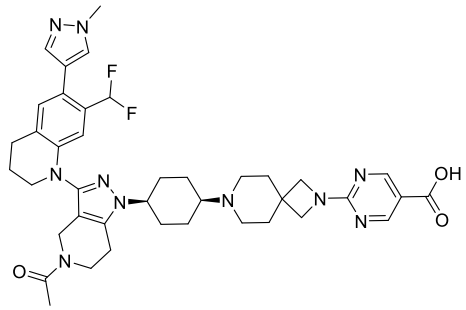
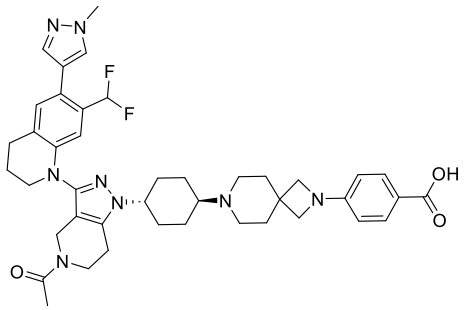
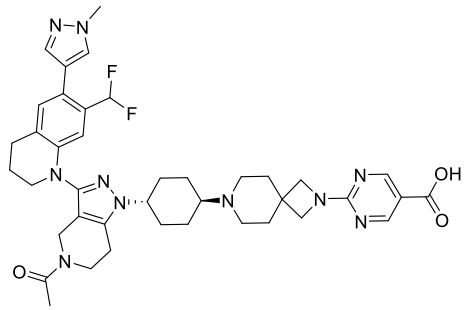
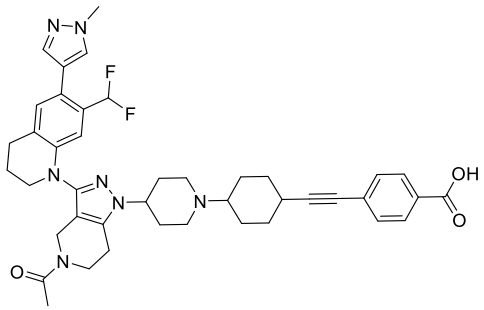
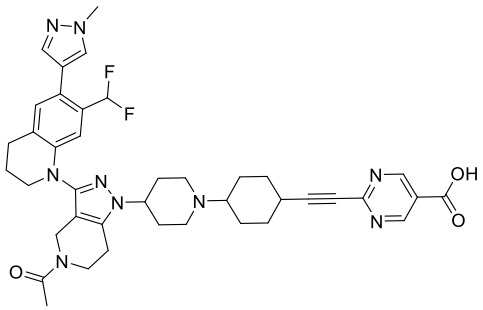
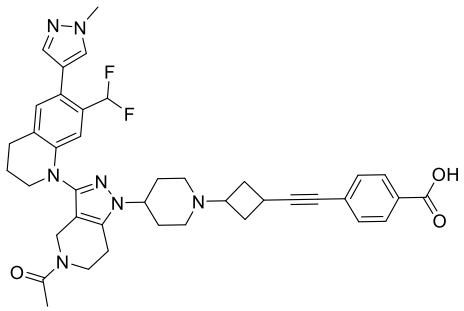
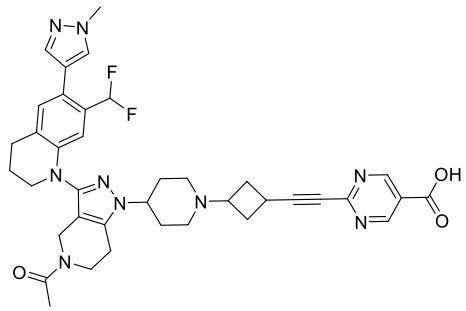

,

,

,

,

,

,

,

,

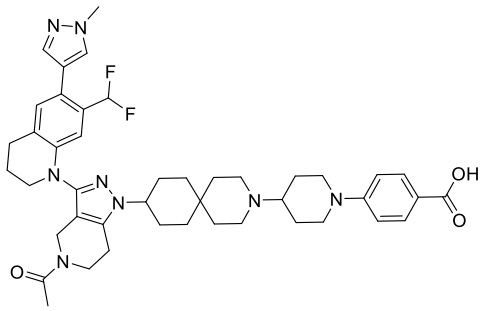
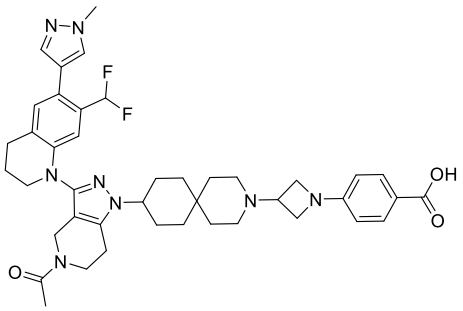
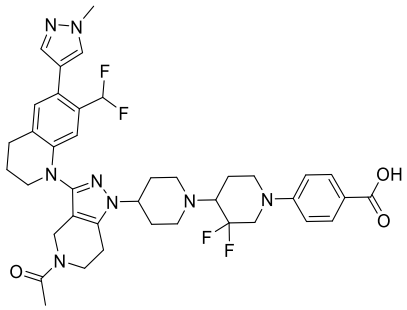
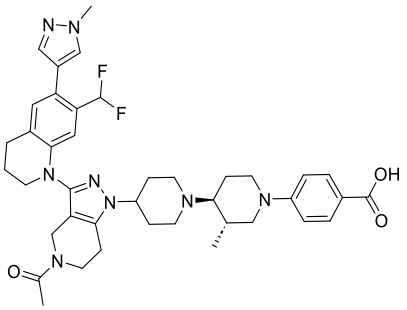
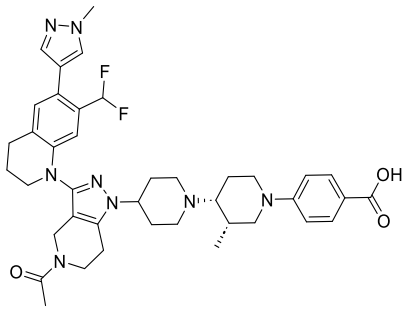
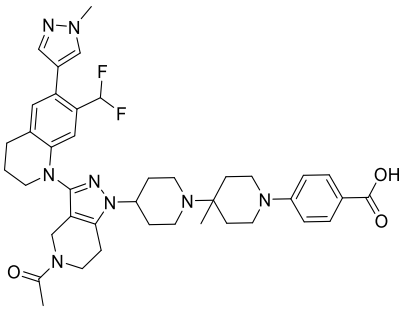
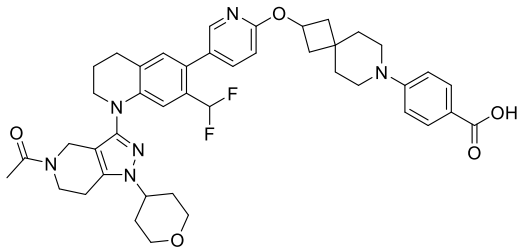
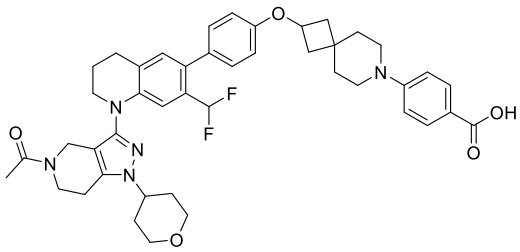
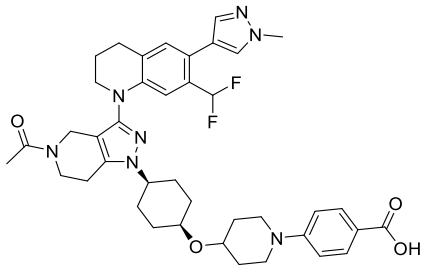
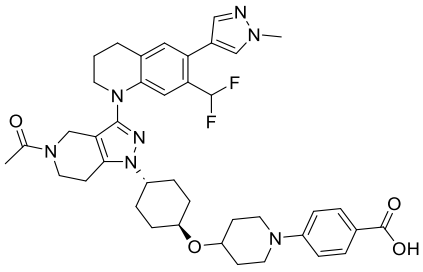

,

,

,

,

,

,

,

,

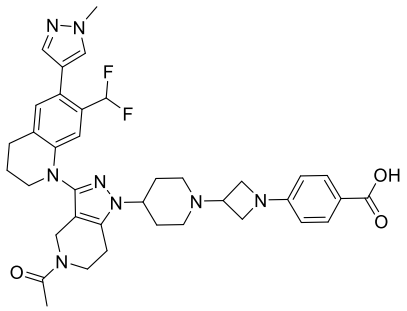
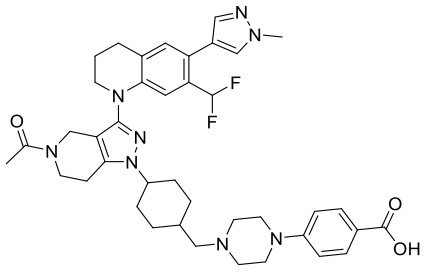
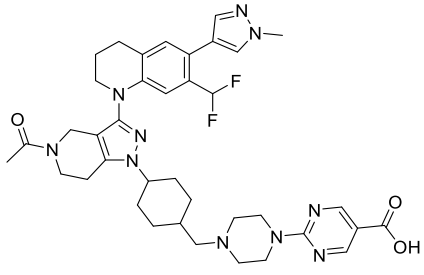
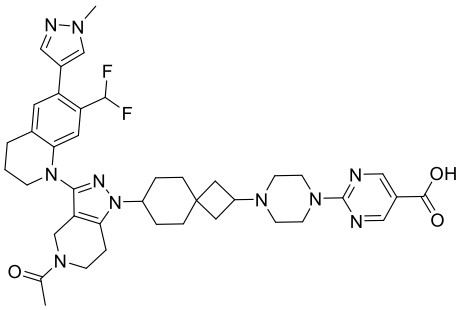
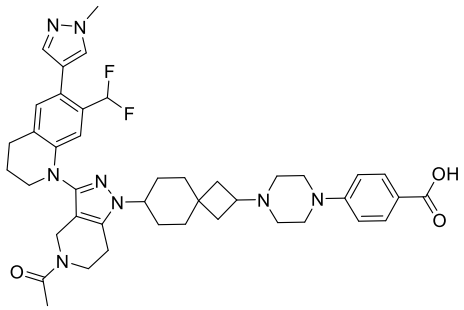
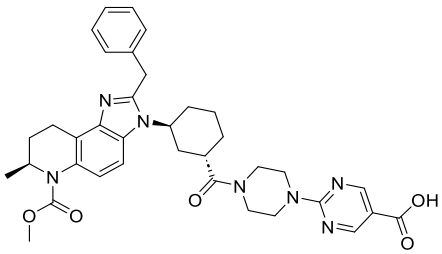
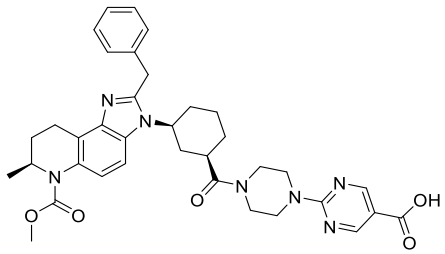
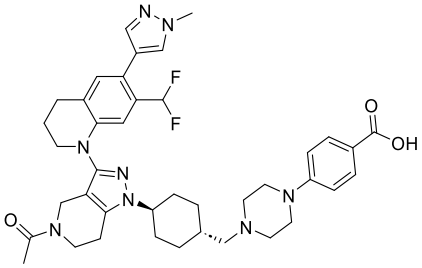
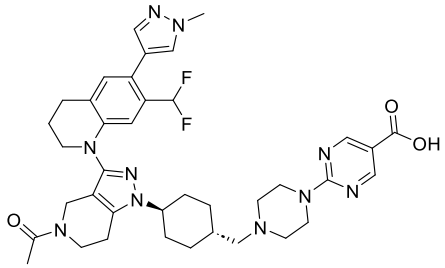
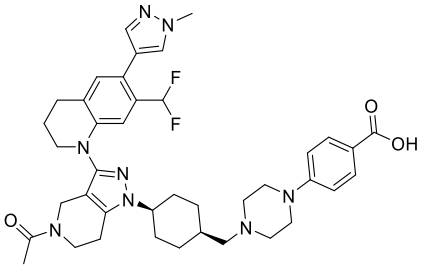

,

,

,

,

,

,

,

,

,

,

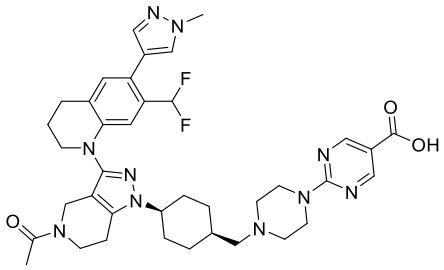
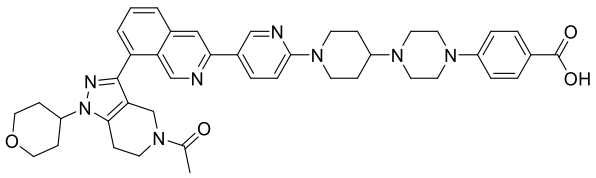
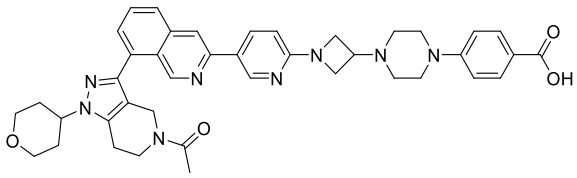
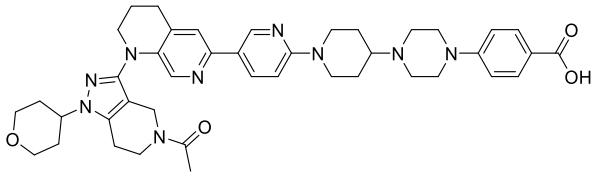
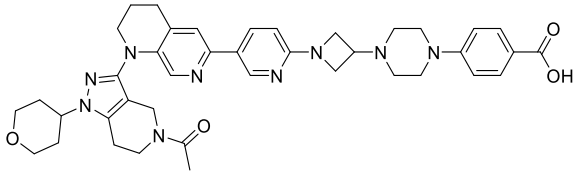
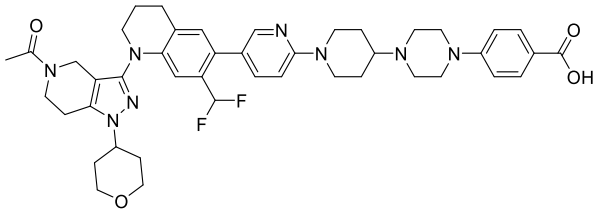
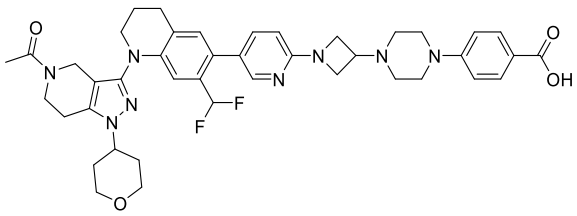
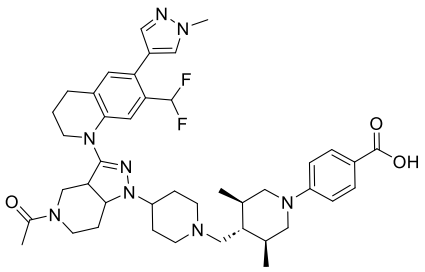
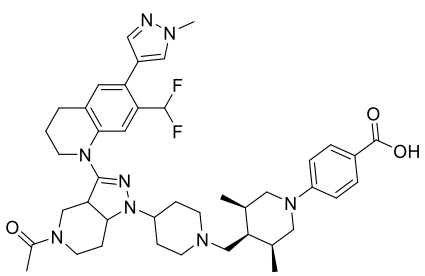
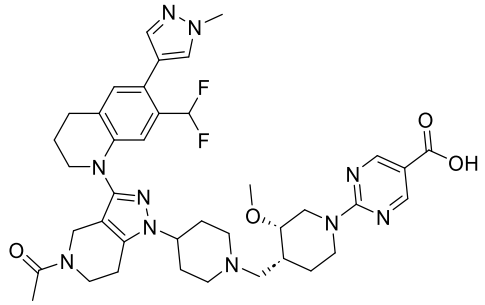

,

,

,

,

,

,

,

,

,

,

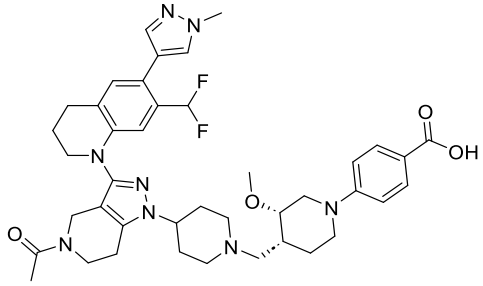
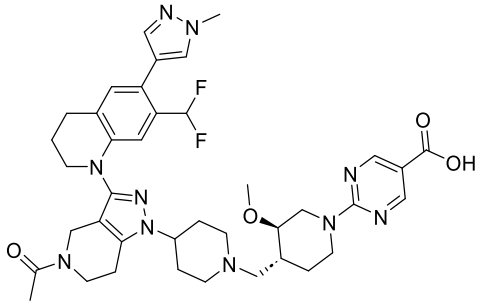
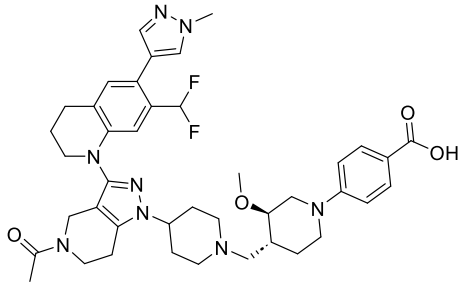
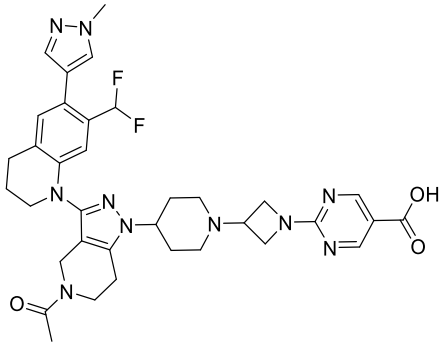
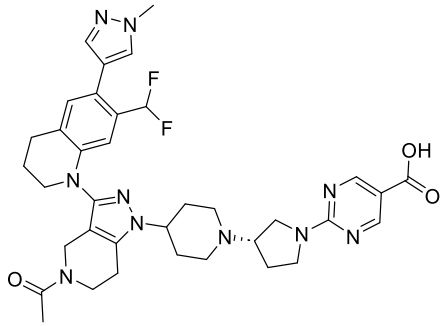
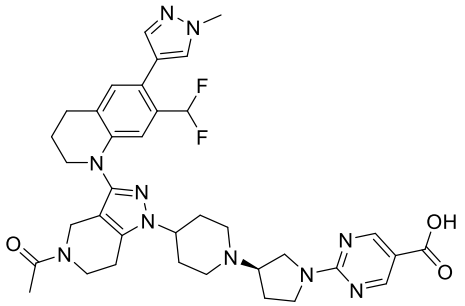
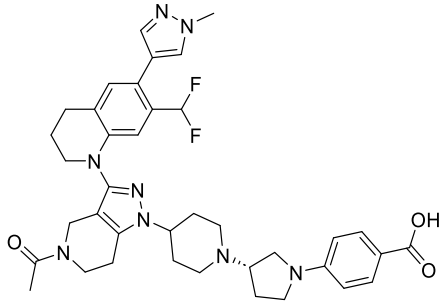
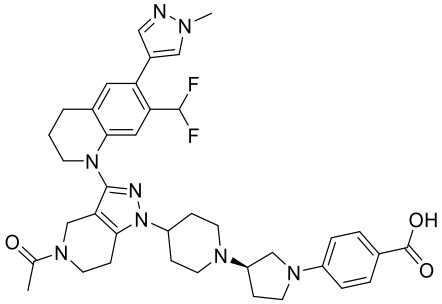
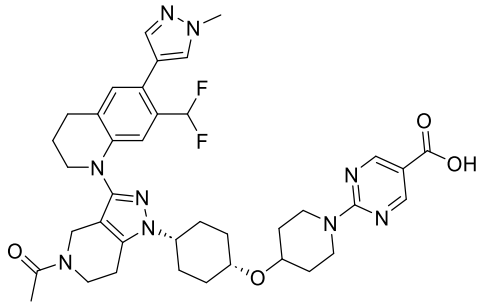
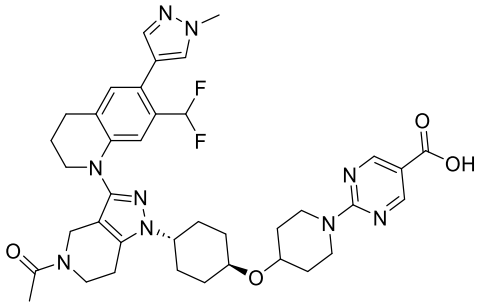

,

,

,

,

,

,

,

,

,

,

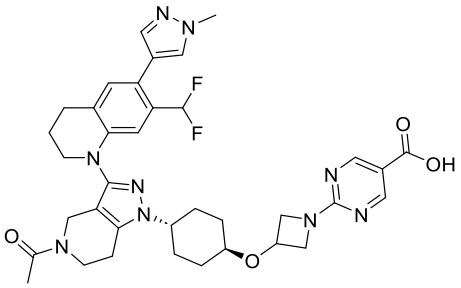
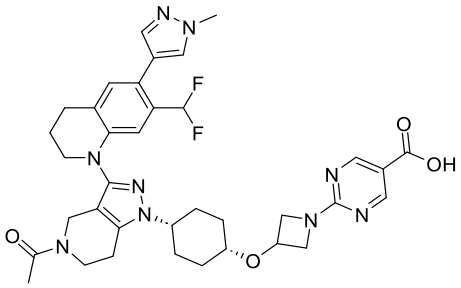
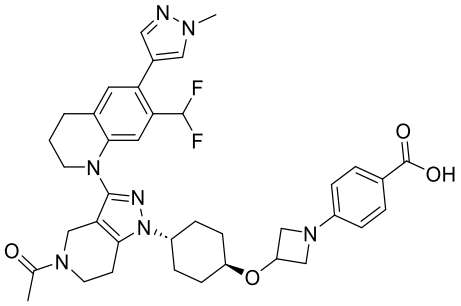
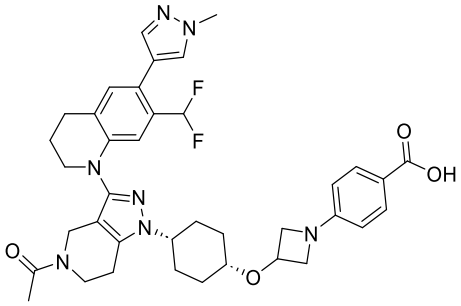
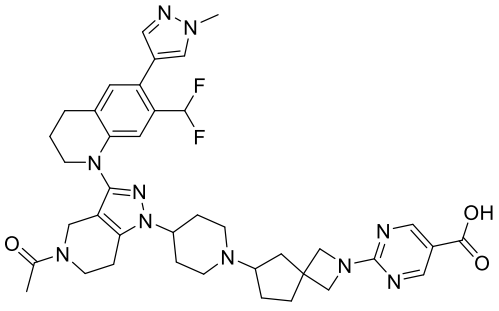
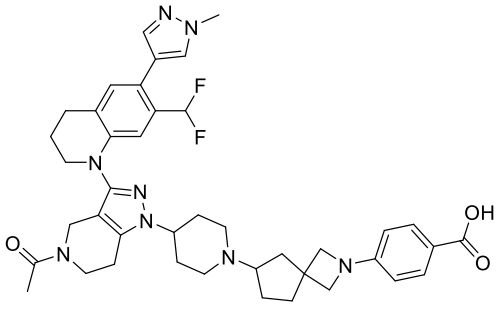
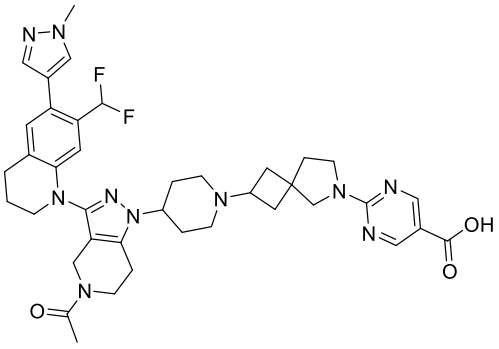
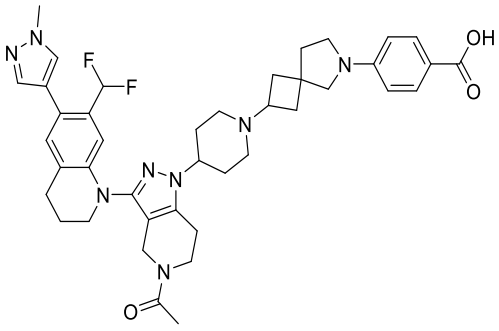
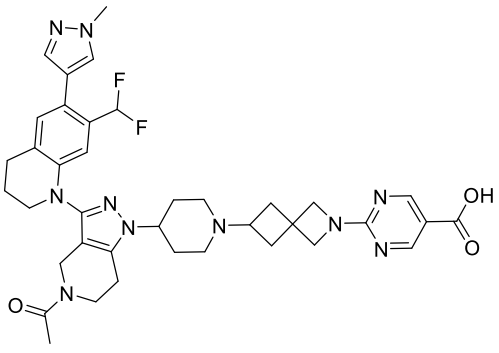
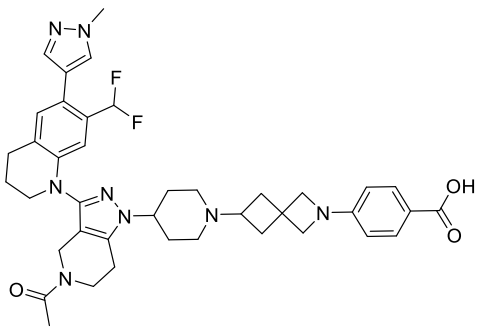

,

,

,

,

,

,

,

,

,

,

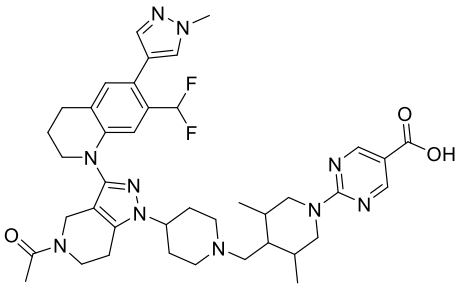
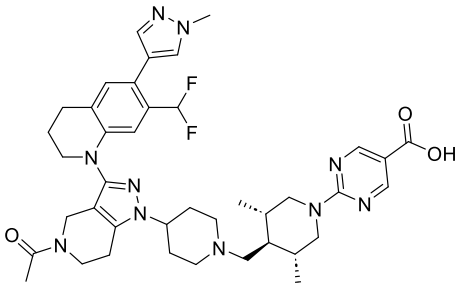
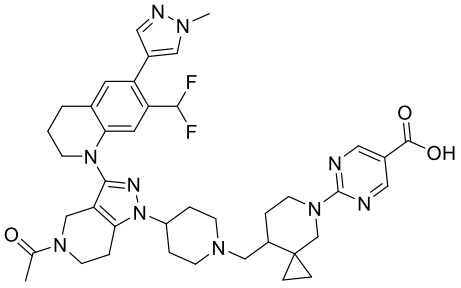
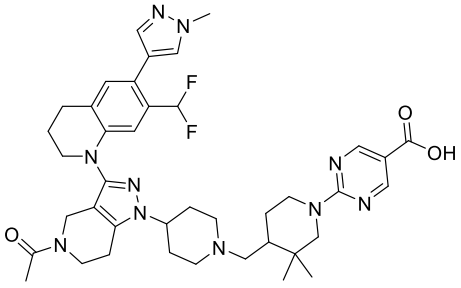
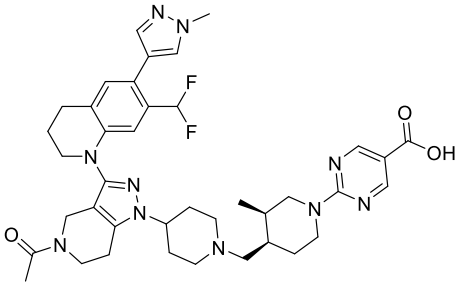
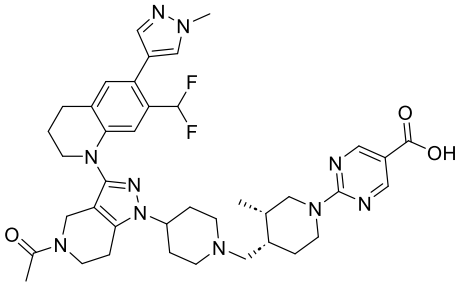
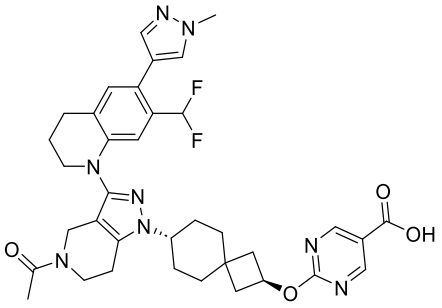
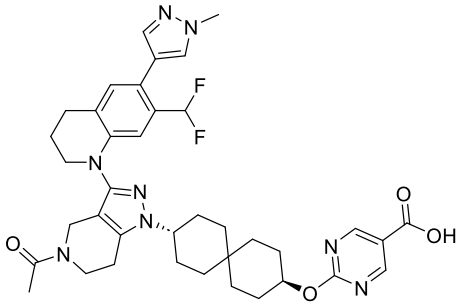
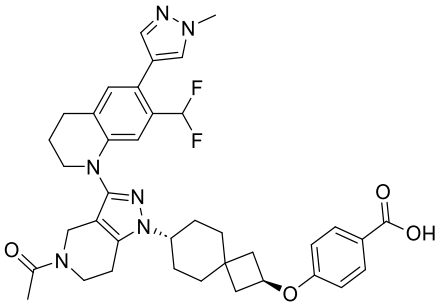
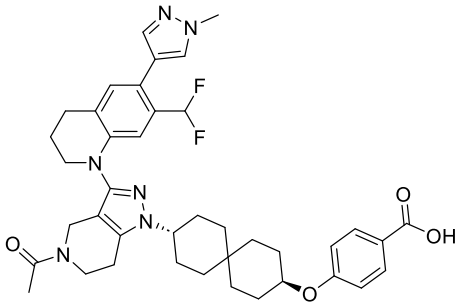

,

,

,

,

,

,

,

,

,

,

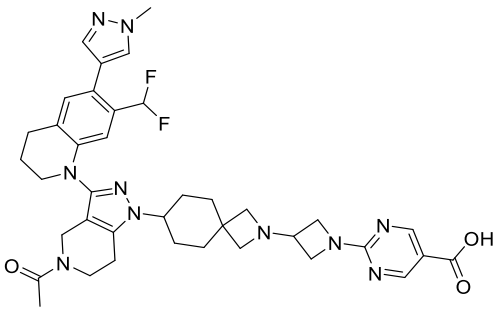
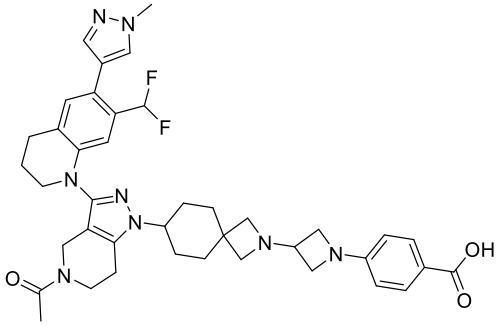
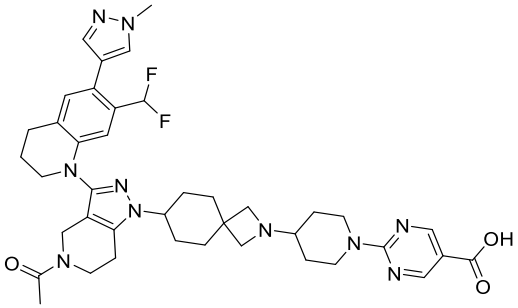
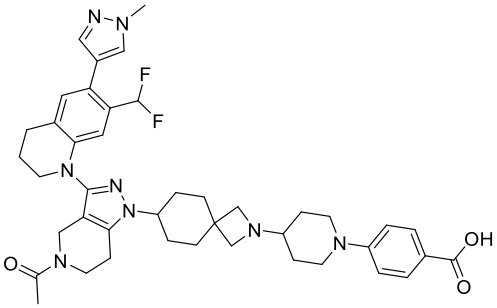
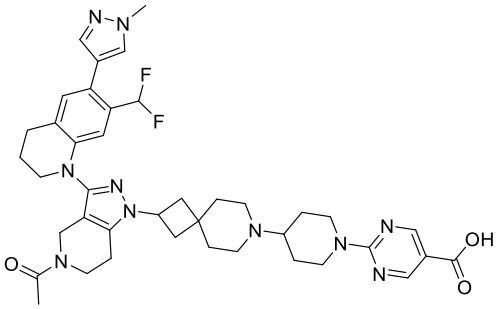
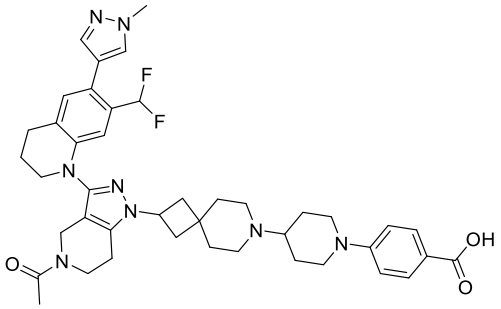
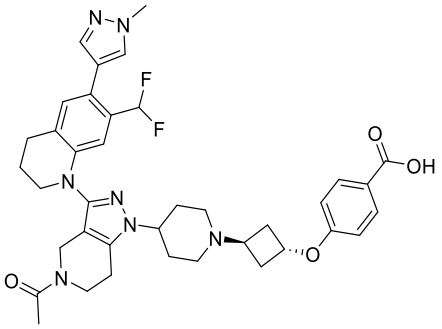
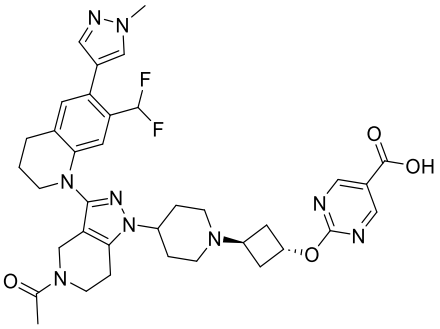
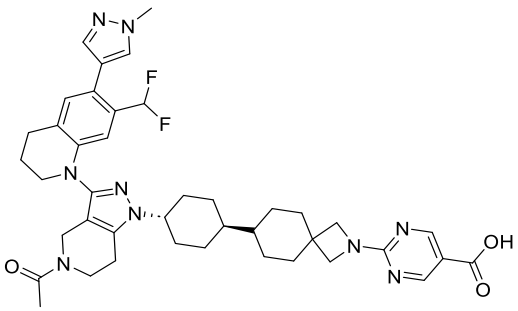
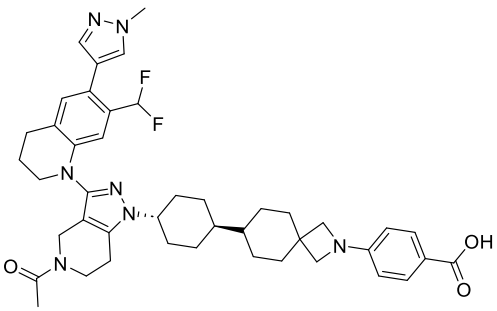

,

,

,

,

,

,

,

,

,

,

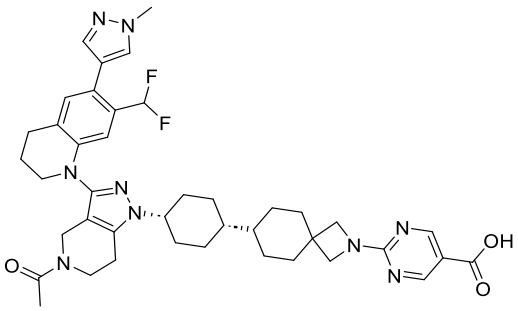
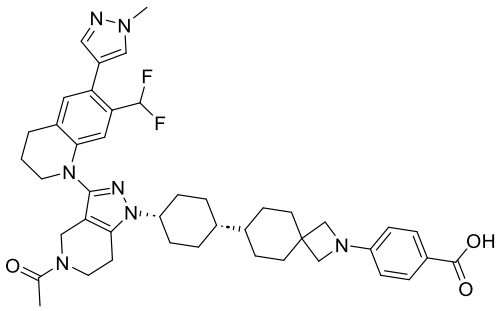
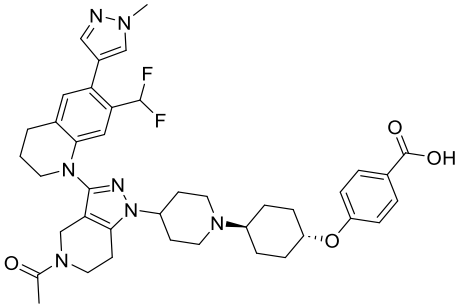
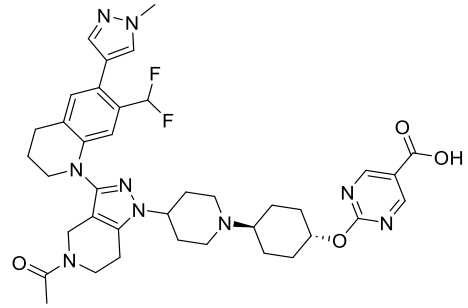
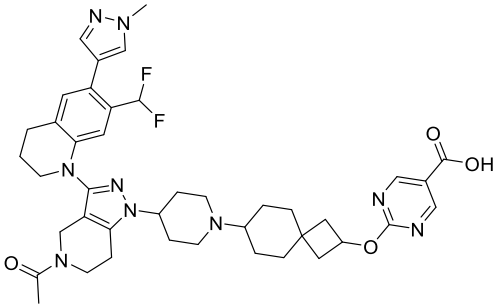
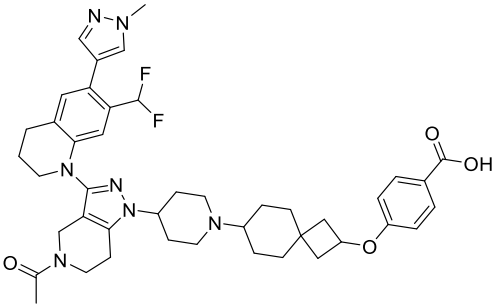
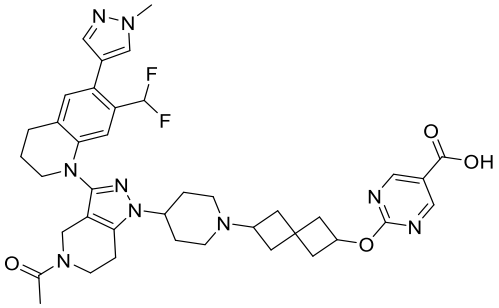
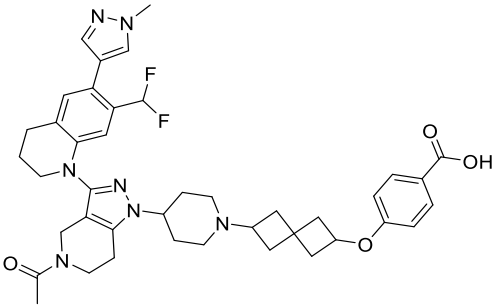
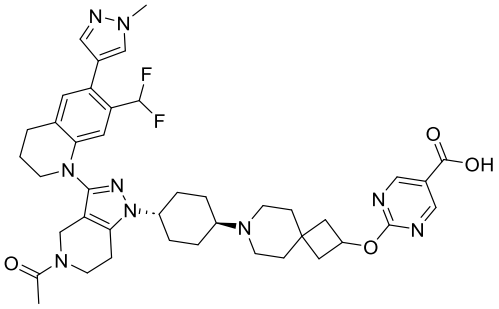
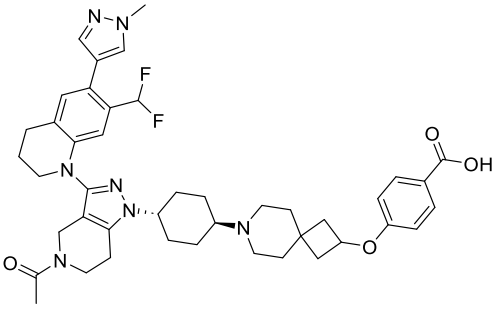

,

,

,

,

,

,

,

,

,

,

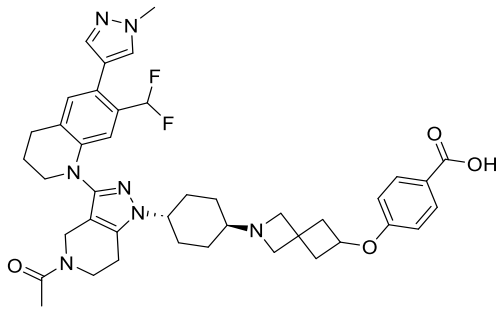
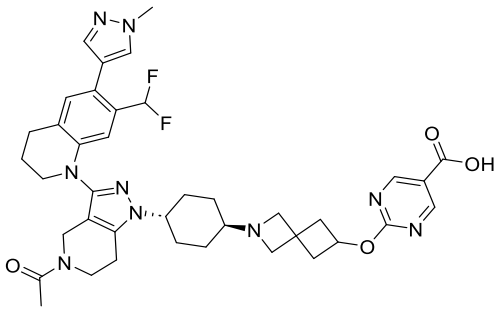
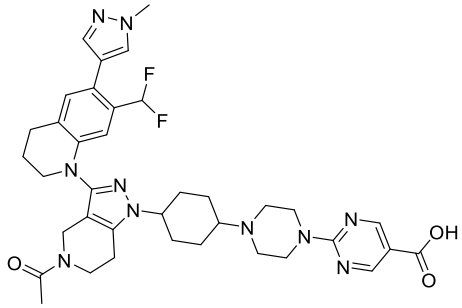
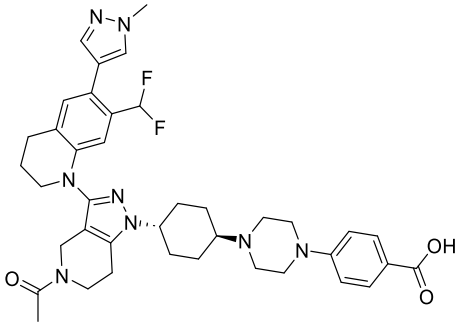
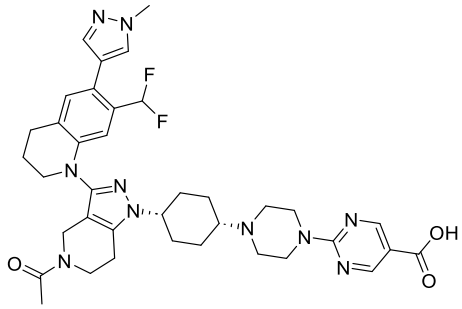
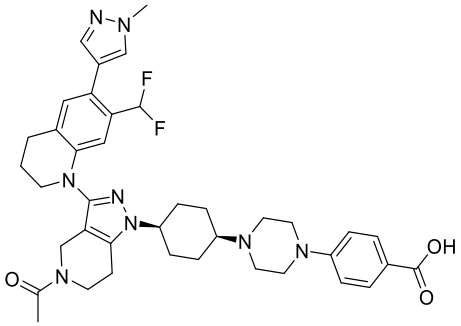
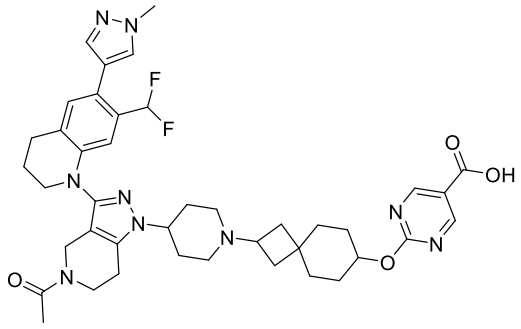
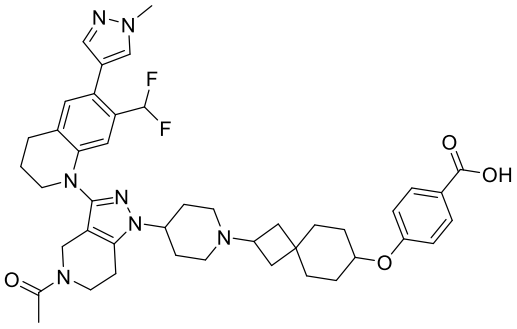
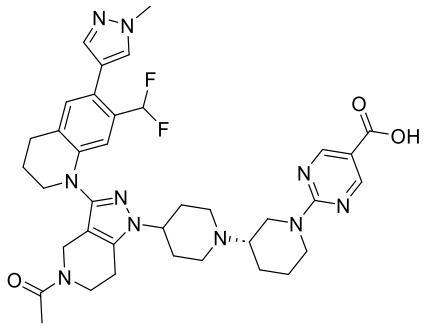
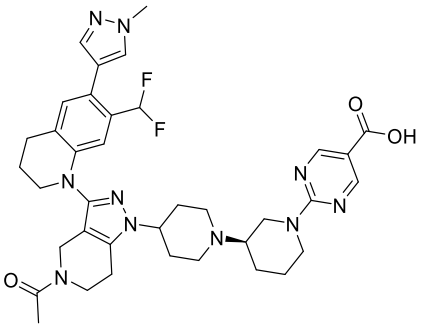

,

,

,

,

,

,

,

,

,

,

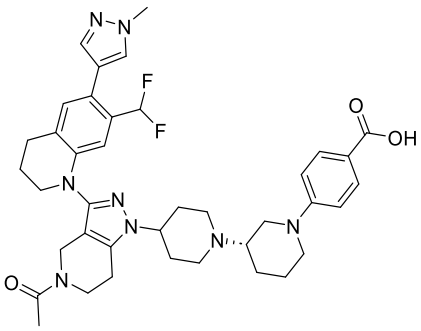
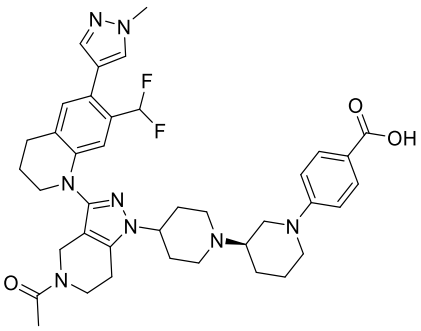
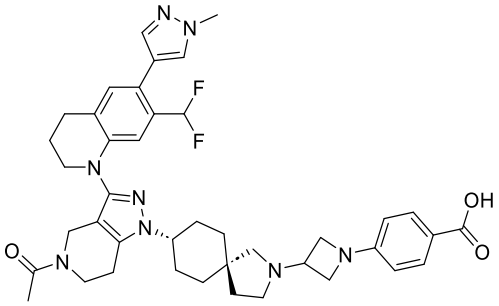
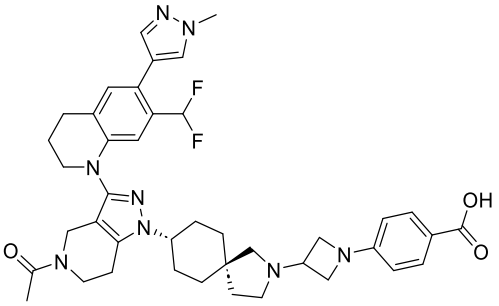
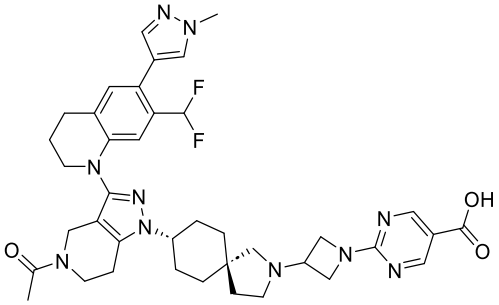
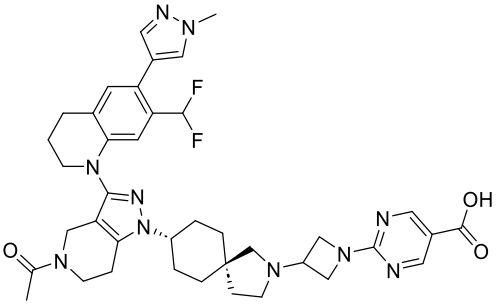
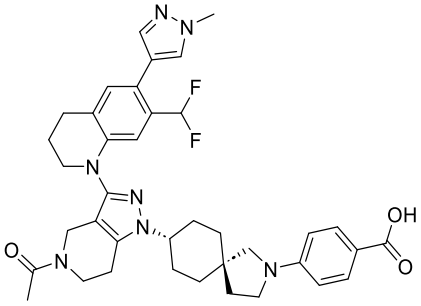
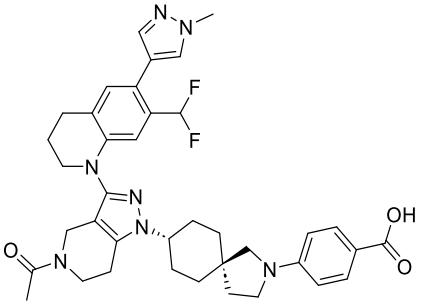
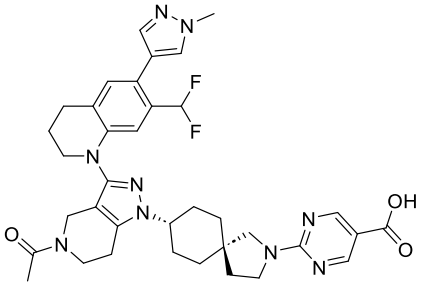
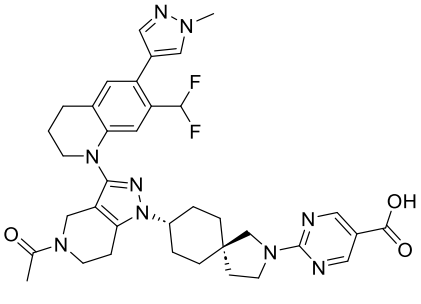

,

,

,

,

,

,

,

,

,

,

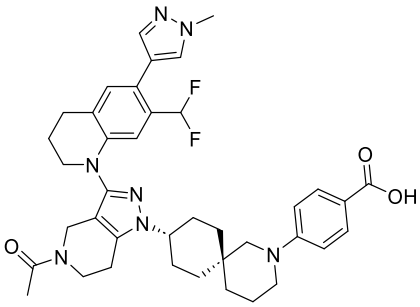
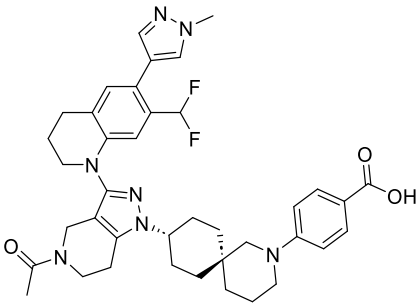
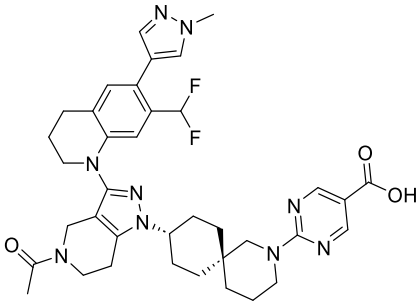
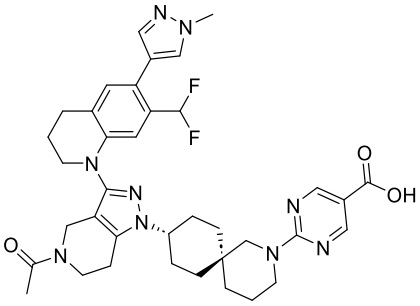
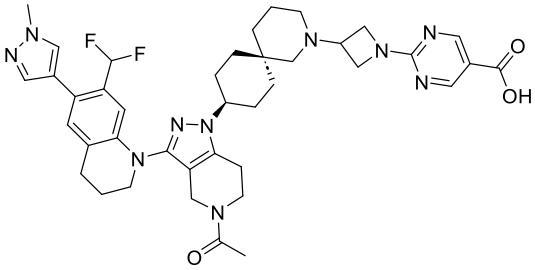
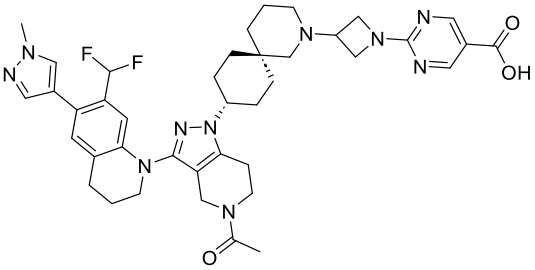
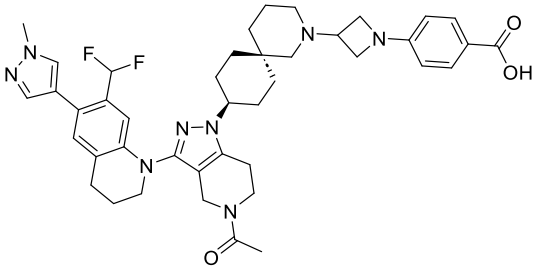
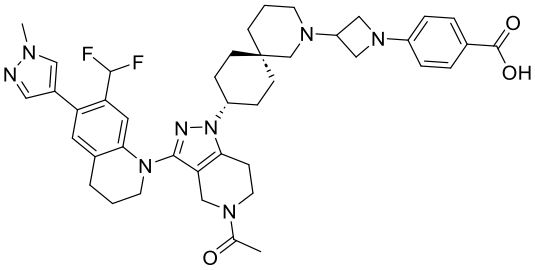
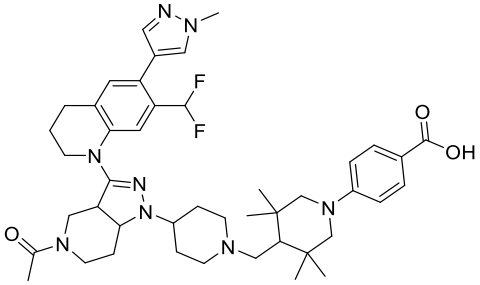
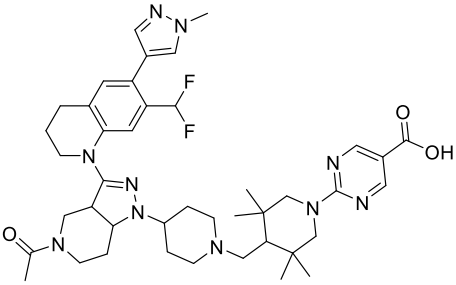

,

,

,

,

,

,

,

,

,

,

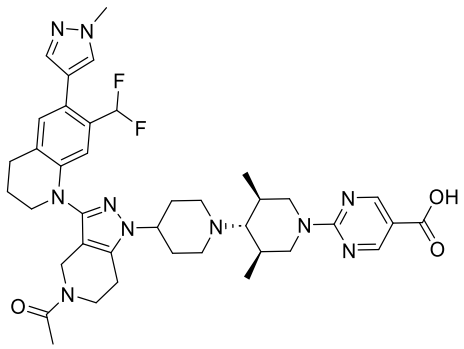
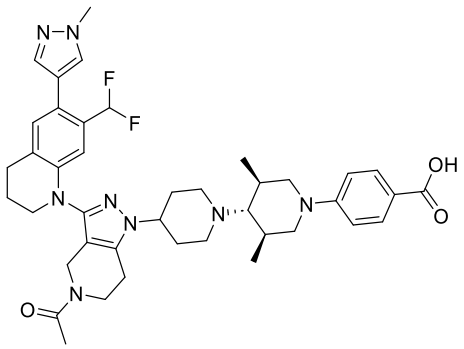
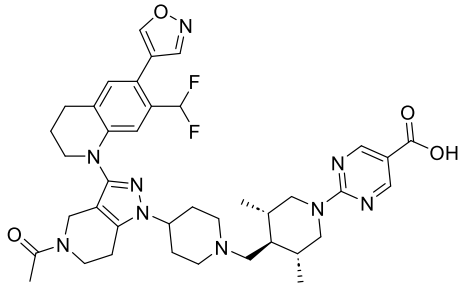
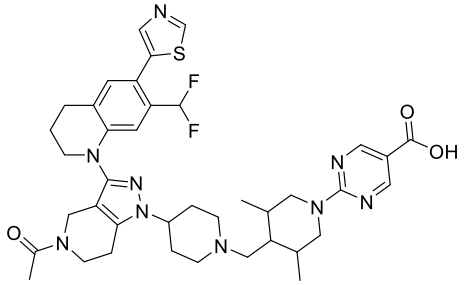
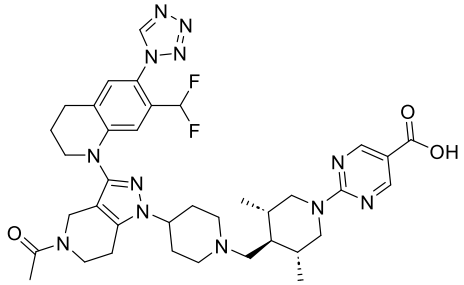
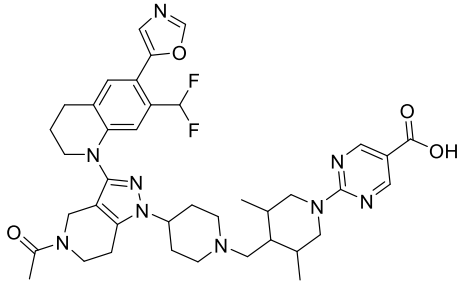
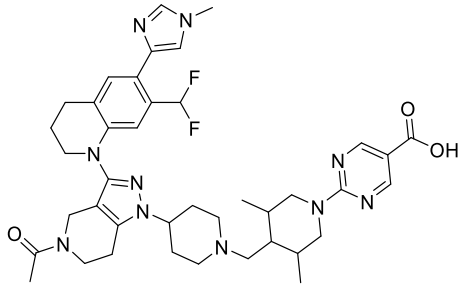
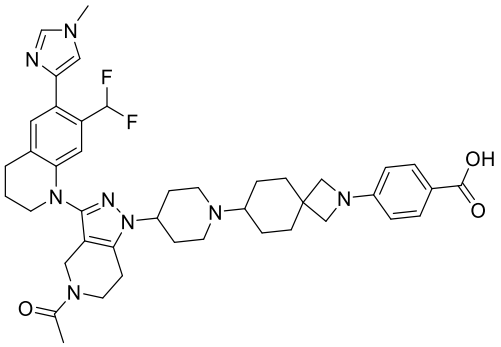
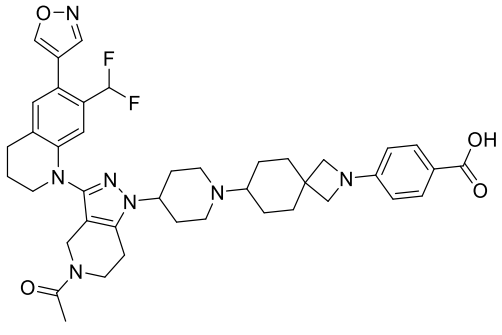
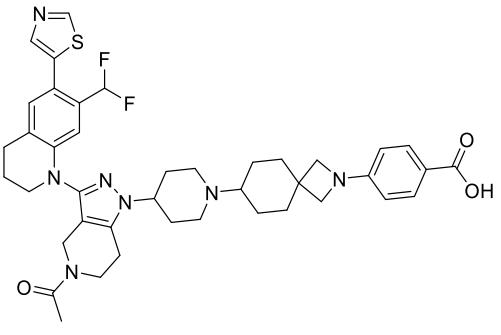

,

,

,

,

,

,

,

,

,

,

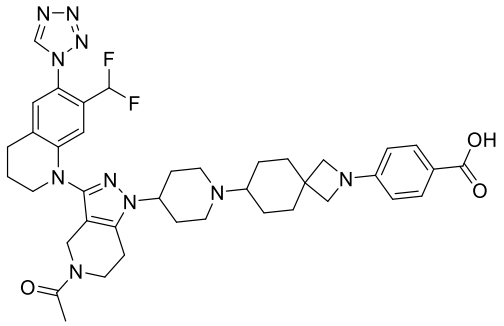
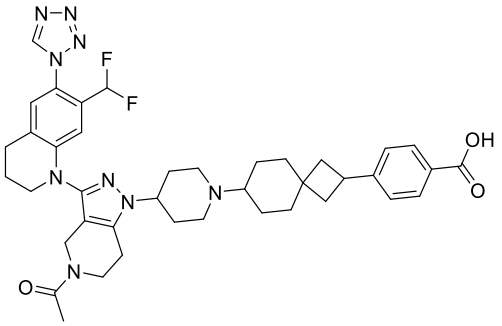
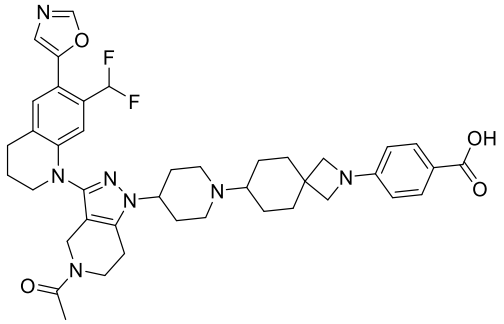
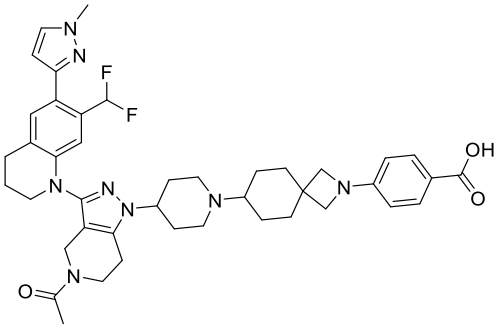
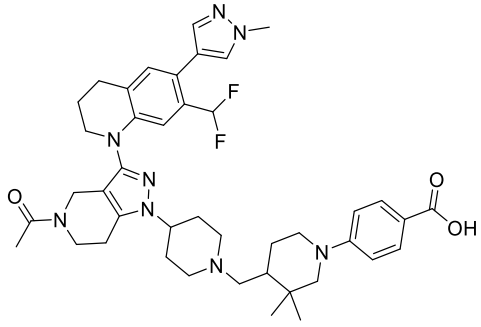
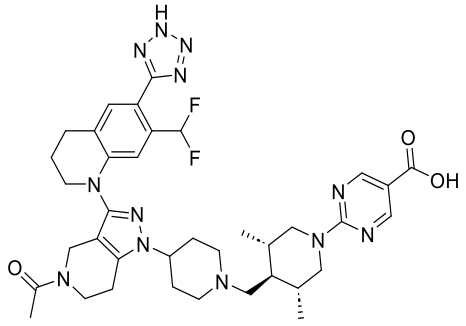
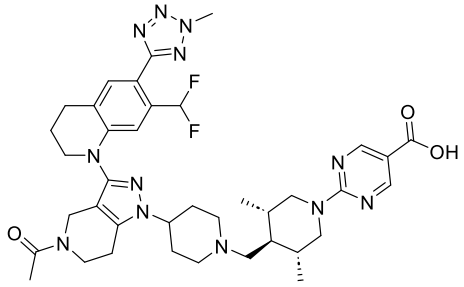
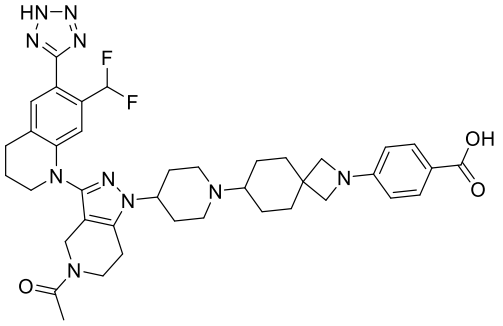
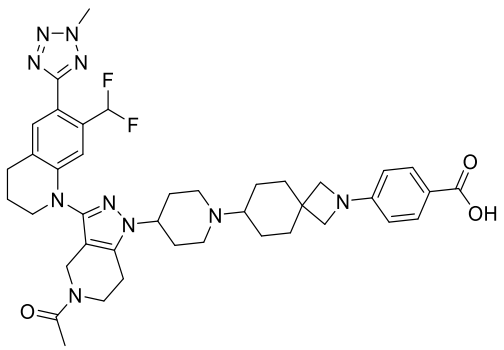
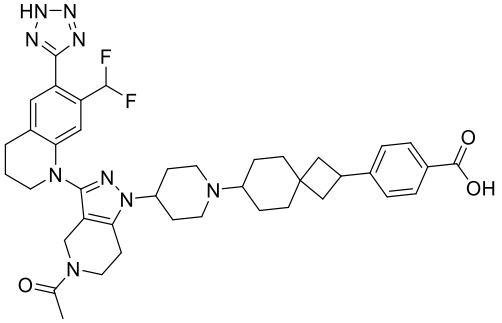

,

,

,

,

,

,

,

,

,

,

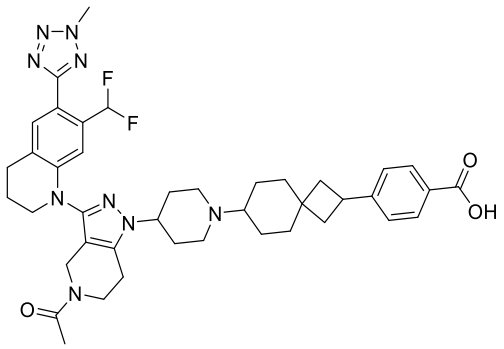
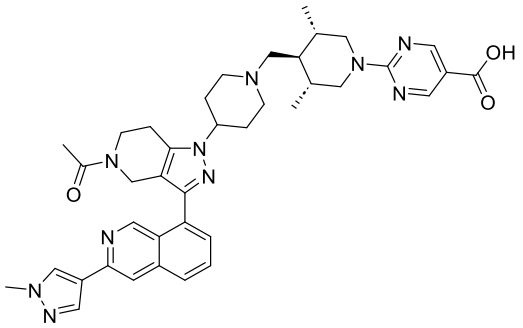
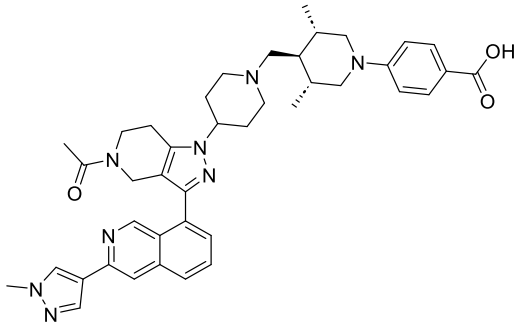
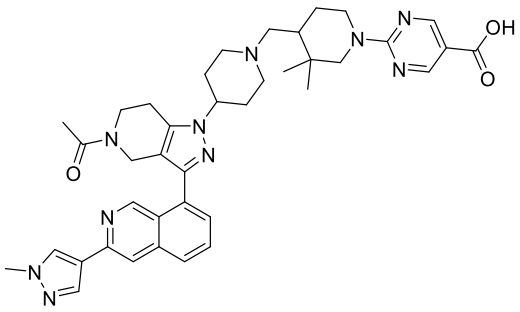
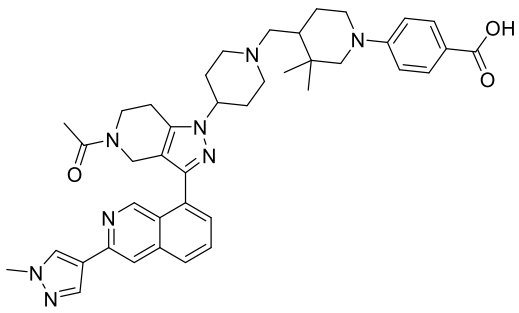
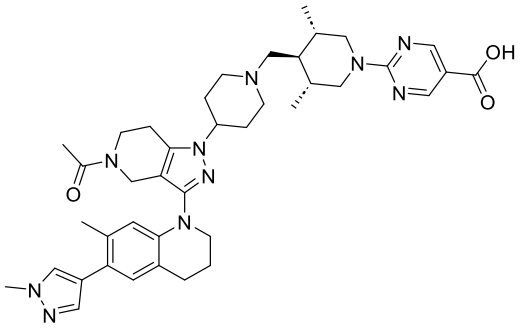
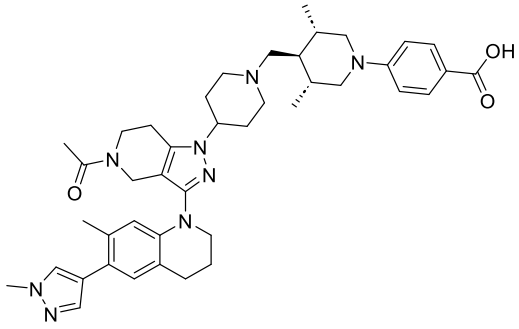
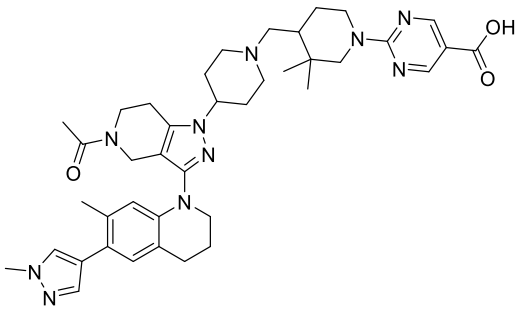
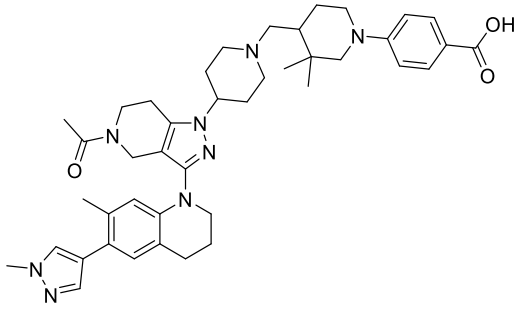

,

,

,

,

,

,

,

,

,

,

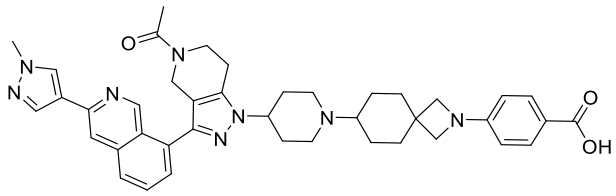
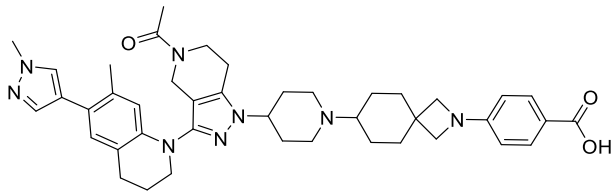
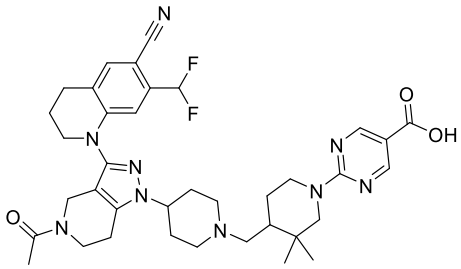
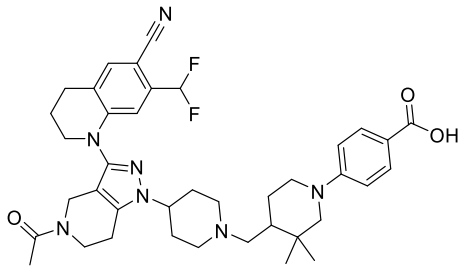
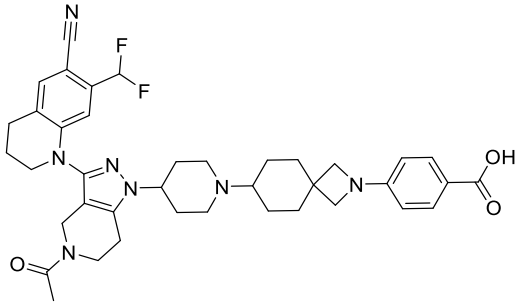
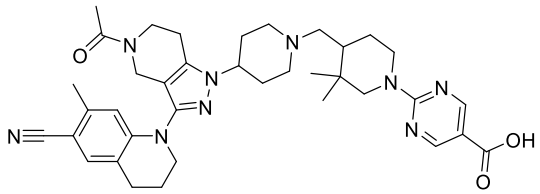
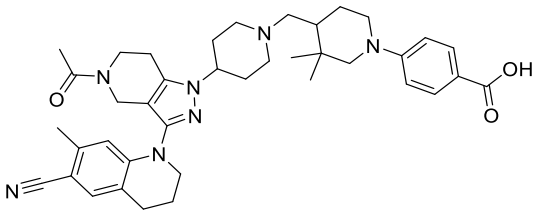
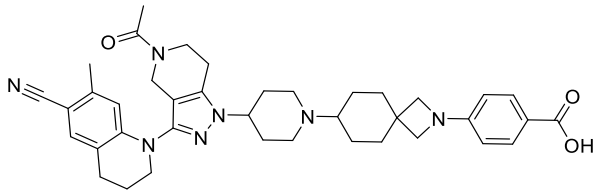
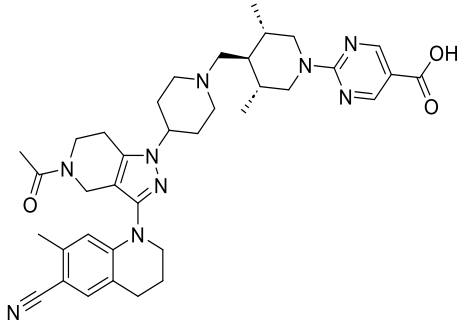
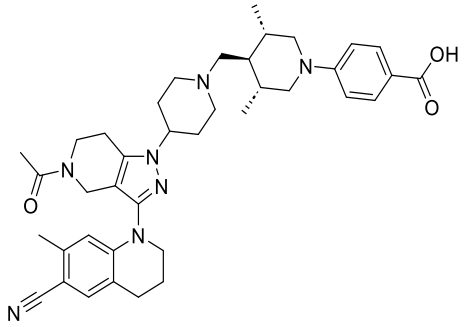
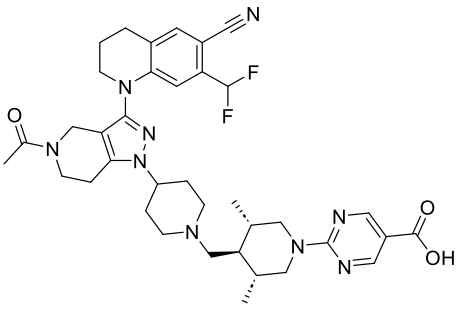

,

,

,

,

,

,

,

,

,

,

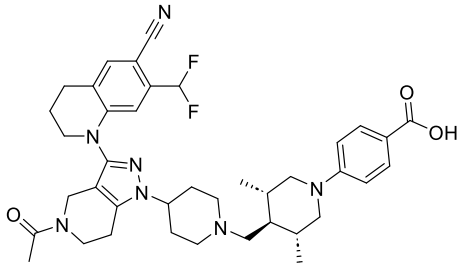
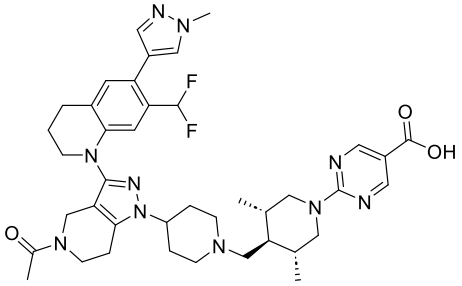
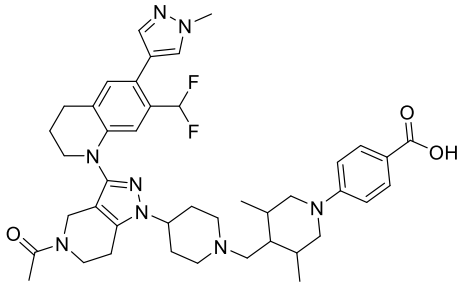
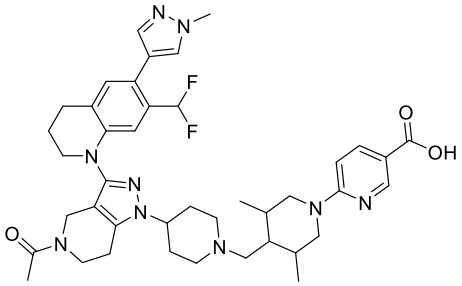
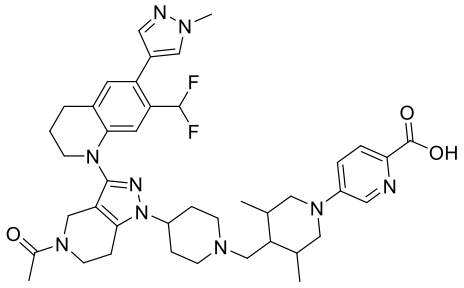
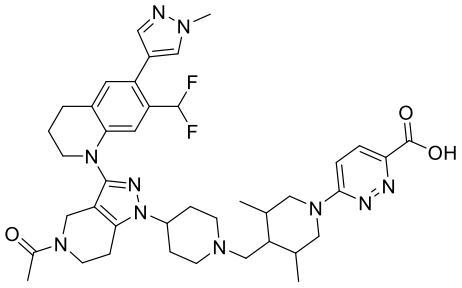
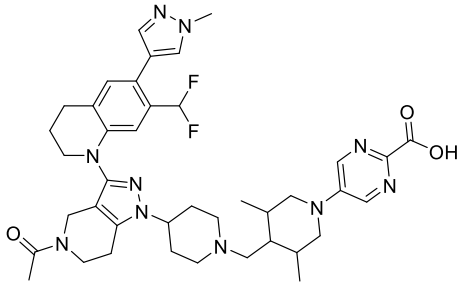
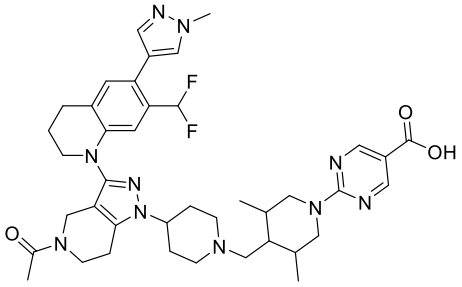
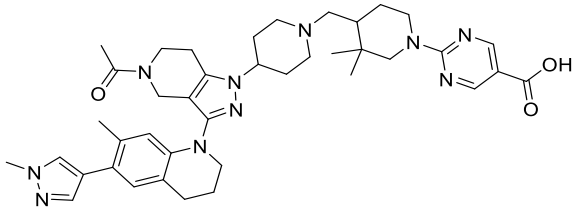
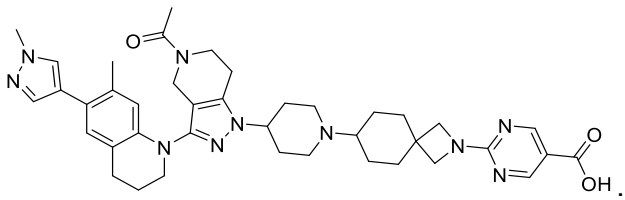

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

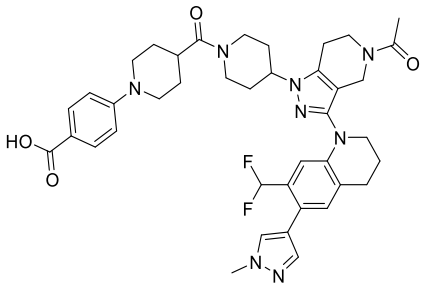
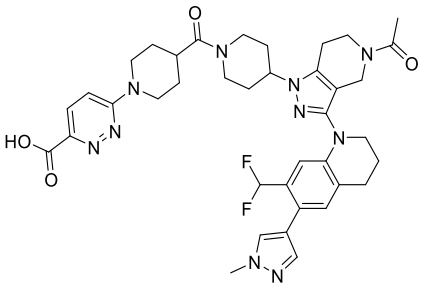
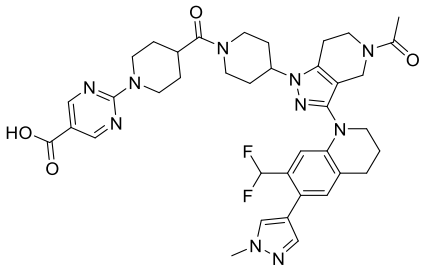
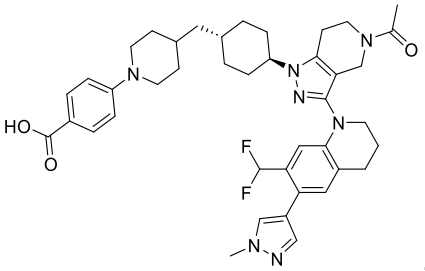
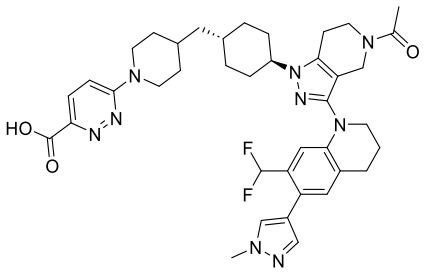
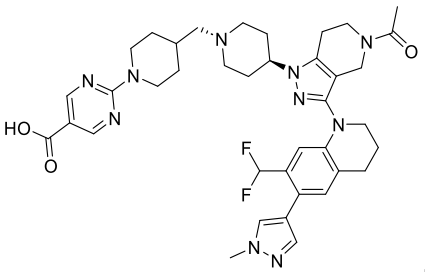
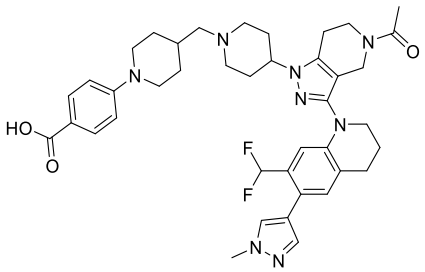
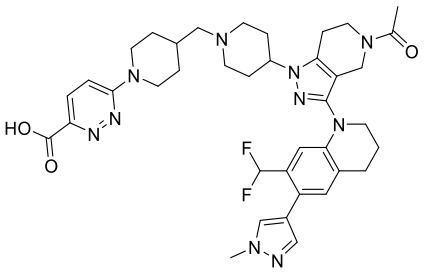
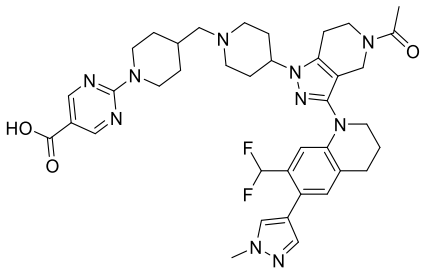
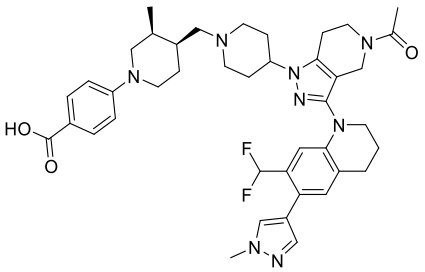
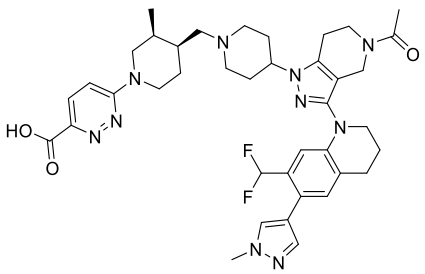
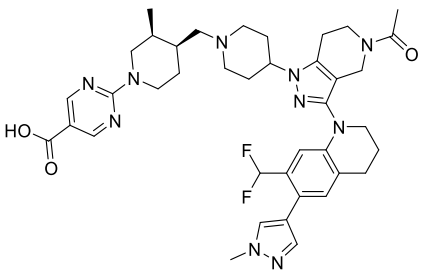

,

,

,

,

,

,

,

,

,

,

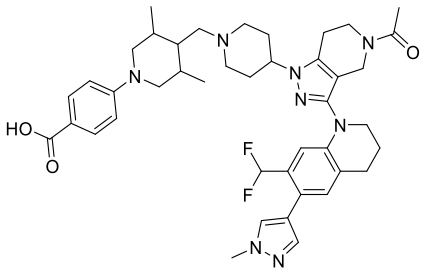
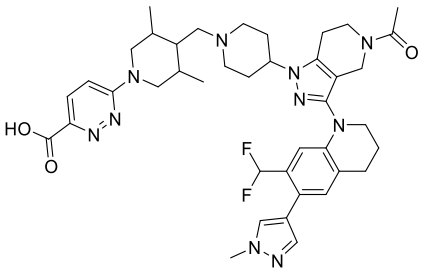
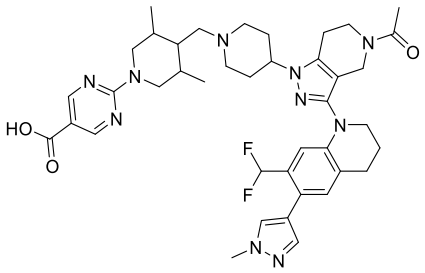
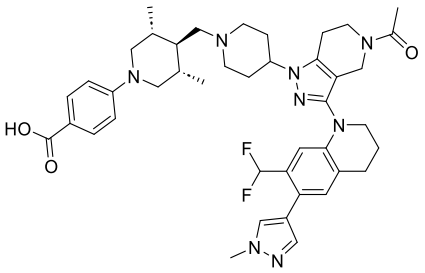
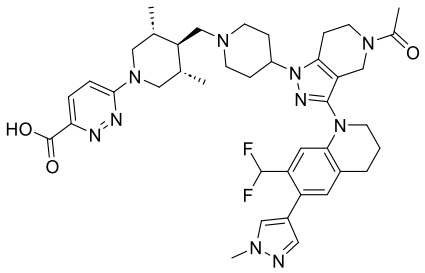
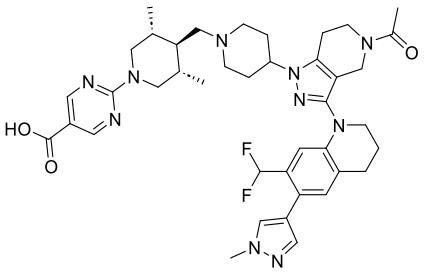
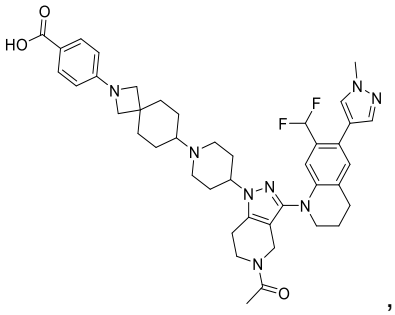
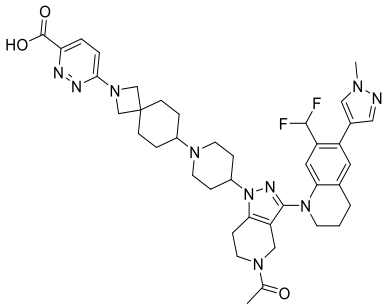
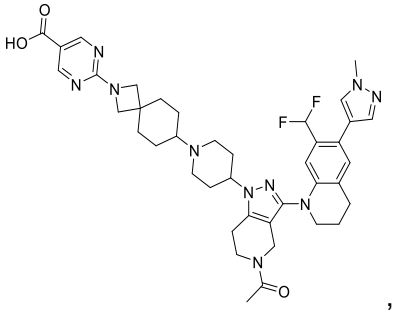
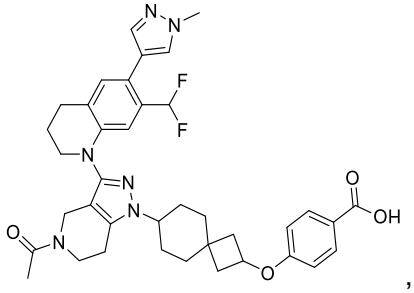

,

,

,

,

,

,

,

,

,

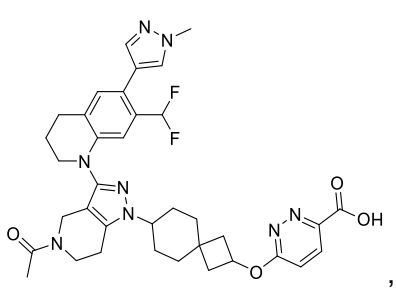
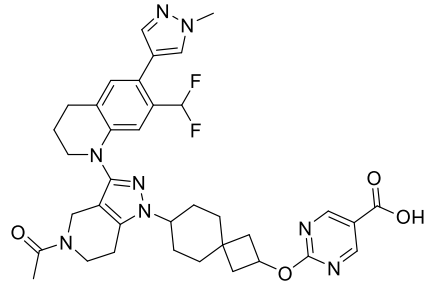
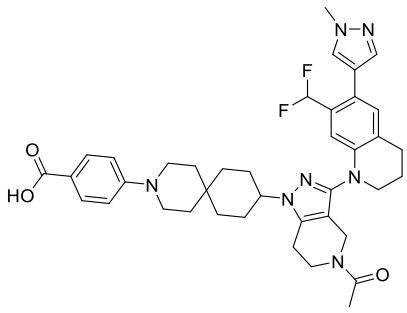
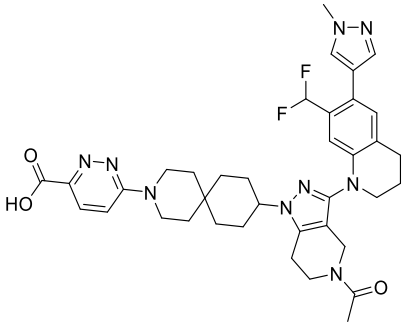
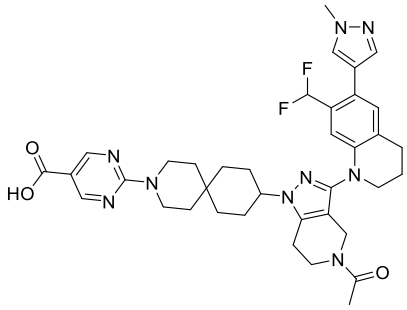
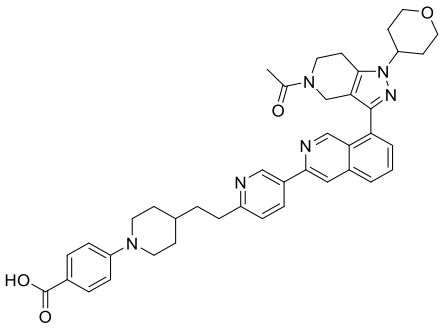
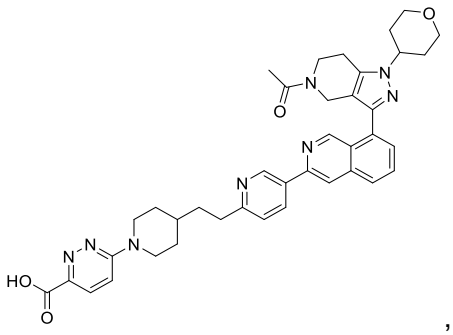
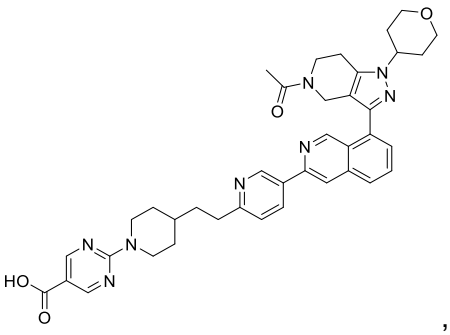
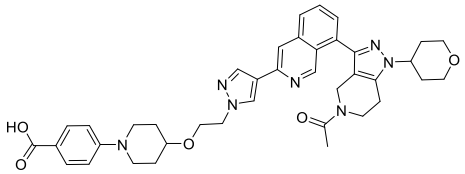
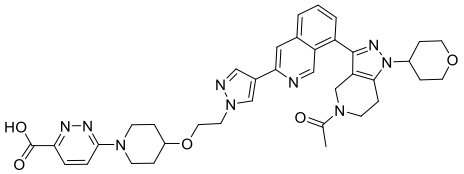
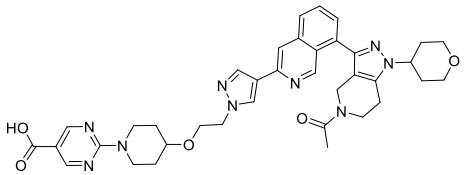

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

o

.

[00310] Forma de realización 121a. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:


,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

o

.

[00311] Forma de realización 122. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, preparado mediante un acoplamiento de amida del compuesto del ejemplo 39e y el compuesto del ejemplo 121.

[00312] Forma de realización 122a. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, preparado mediante un acoplamiento de amida del compuesto del ejemplo 39f y el compuesto del ejemplo 121.

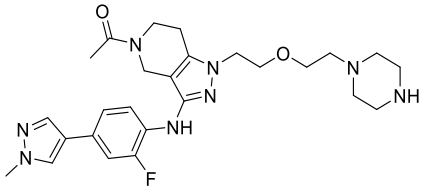
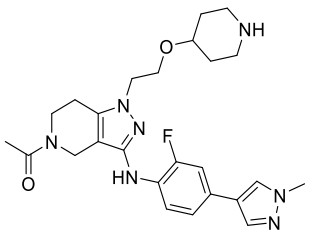
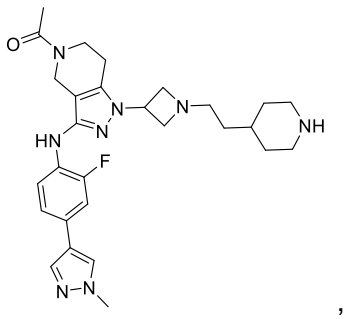
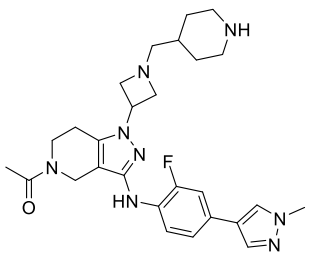
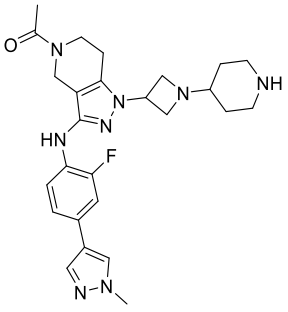
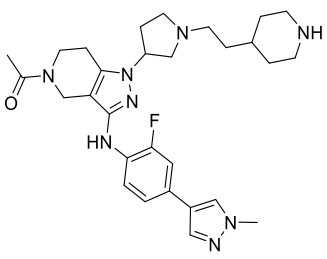
[00313] Forma de realización 122b. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, preparado mediante un acoplamiento de amida del compuesto del ejemplo 39g y el compuesto del ejemplo 121.

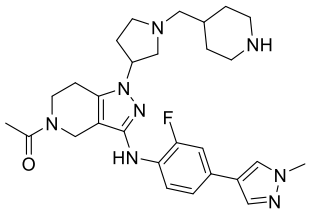
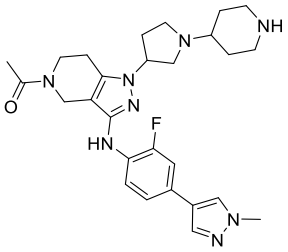
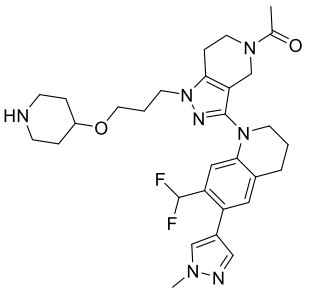
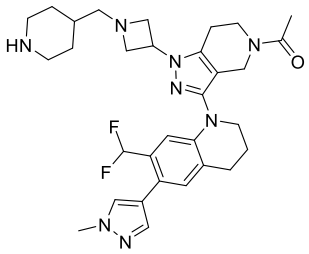
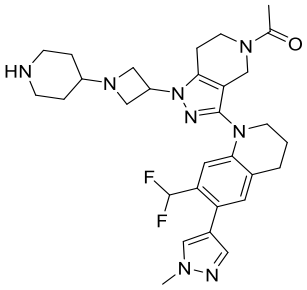
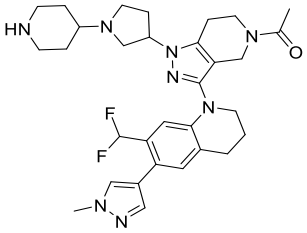
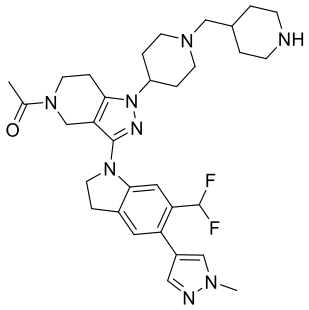
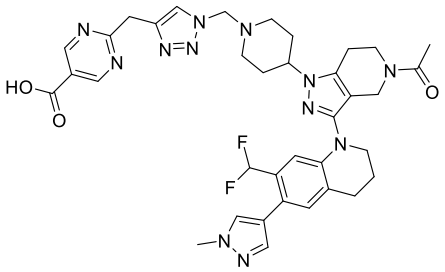
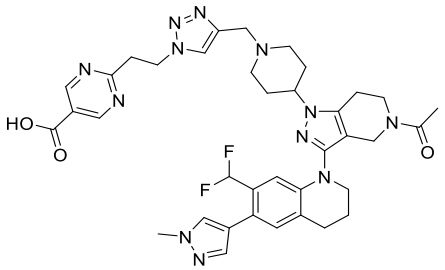
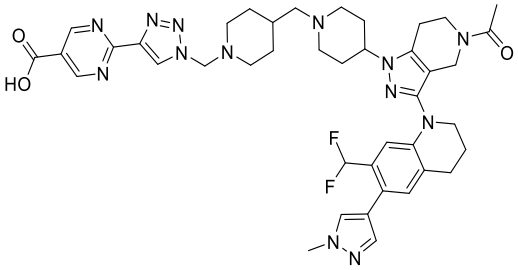
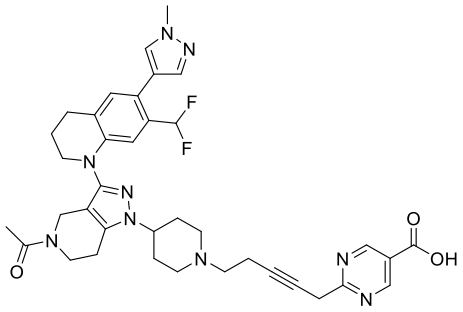
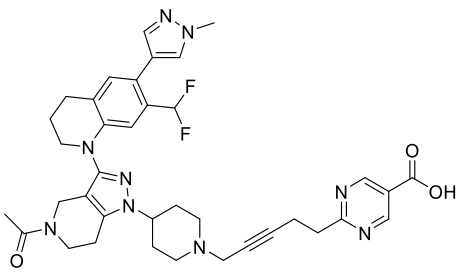
[00314] Forma de realización 123c. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, preparado mediante un acoplamiento de amida del compuesto del ejemplo 39e y el compuesto del ejemplo 121a.

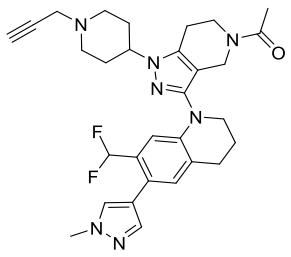
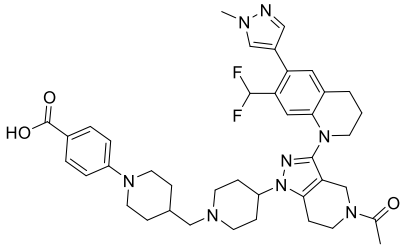
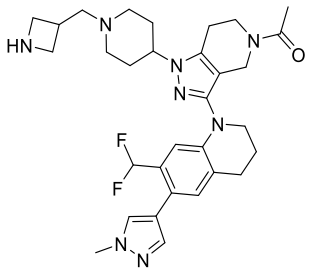
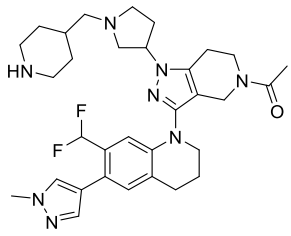
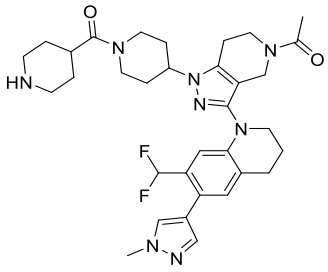
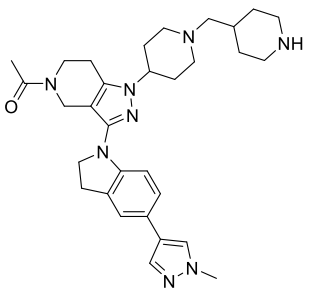
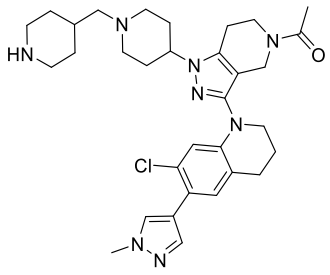
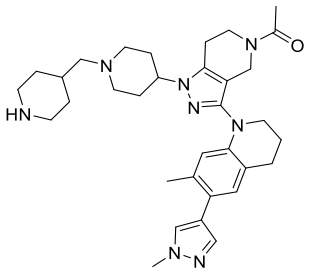
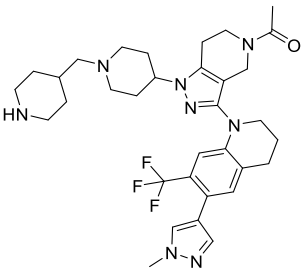
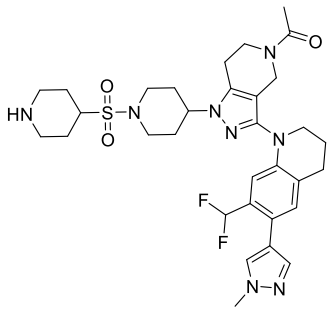
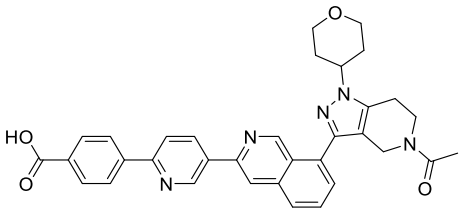
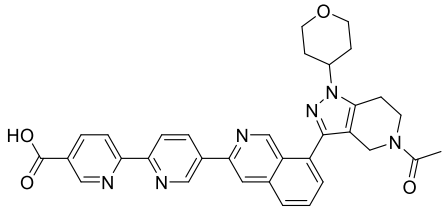
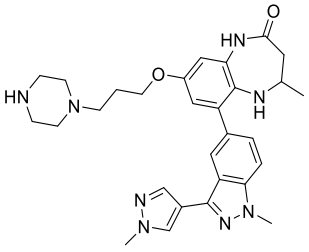
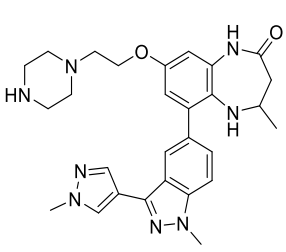
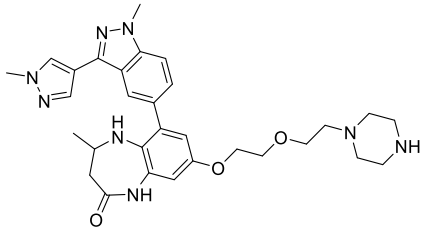
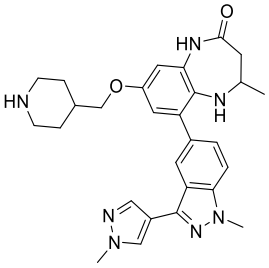
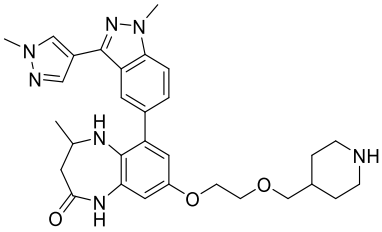
[00315] Forma de realización 123d. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, preparado mediante un acoplamiento de amida del compuesto del ejemplo 39f y el compuesto del ejemplo 121a.

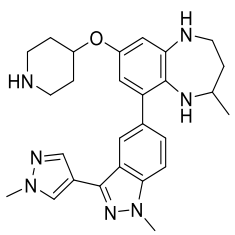
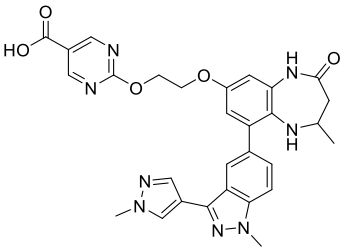
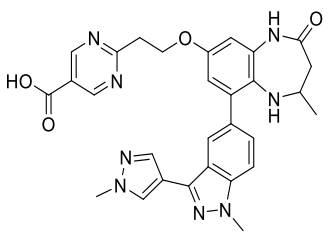
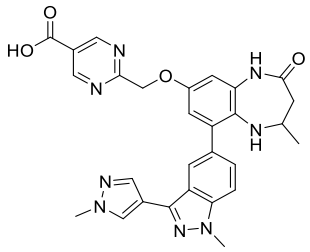
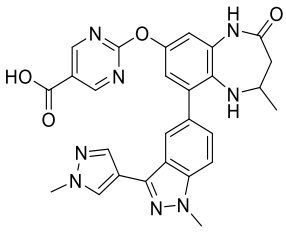
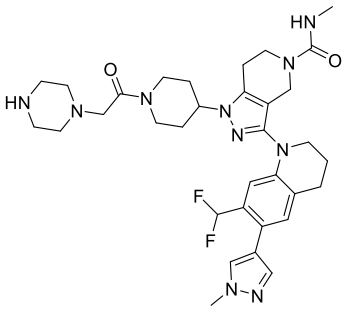
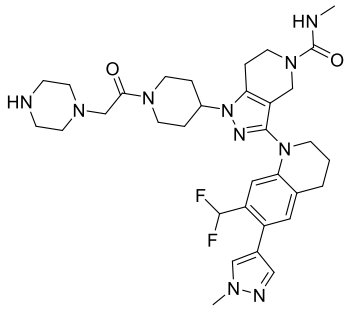
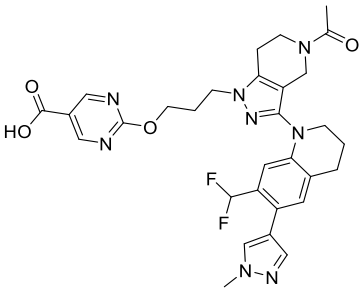
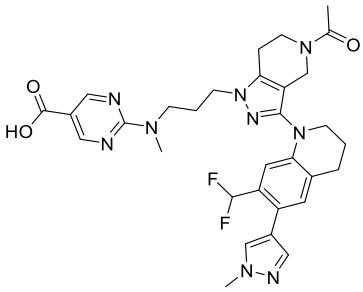
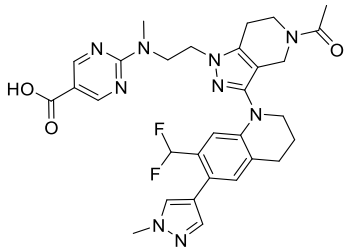
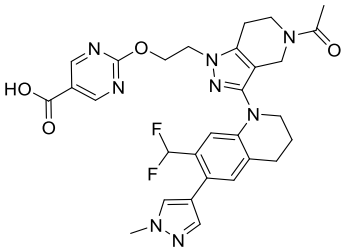
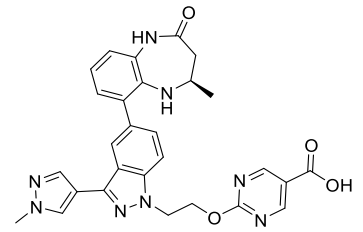
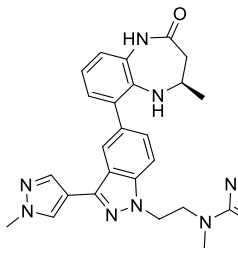
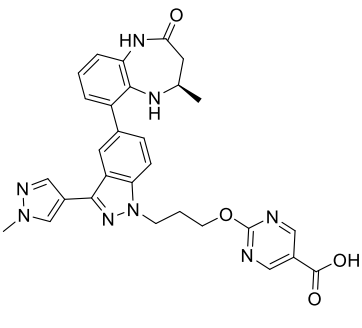
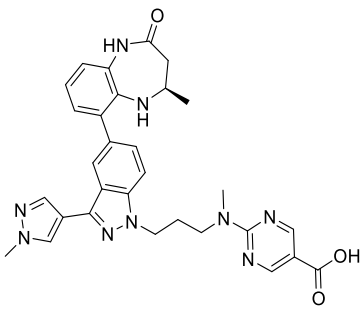
[00316] Forma de realización 123e. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, preparado mediante un acoplamiento de amida del compuesto del ejemplo 39g y el compuesto del ejemplo 121a.

[00317] Forma de realización 124. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:


,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

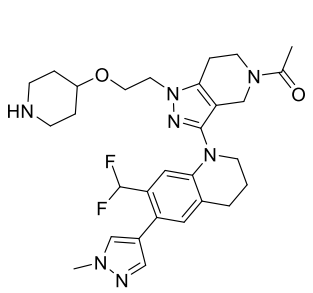
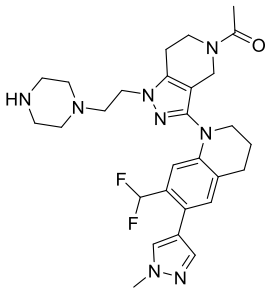
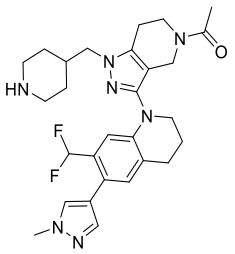
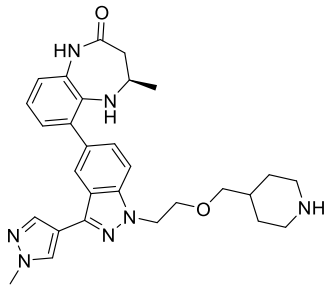
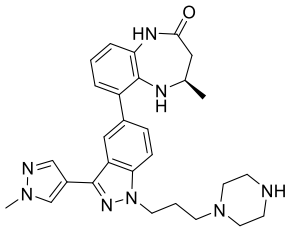
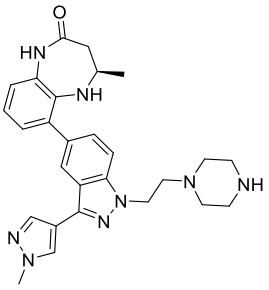
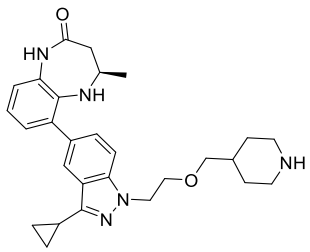
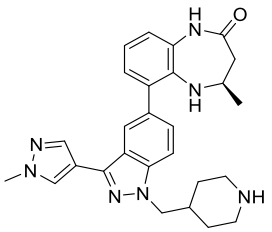
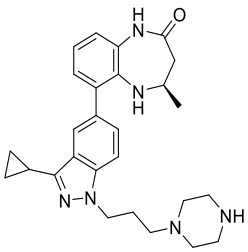
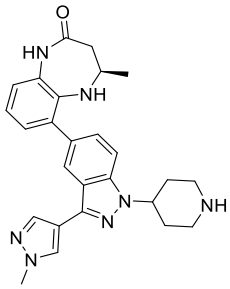
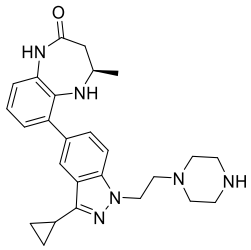
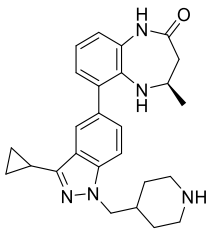
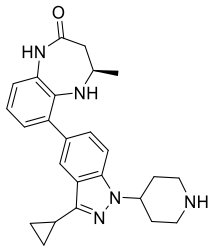
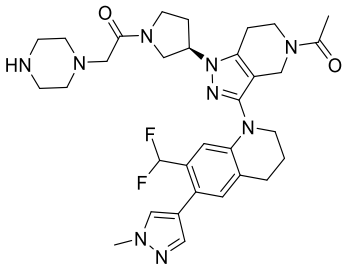
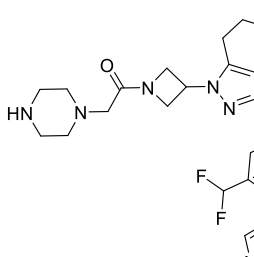

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

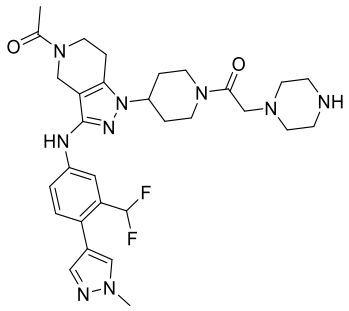
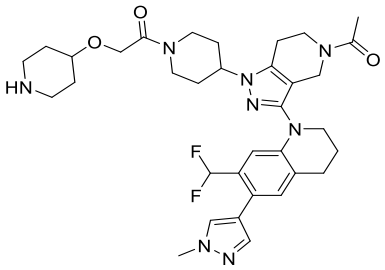
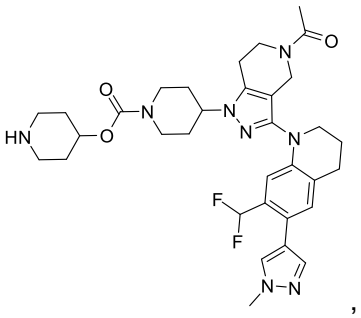
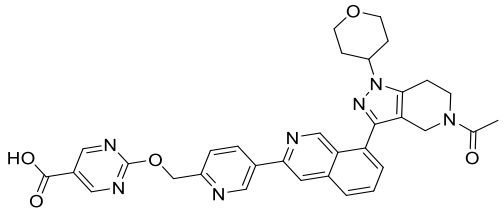
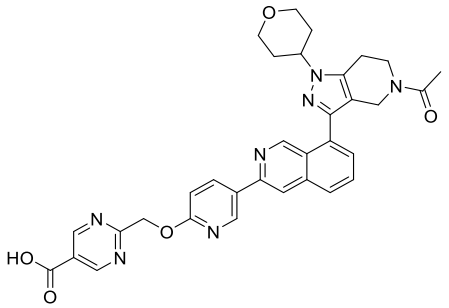
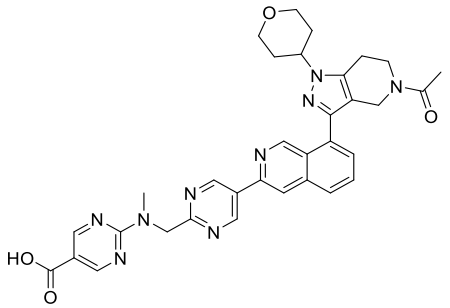
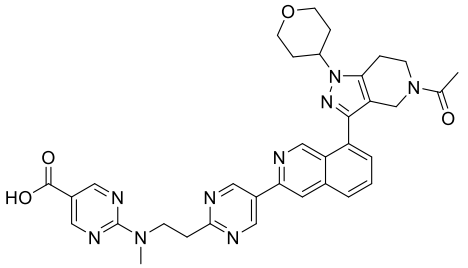
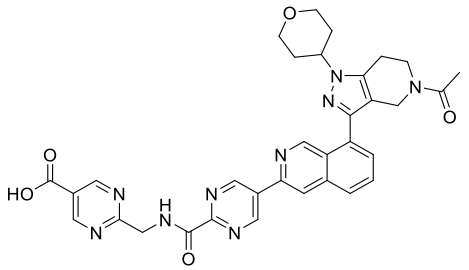
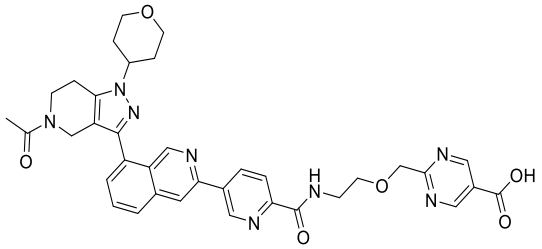
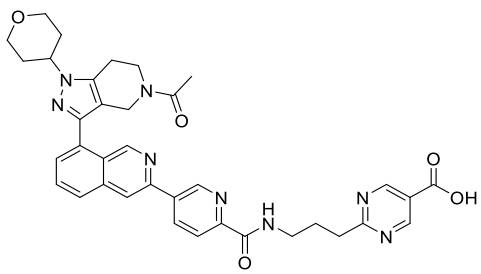
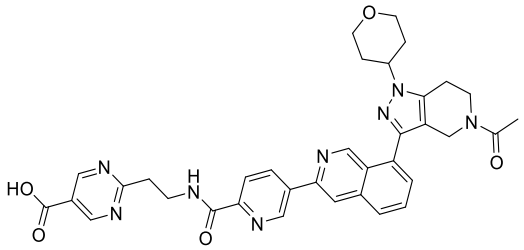
,

,

,

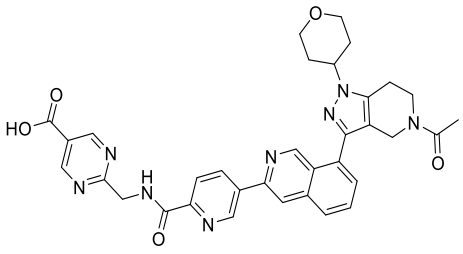
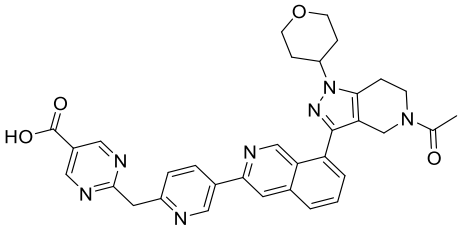
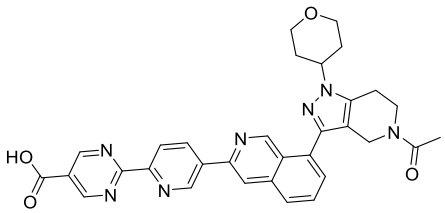
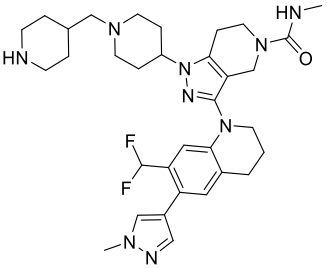
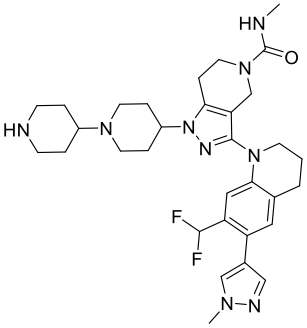
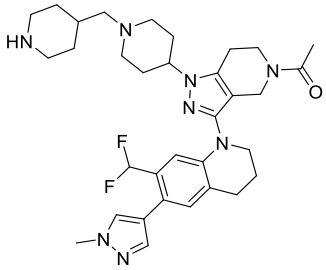
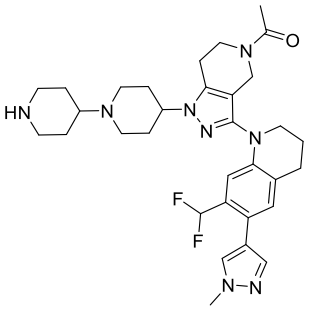
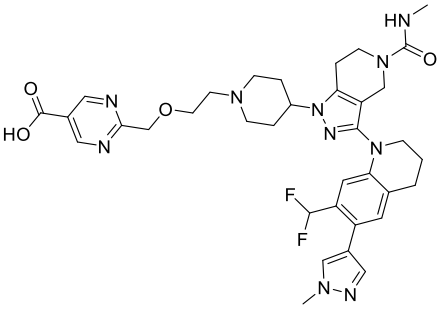
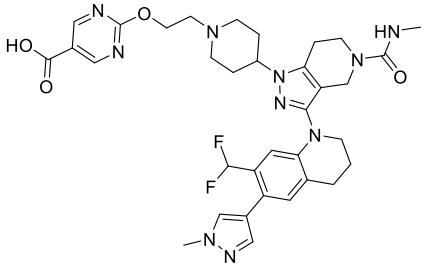
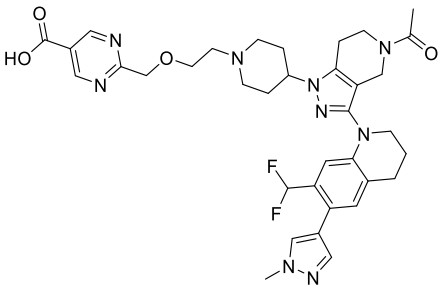
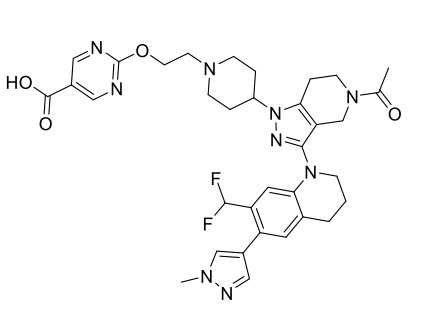
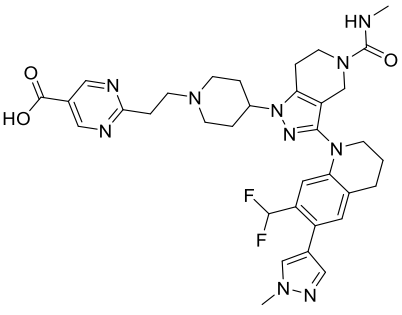
,

,


,

,

,

,

,

,

,

,

,

,

,

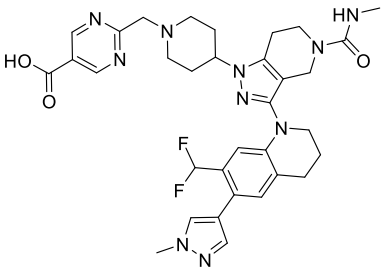
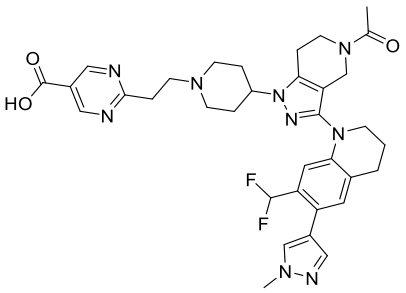
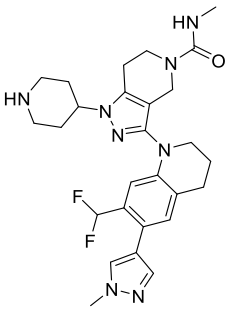
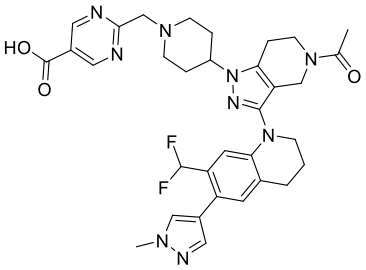
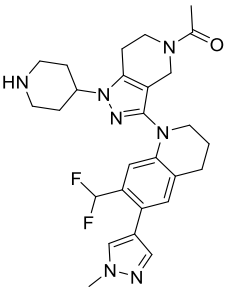
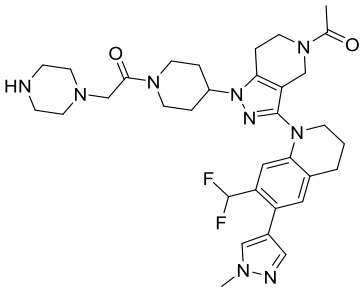
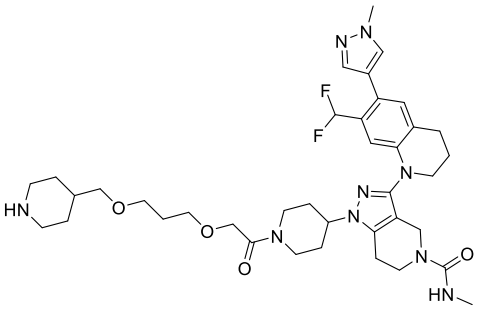
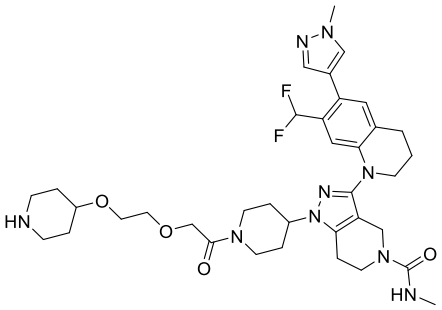
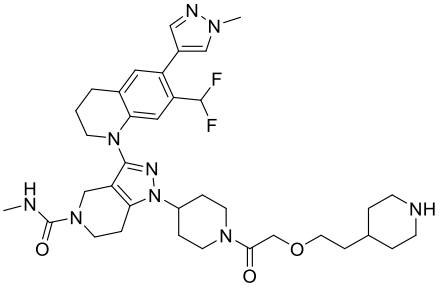
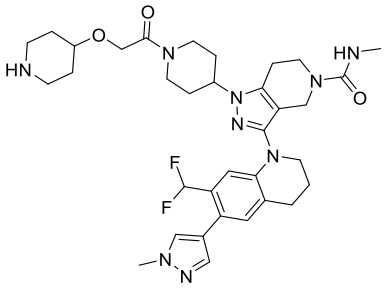
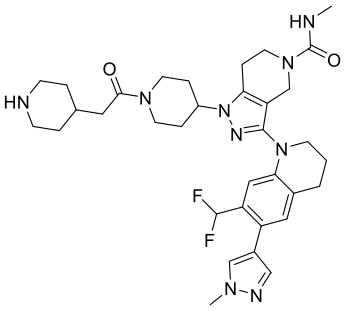
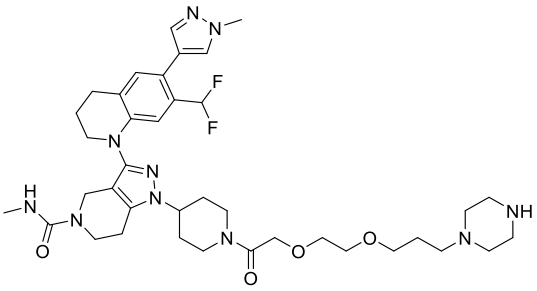
,

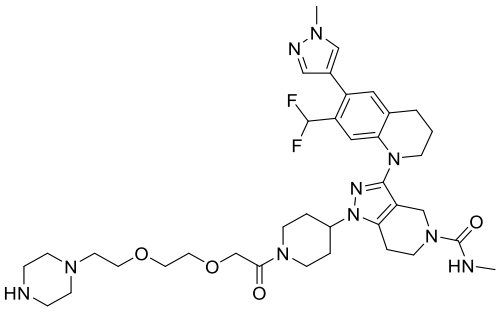
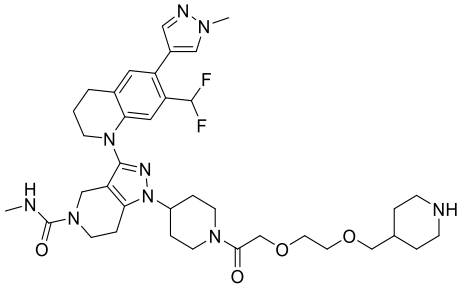
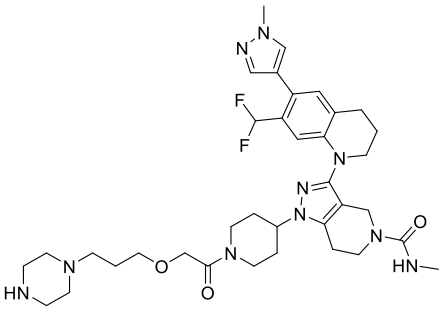
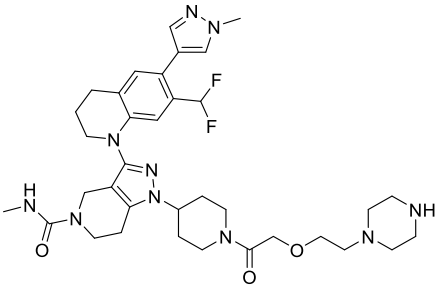
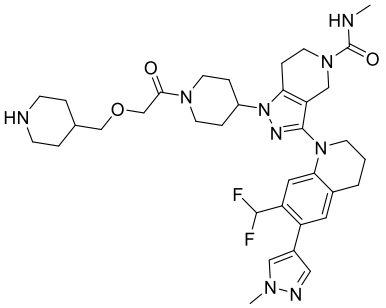
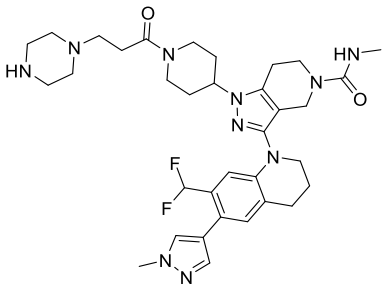
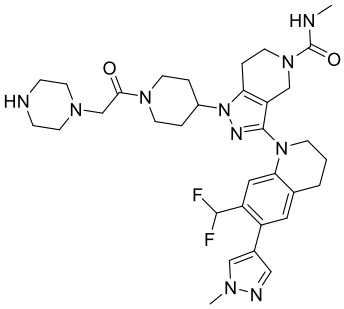
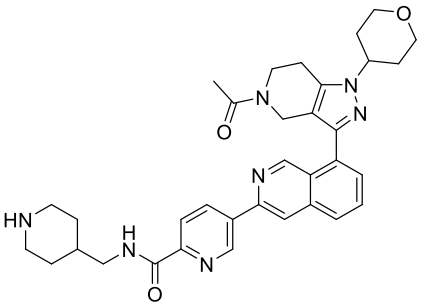
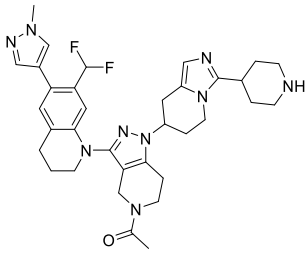
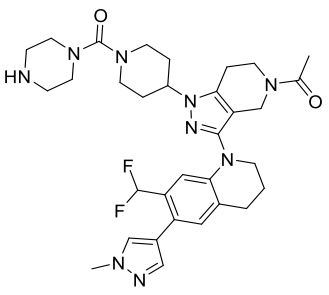
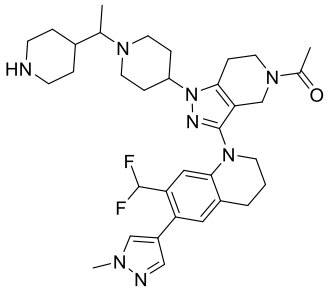
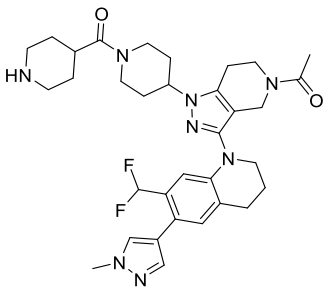
,

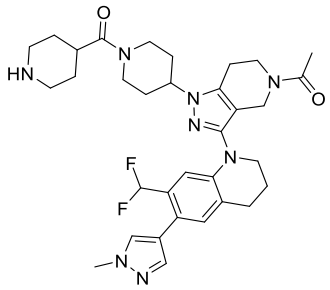
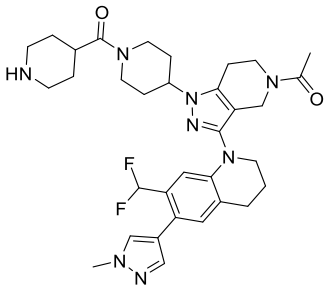
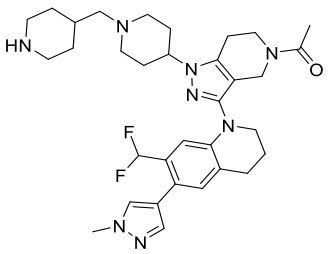
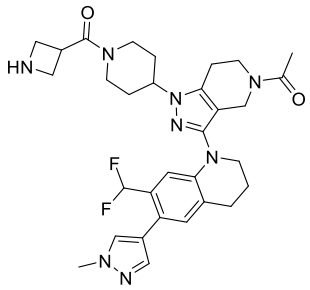
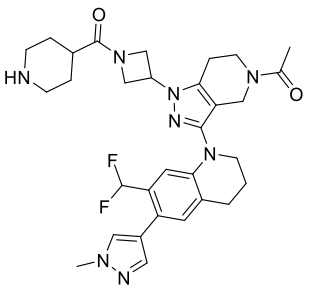
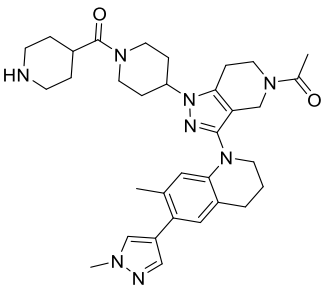
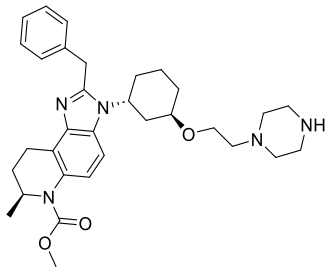
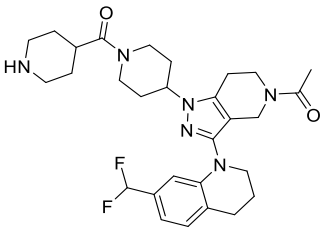
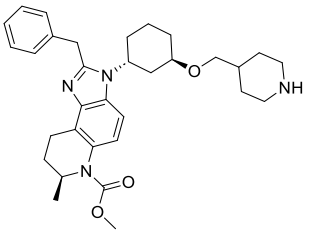
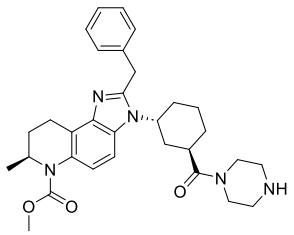
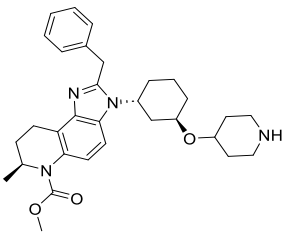
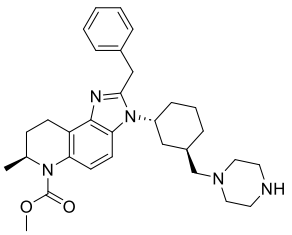
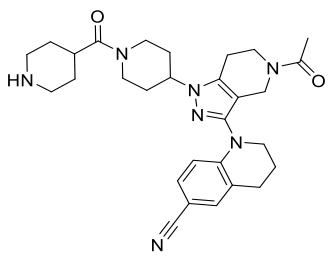
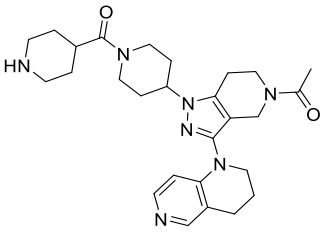
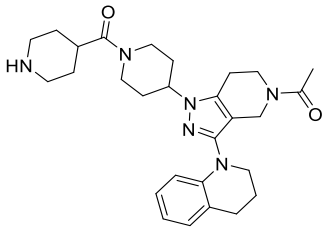
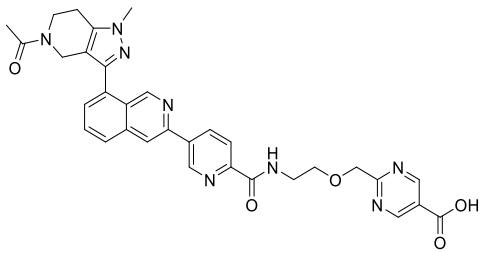
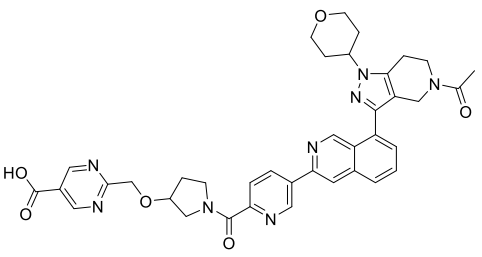

,

,

,

,

,

,

,

,

,

,

,

,

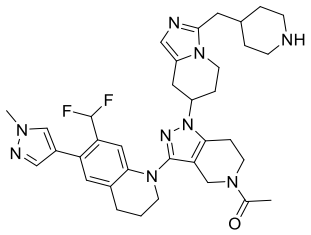
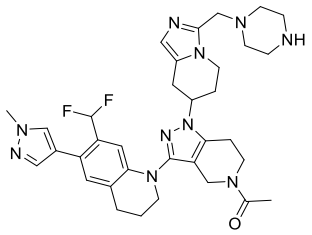
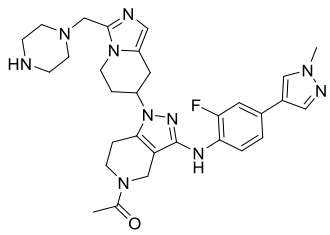
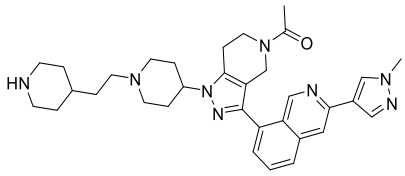
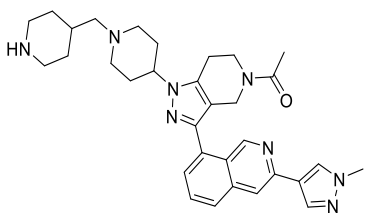
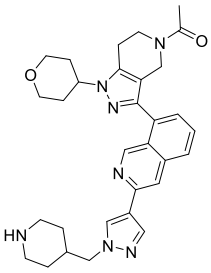
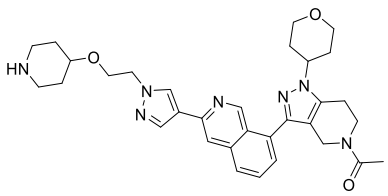
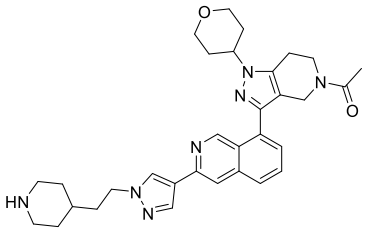
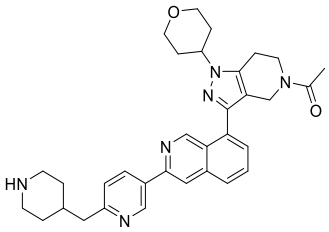
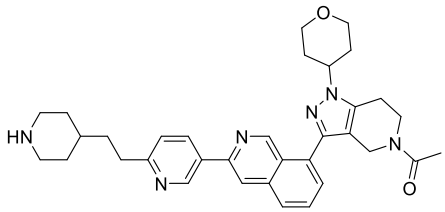
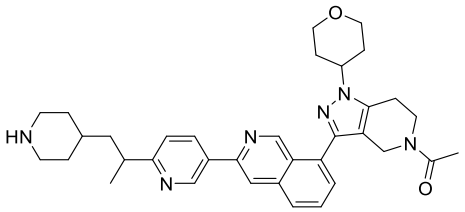
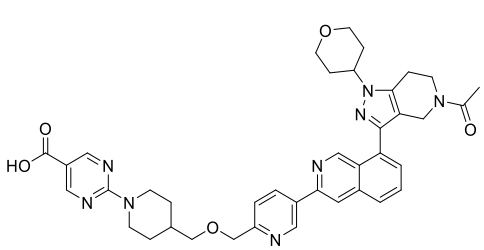
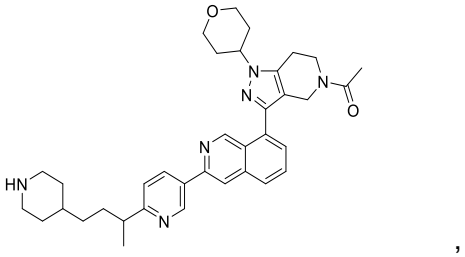
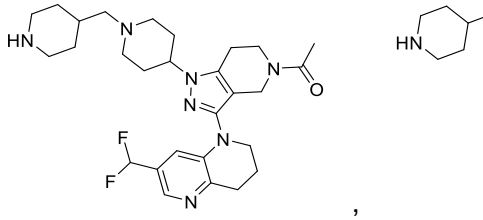
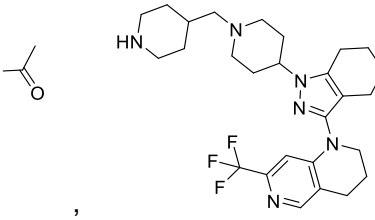
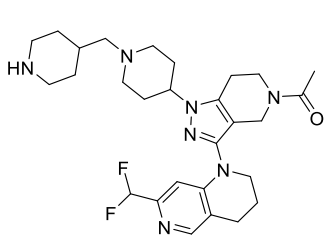
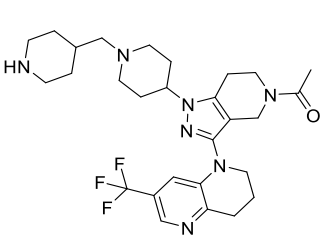
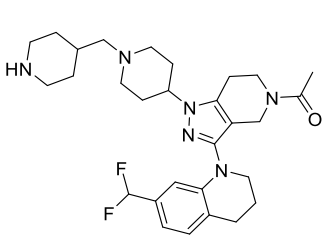
,

,


,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

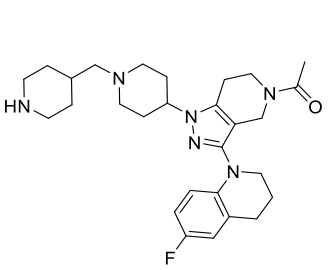
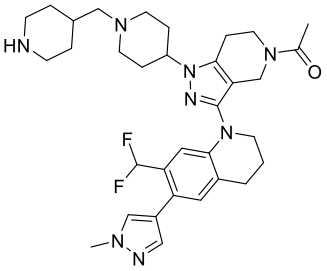
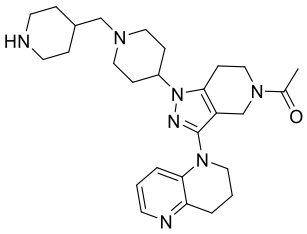
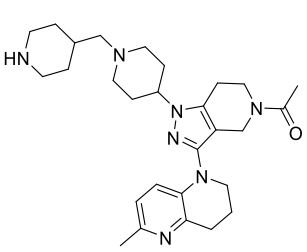
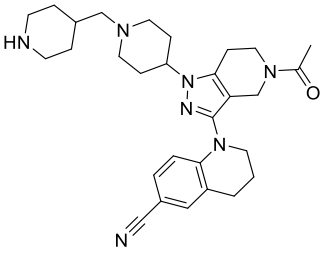
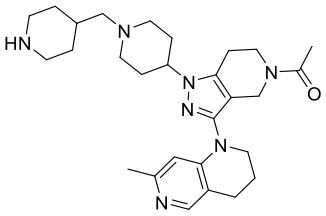
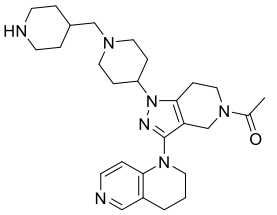
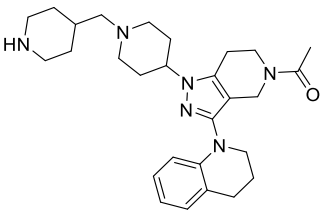
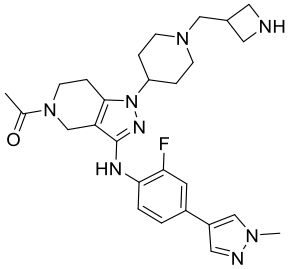
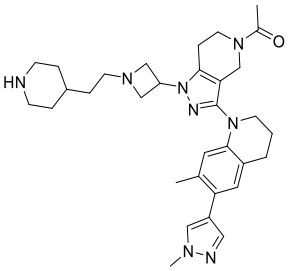
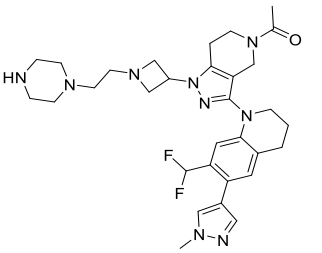
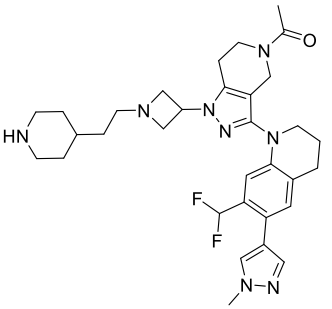

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

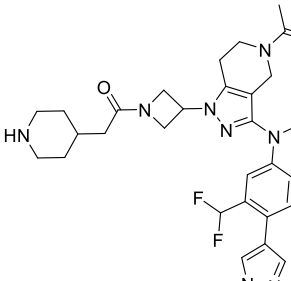
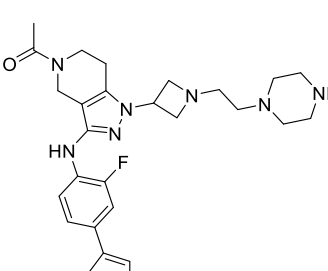
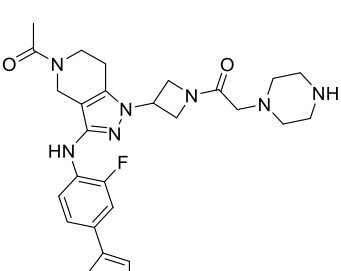
,

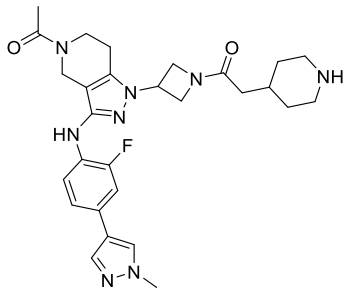
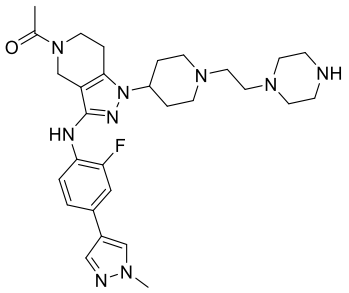
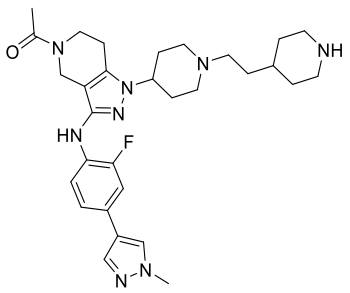
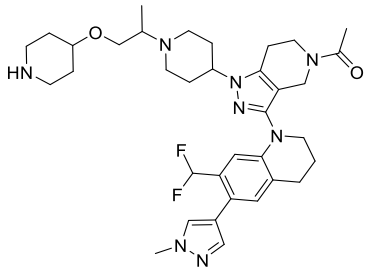
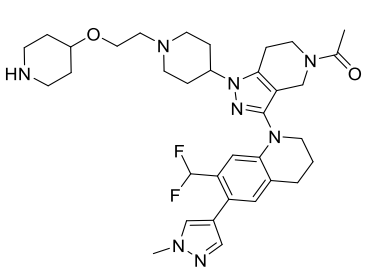
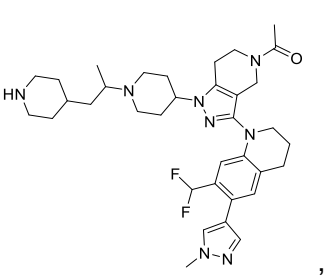
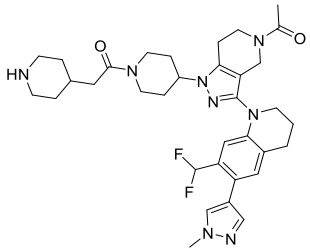
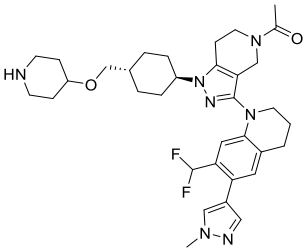
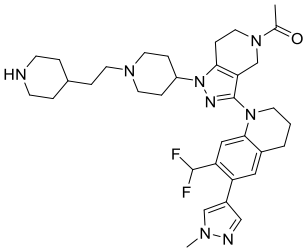
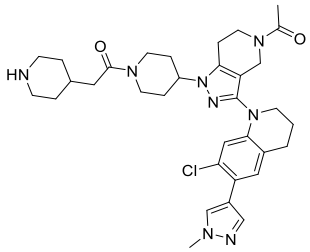
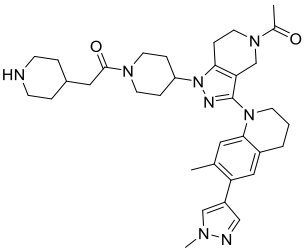
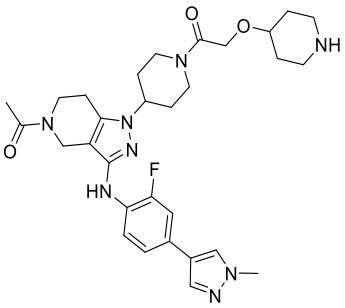
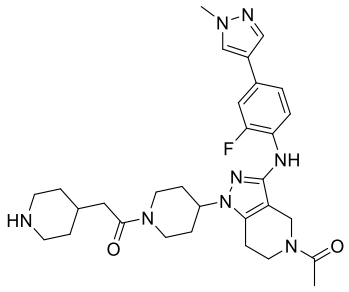
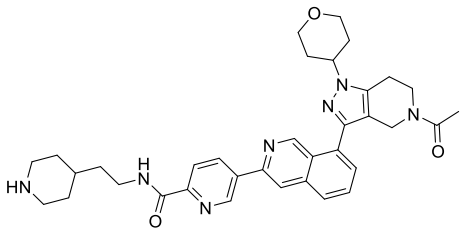
,

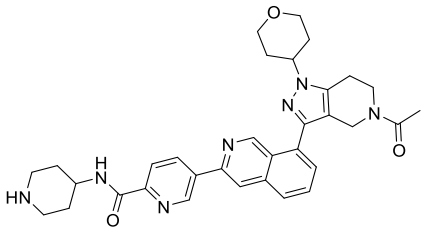
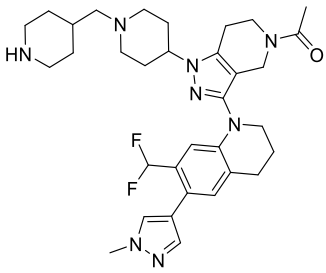
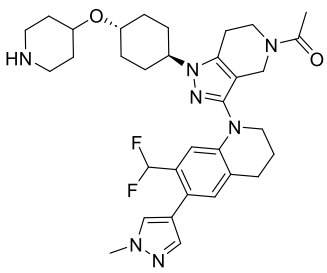
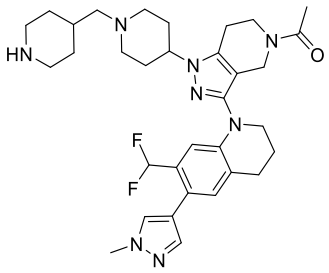
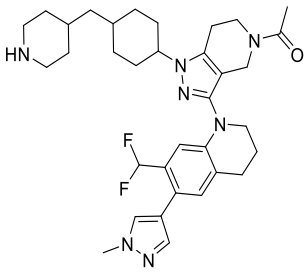
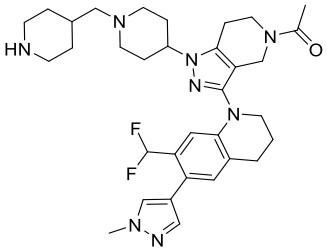
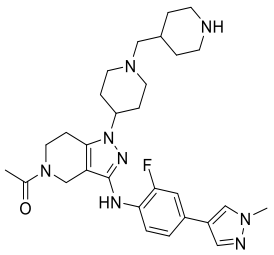
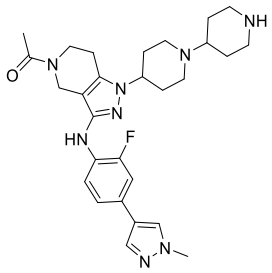
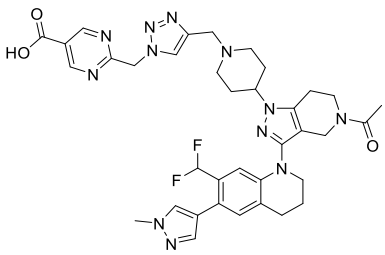
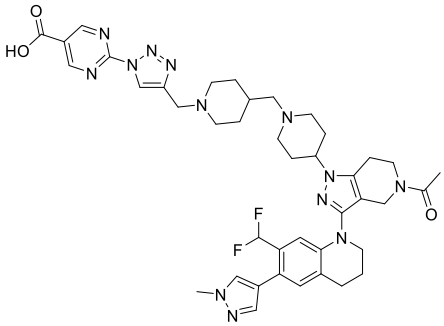
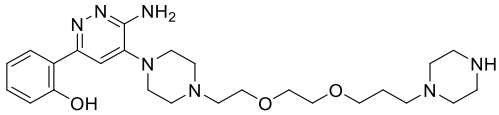
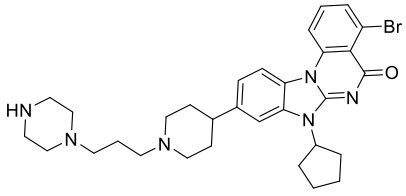
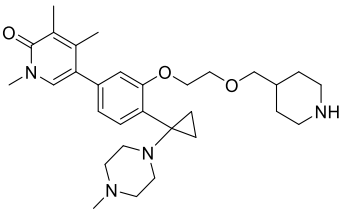
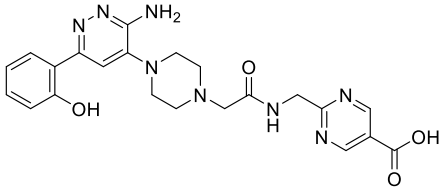
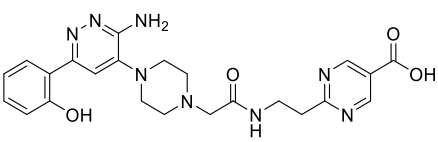

,

,

,

,

,

,

,

,

,

,

,

,

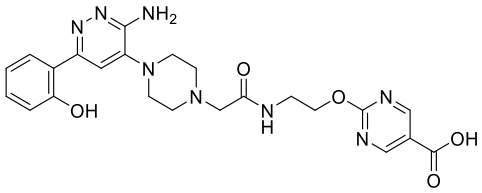
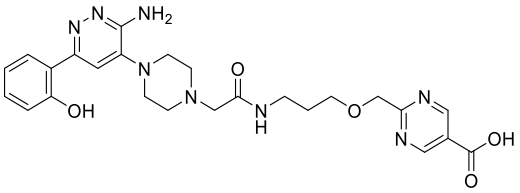
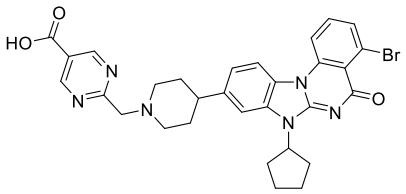
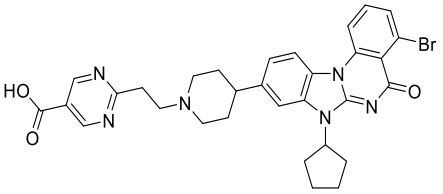
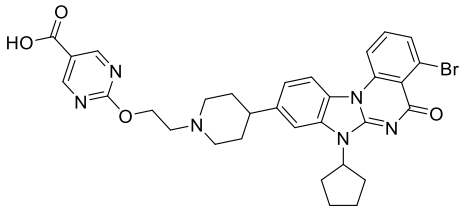
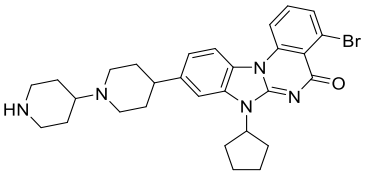
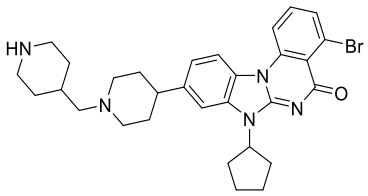
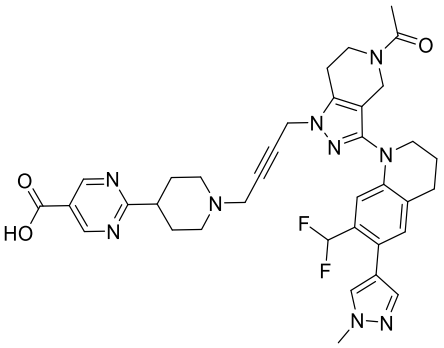
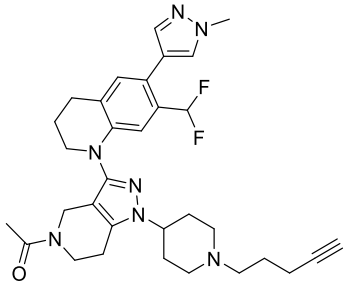
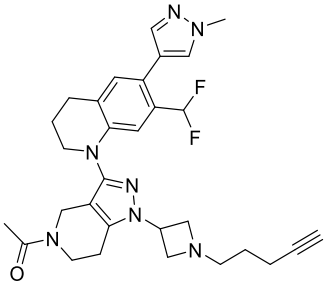
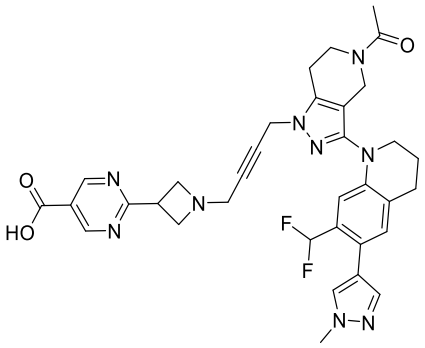
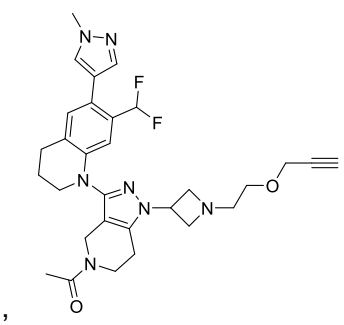
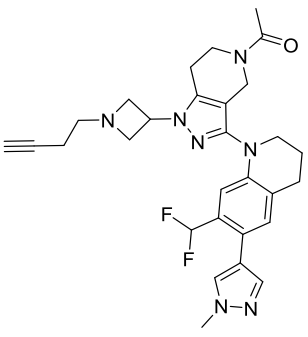
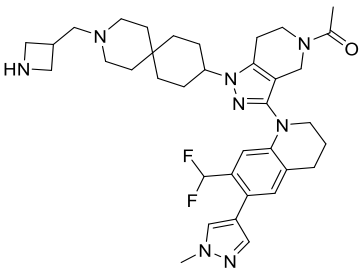
,

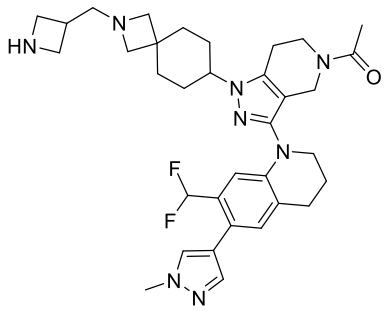
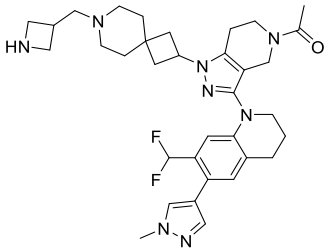
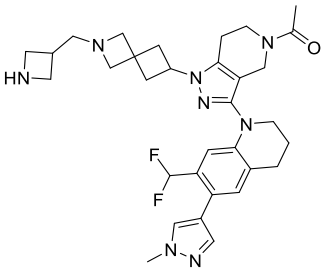
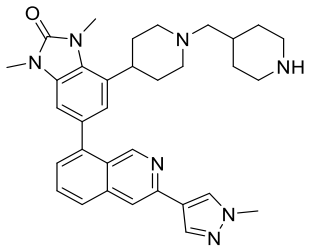
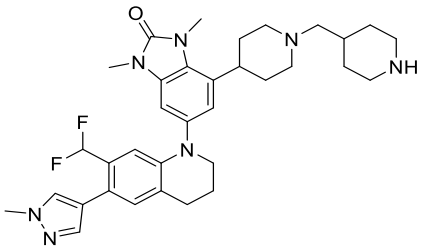
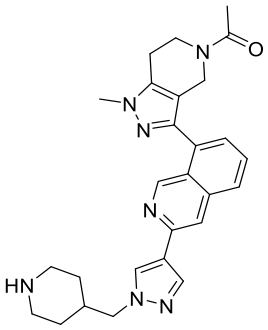
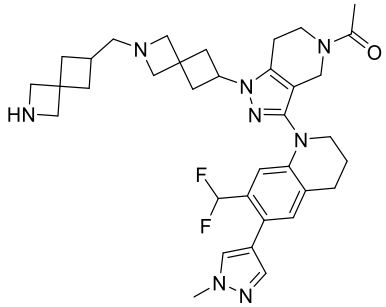
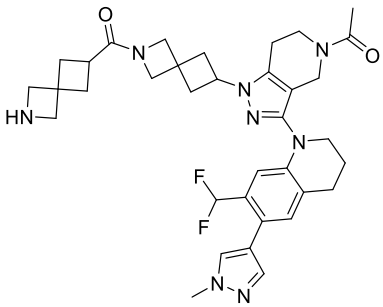
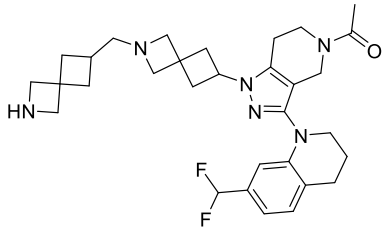
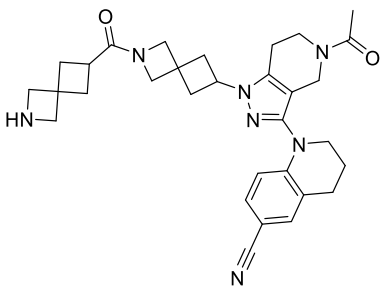
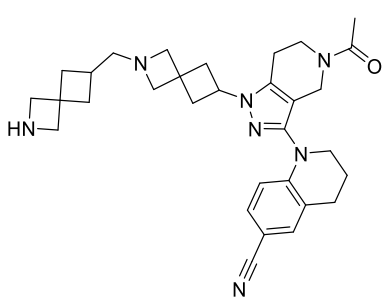
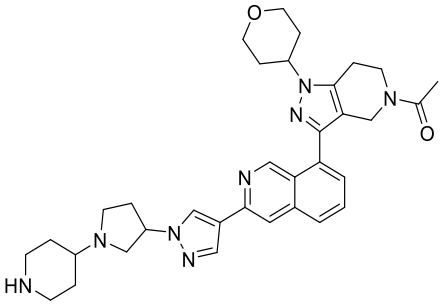
,

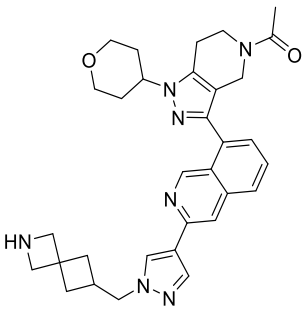
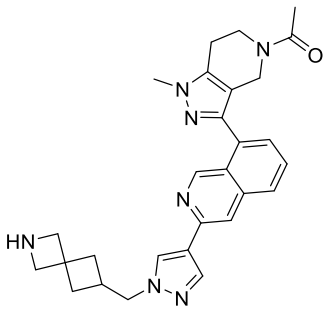
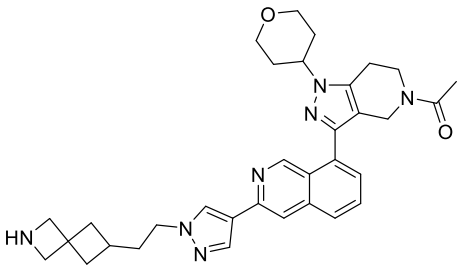
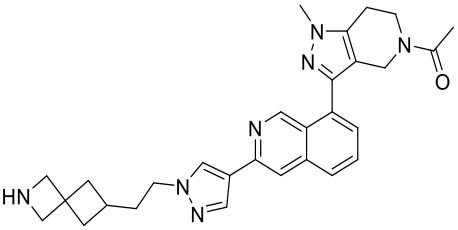
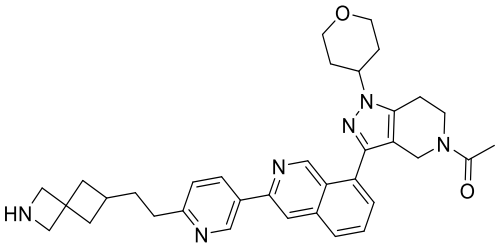
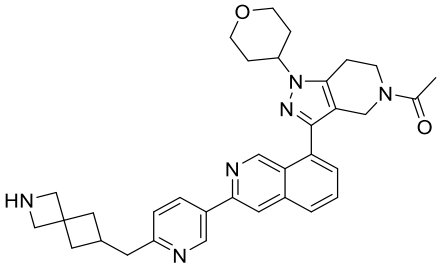
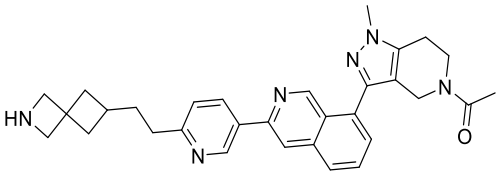
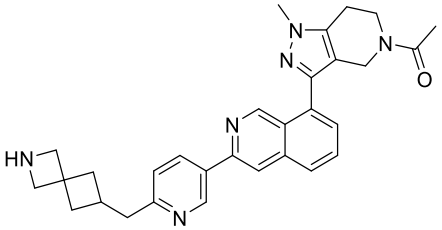
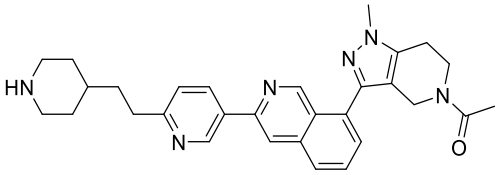
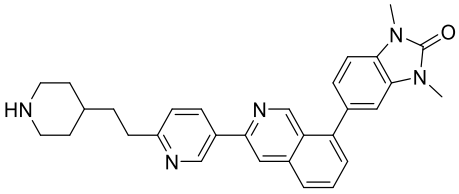
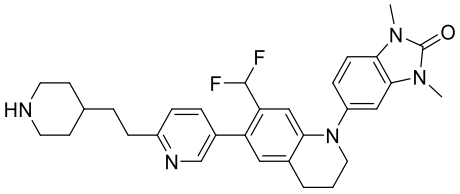
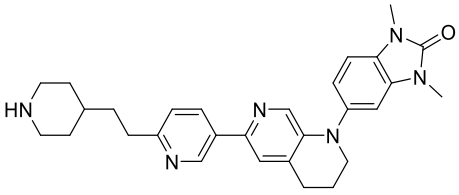
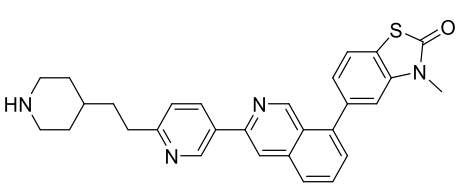
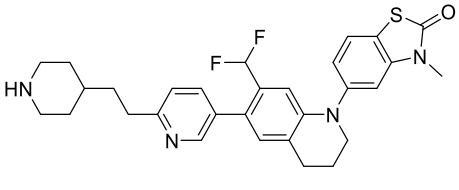
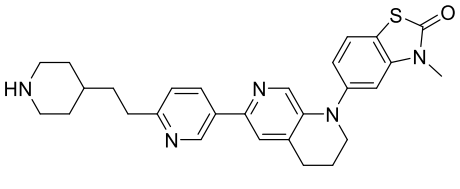
,

,

,

,

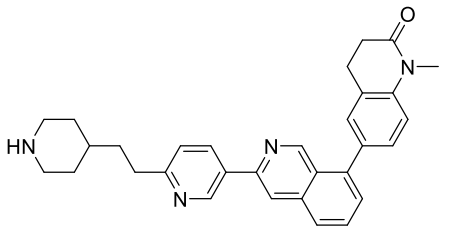
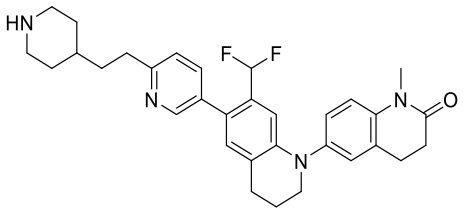
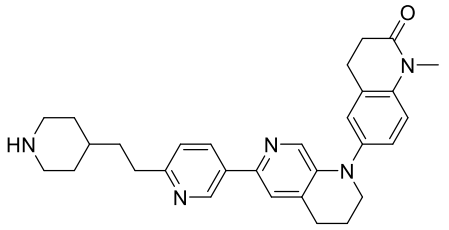
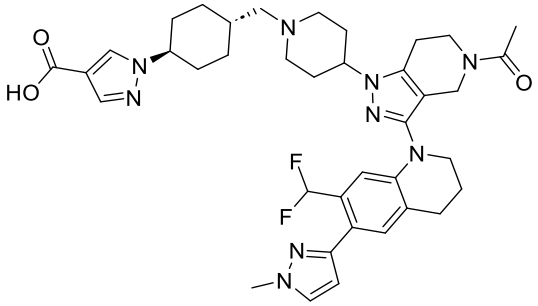
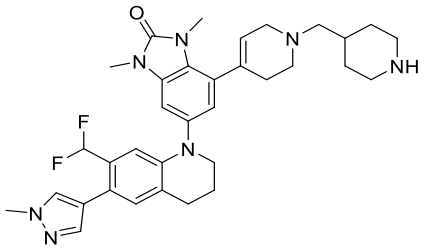
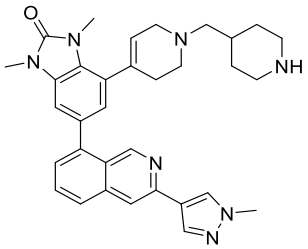
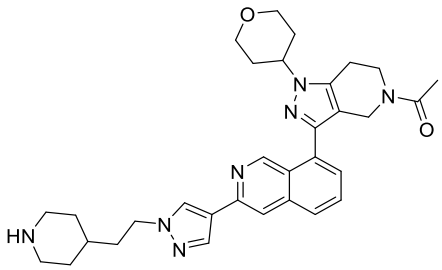
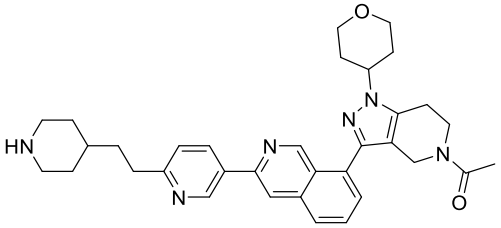
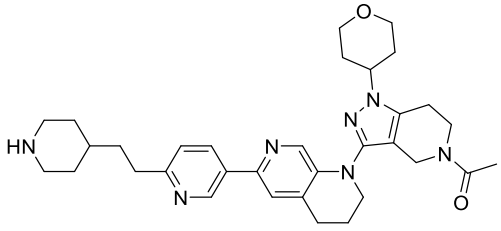
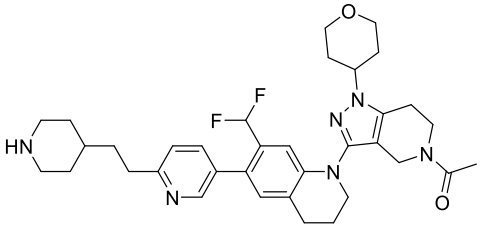
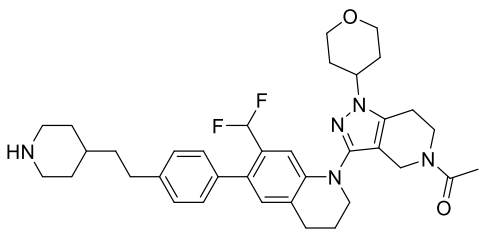
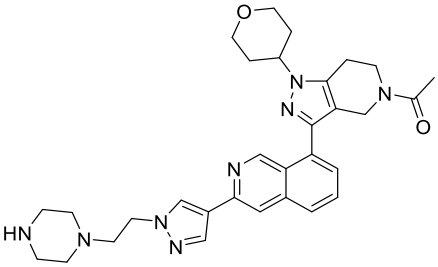

,

,

,

,

,

,

,

,

,

,

,

,

,

,

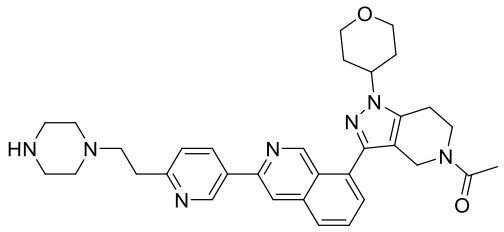
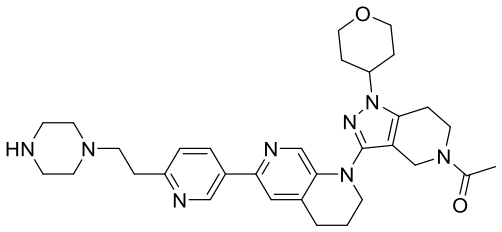
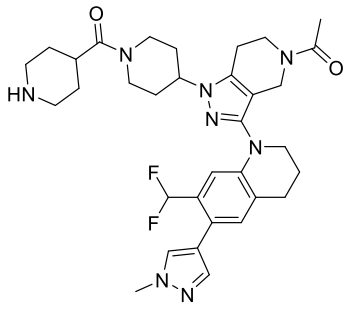
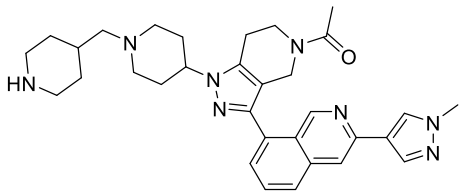
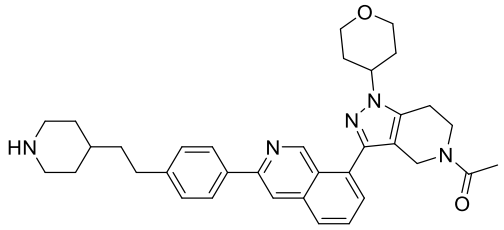
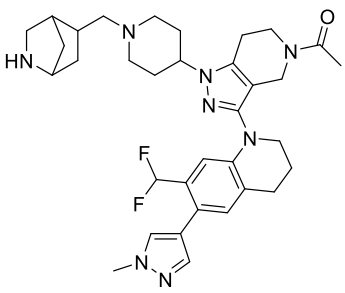
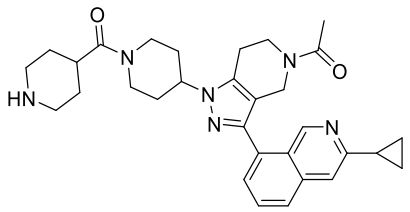
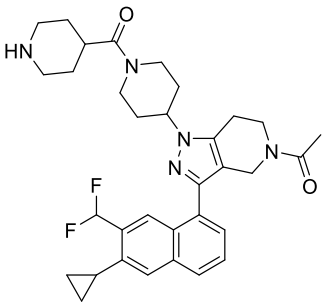
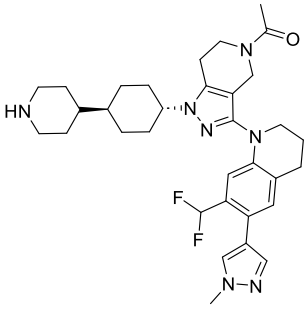
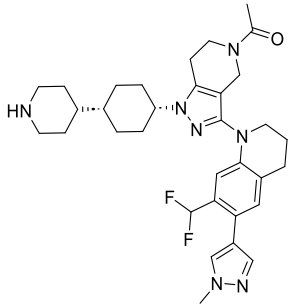
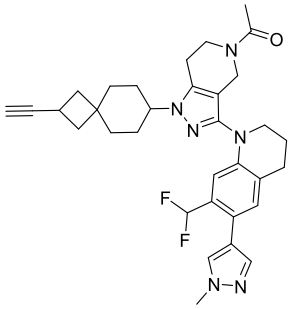
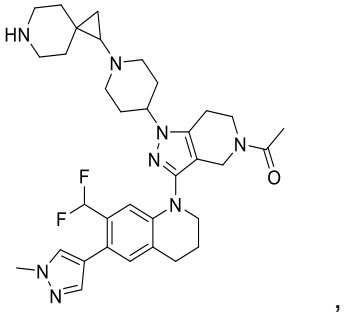

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,



,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

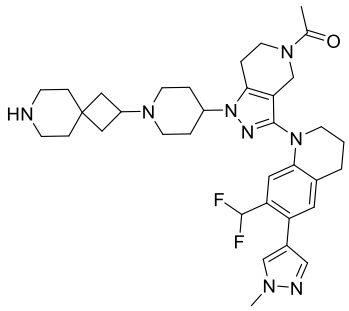
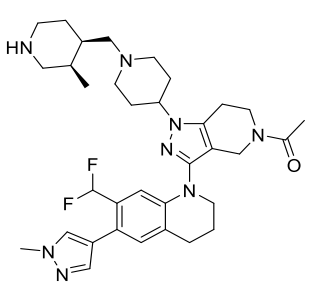
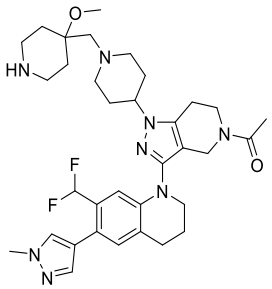
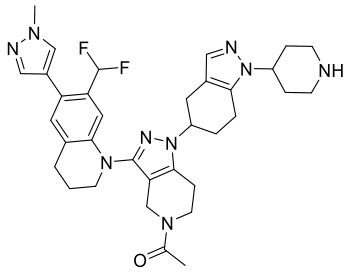
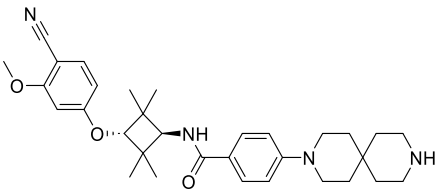
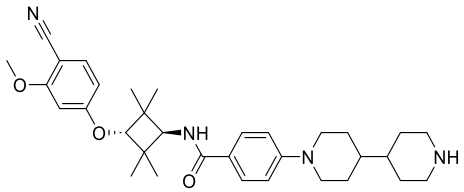
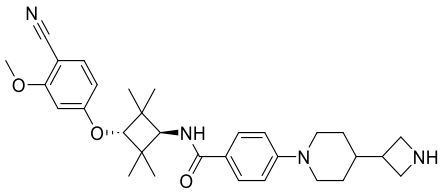
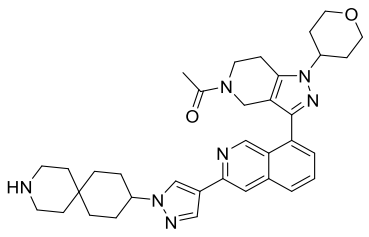
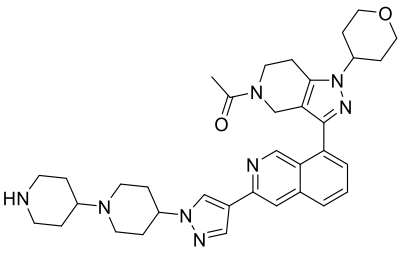
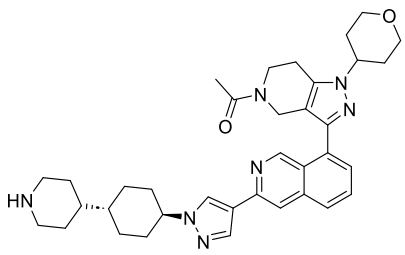
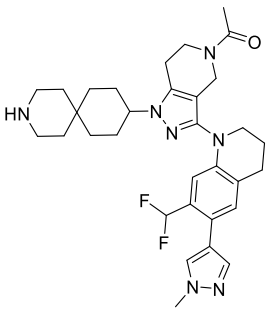
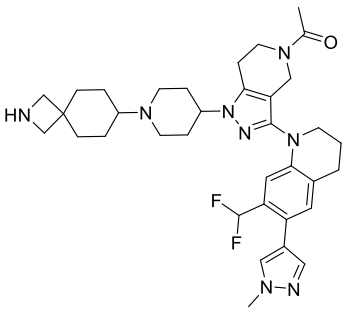
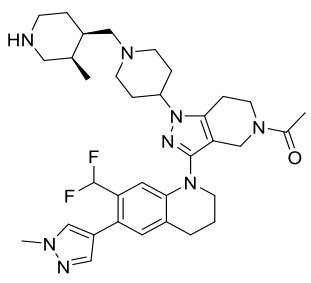
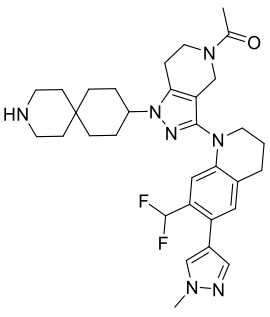
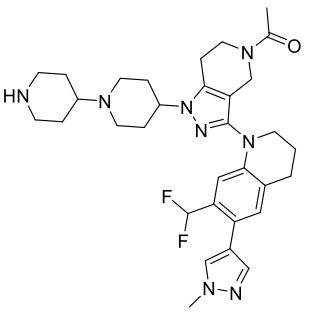

,

,

,

,

,

,

,

,

,

,

,

,

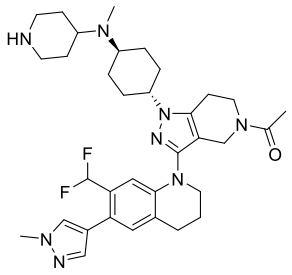
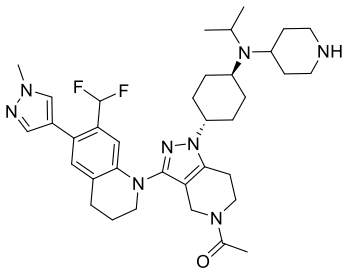
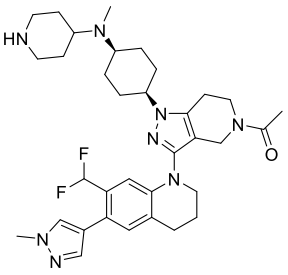
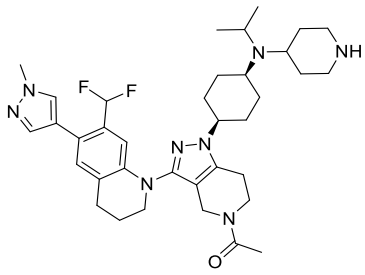
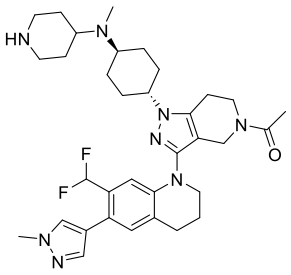
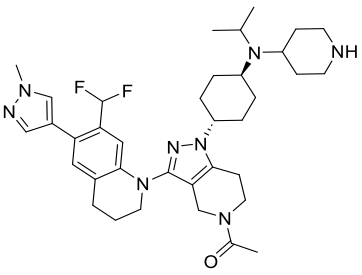
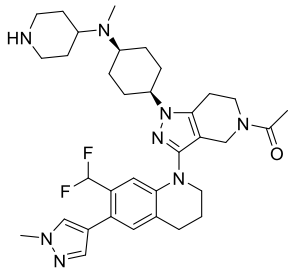
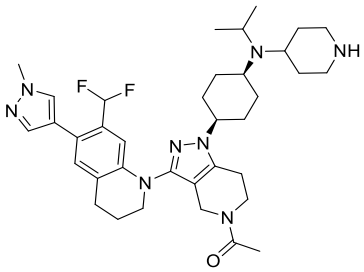
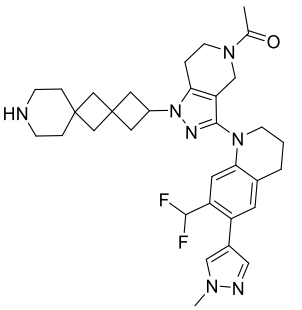
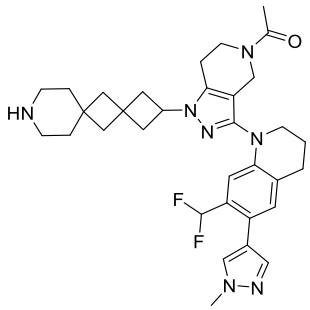
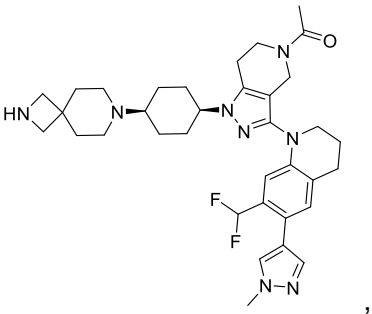
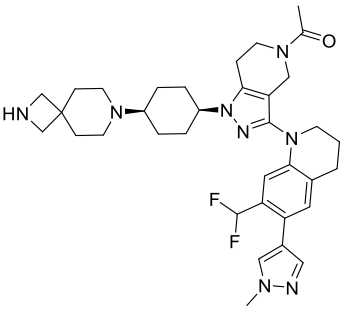
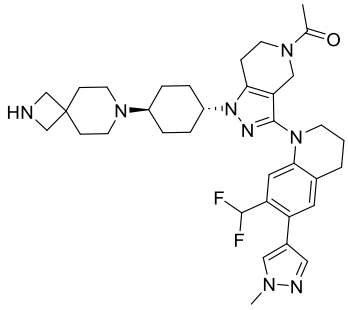
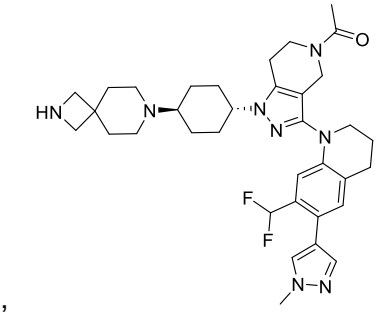
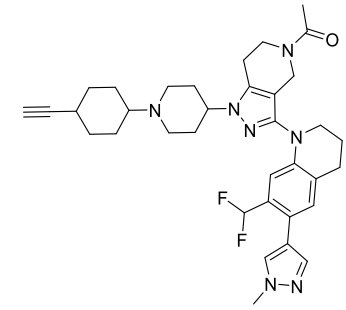

,

,

,

,

,

,

,

,

,

,

,

,

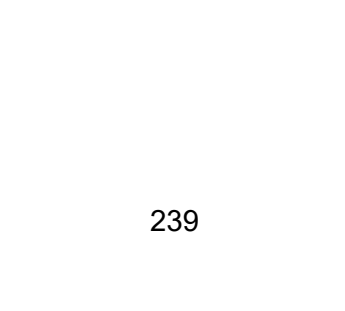
,

,

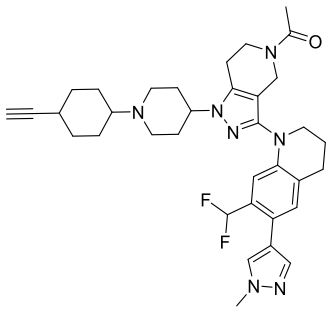
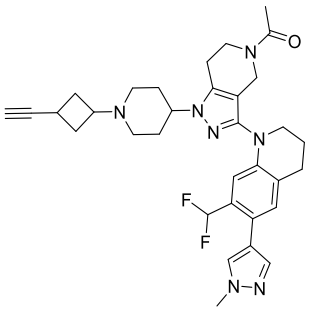
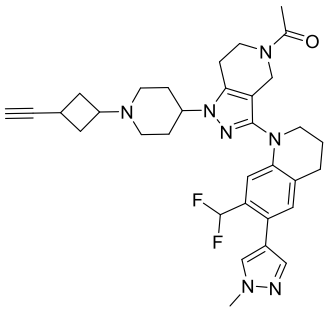
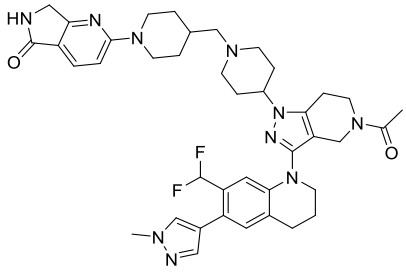
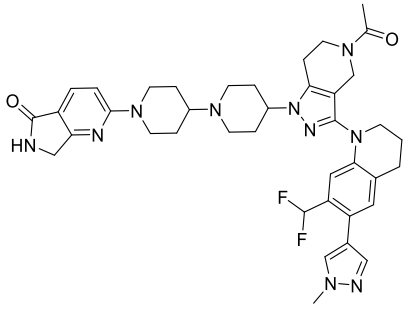
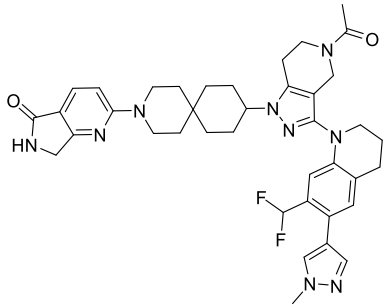
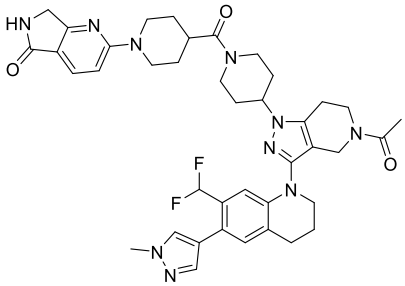
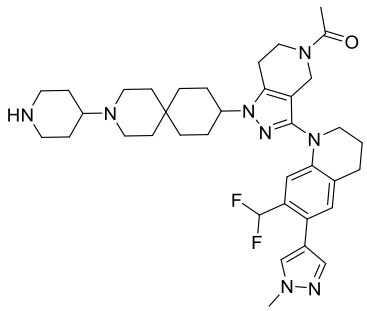
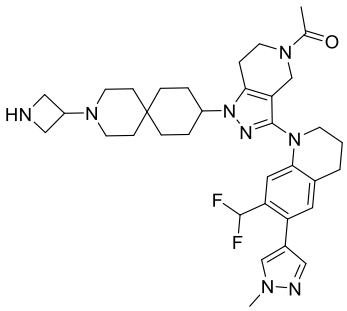
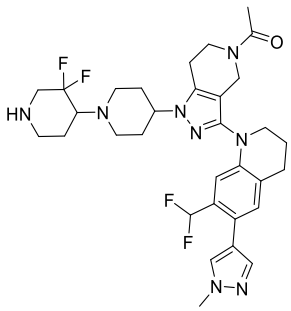
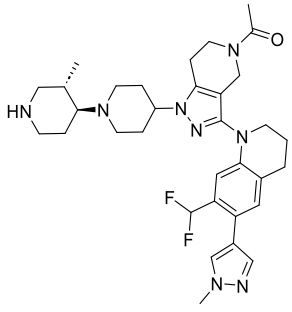
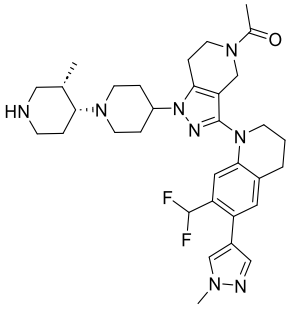
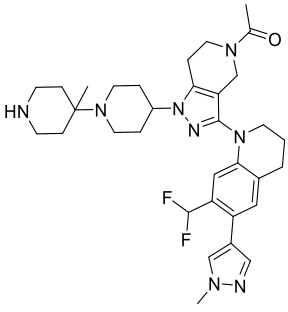
,

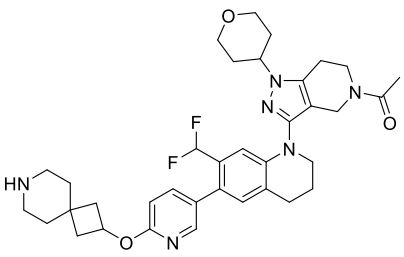
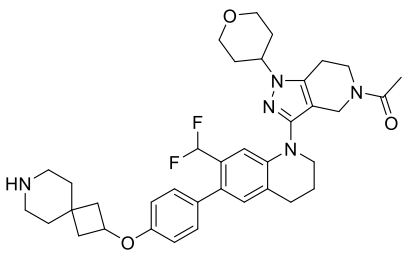
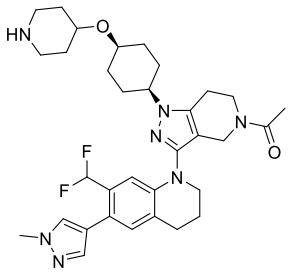
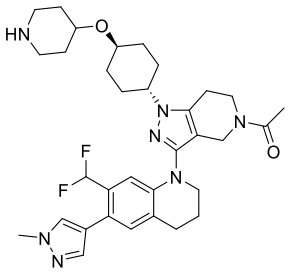
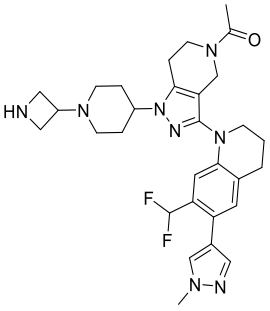
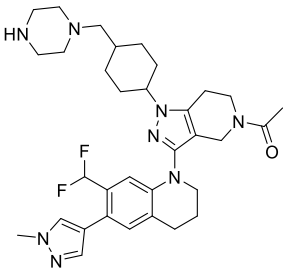
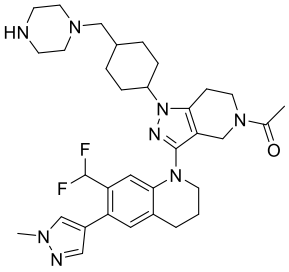
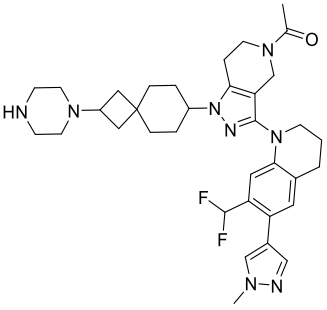
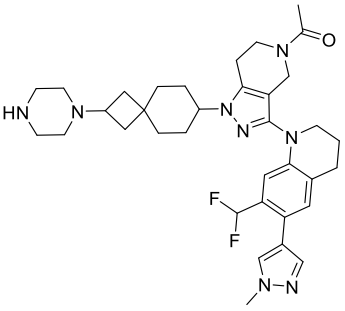
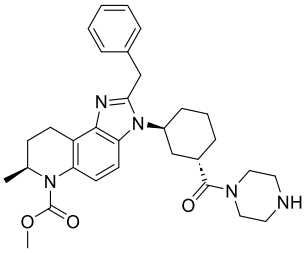
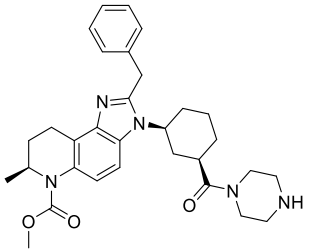
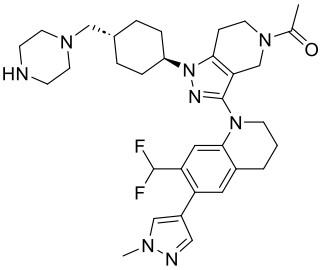
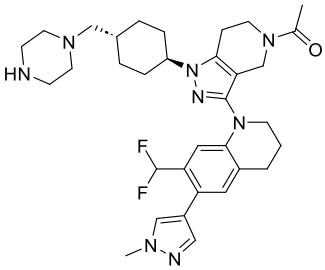
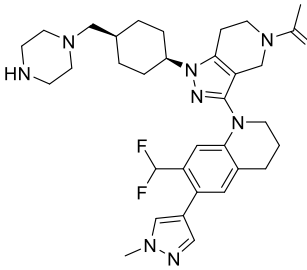
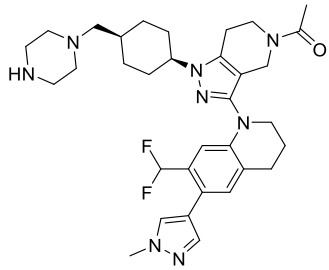
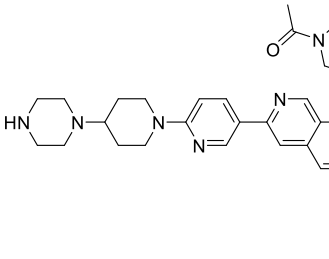
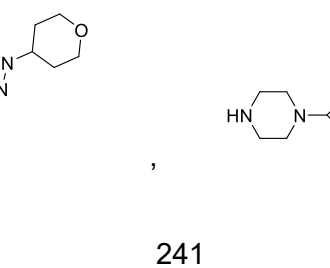
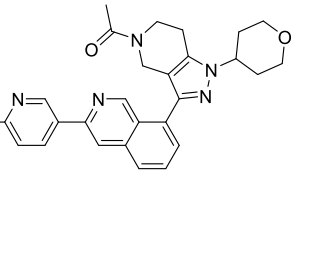

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

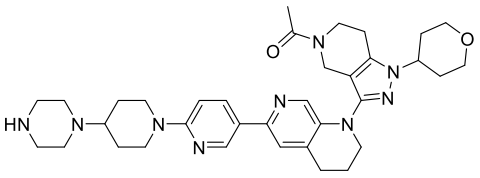
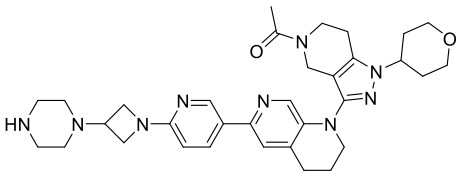
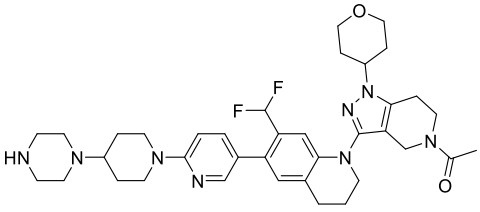
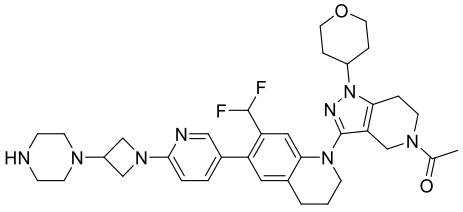
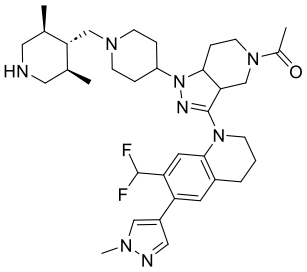
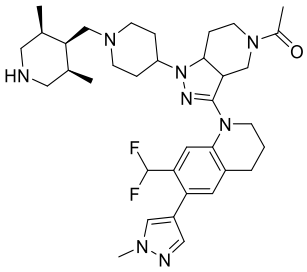
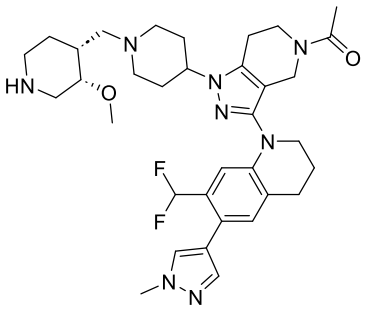
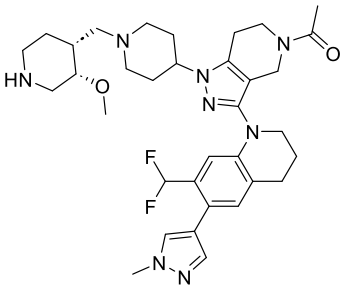
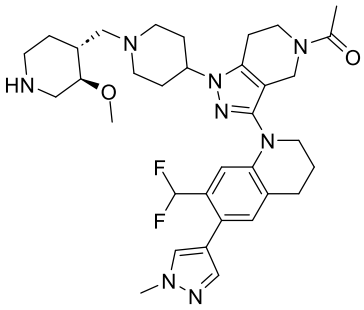
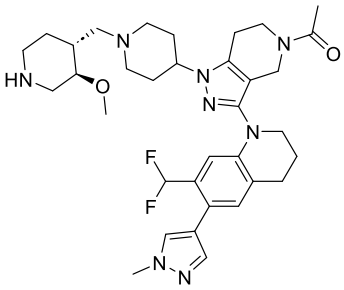
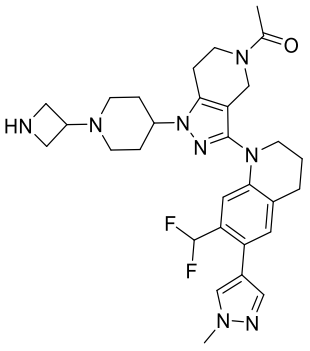
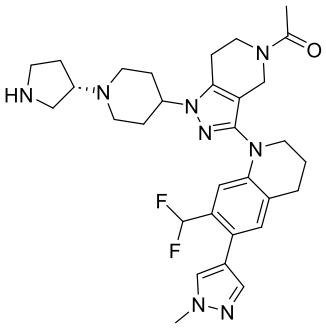
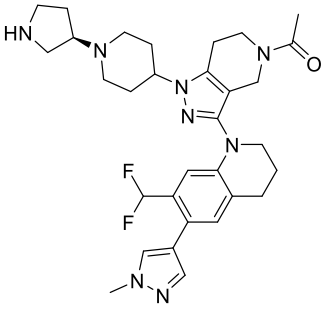
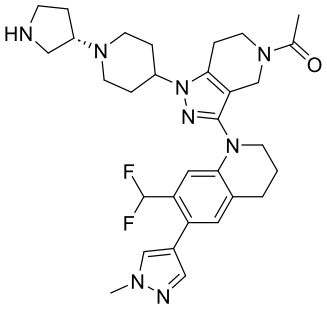
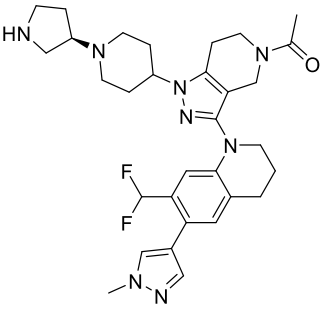
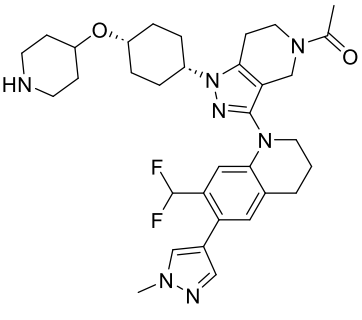
,

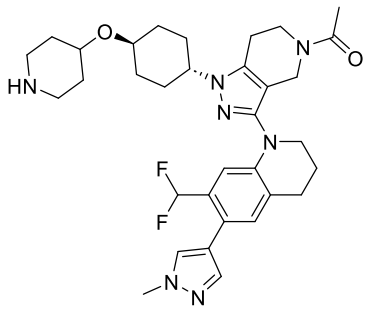
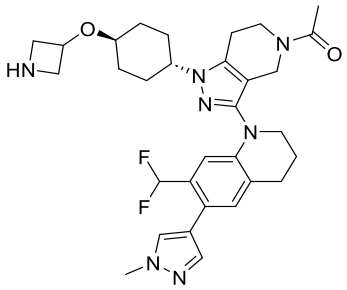
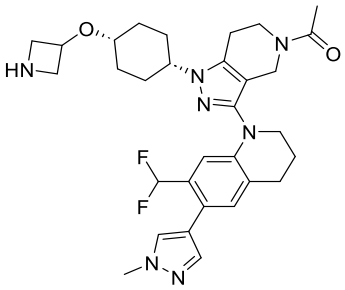
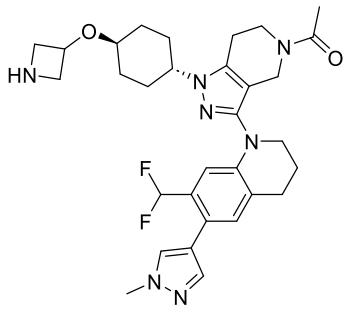
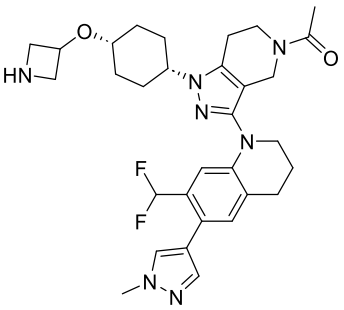
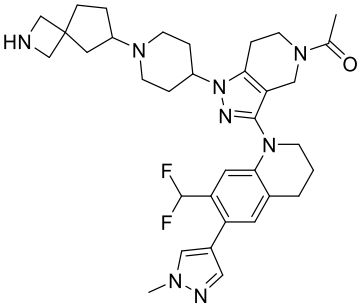
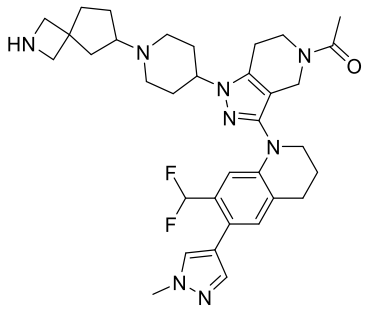
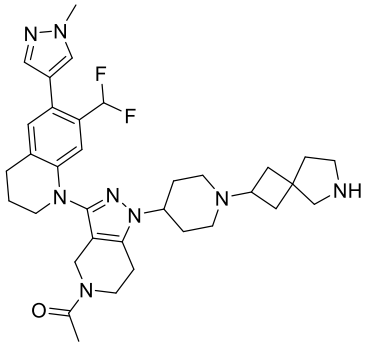
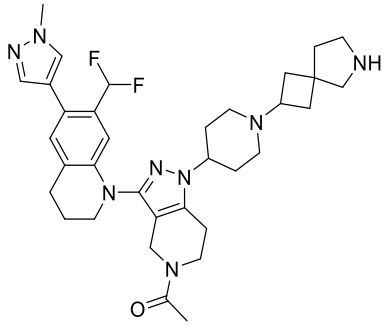
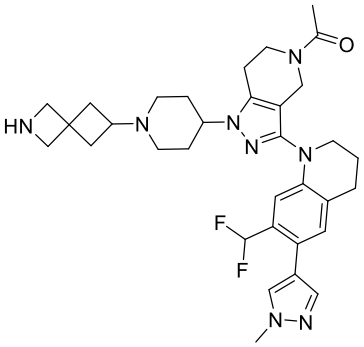
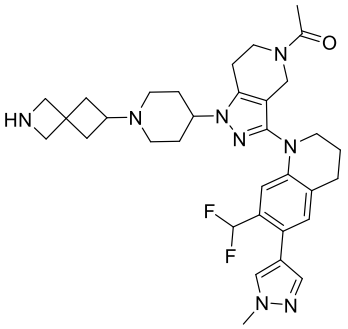
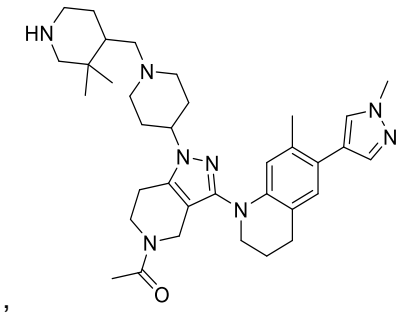
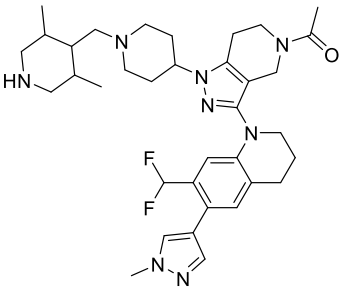
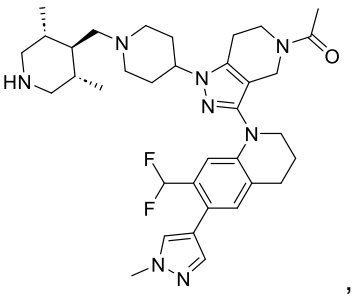

,

,

,

,

,

,

,

,

,

,

,

,

,

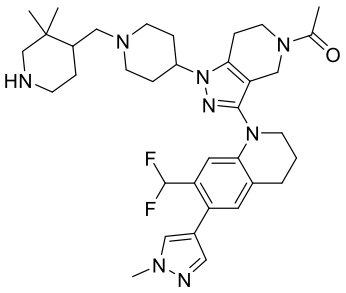
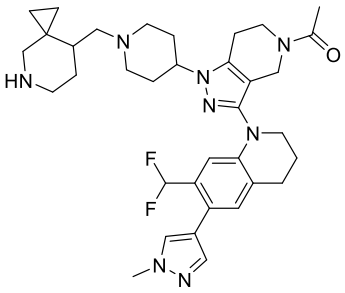
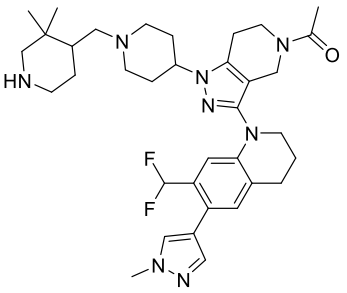
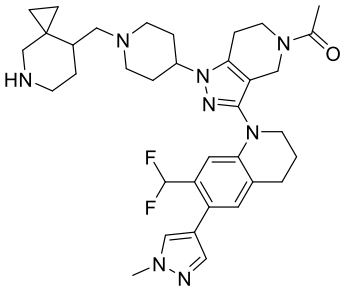
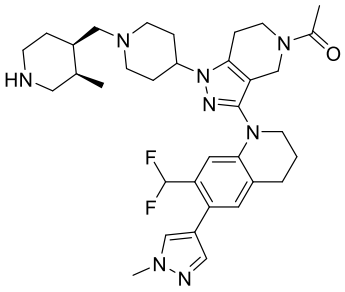
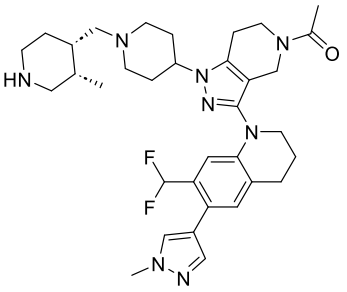
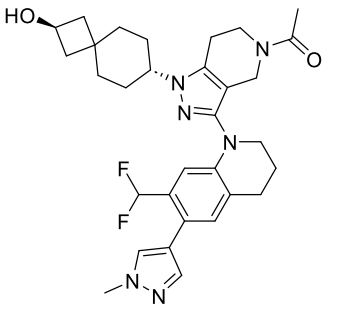
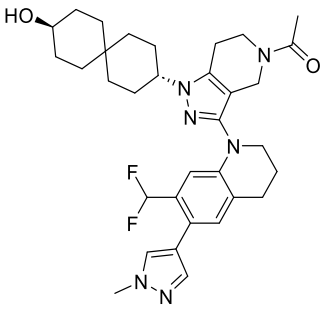
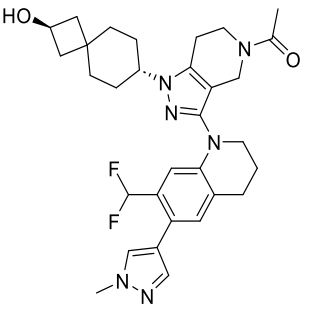
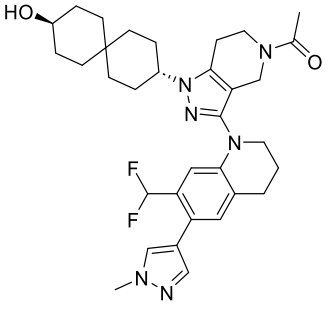
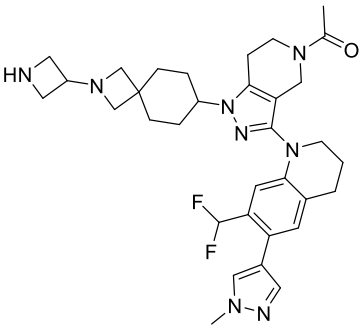
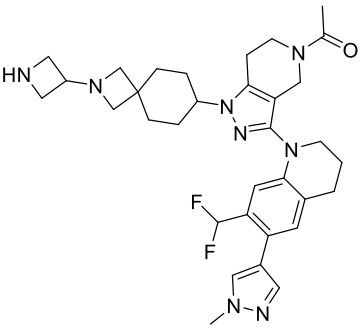
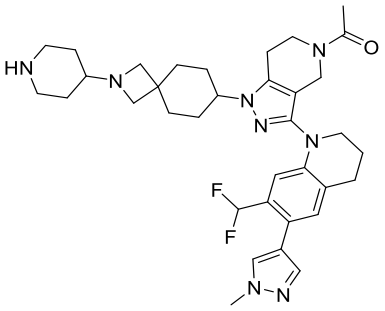
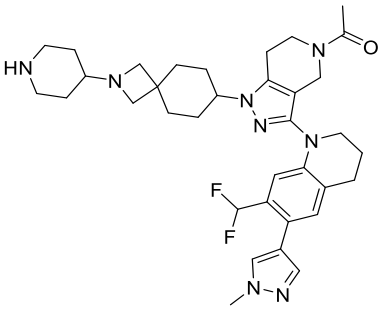

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

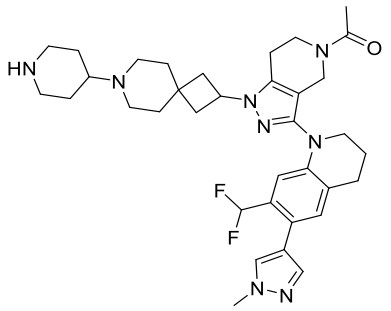
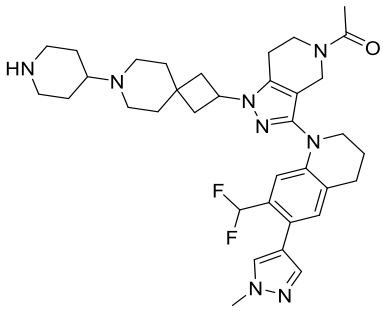
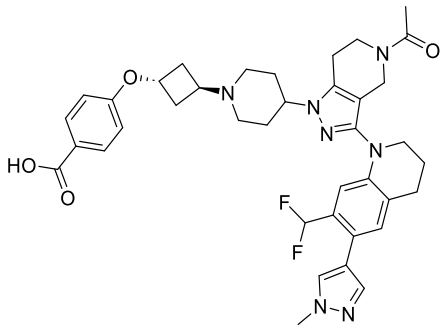
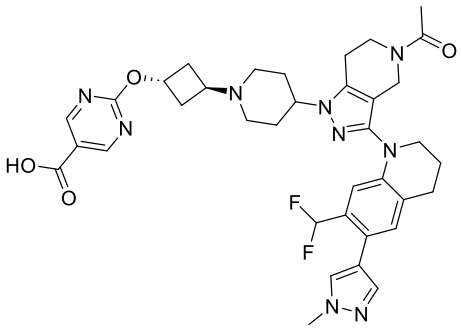
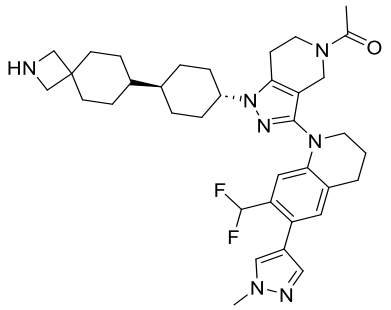
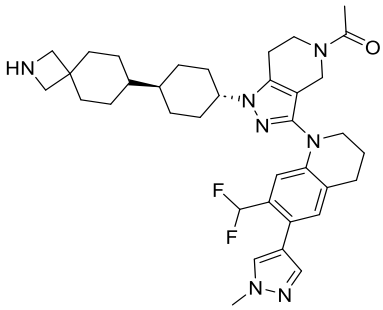
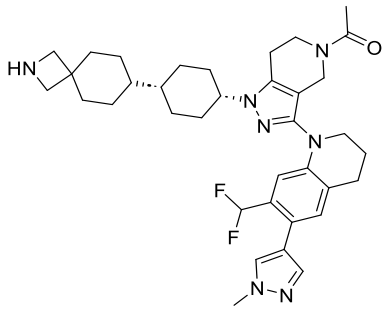
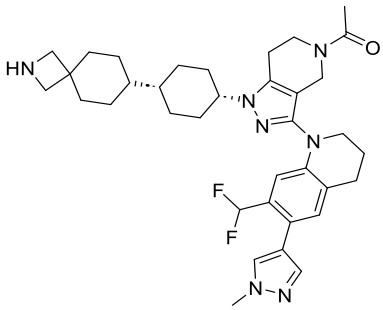
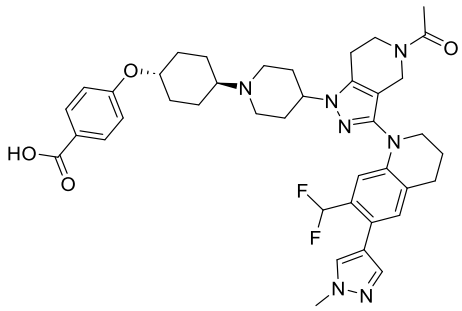
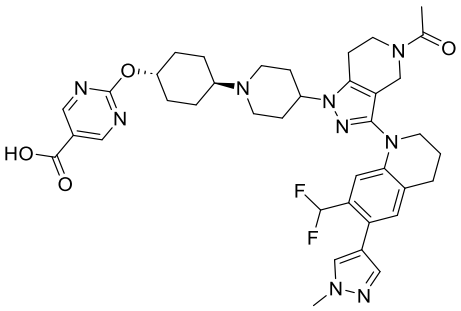
,

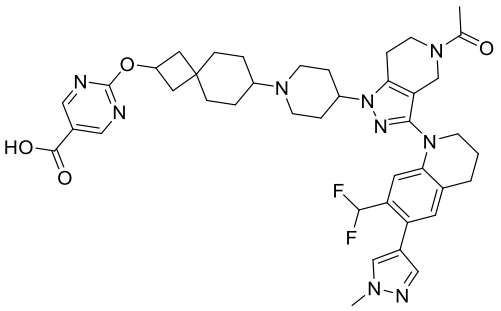
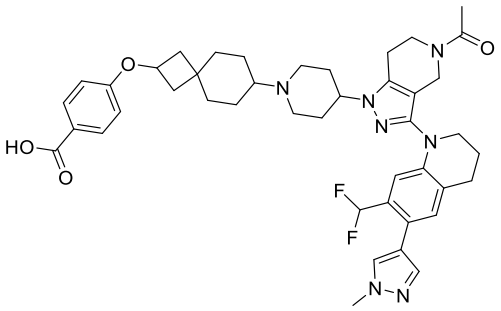
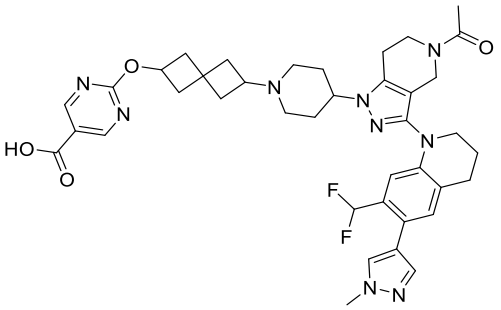
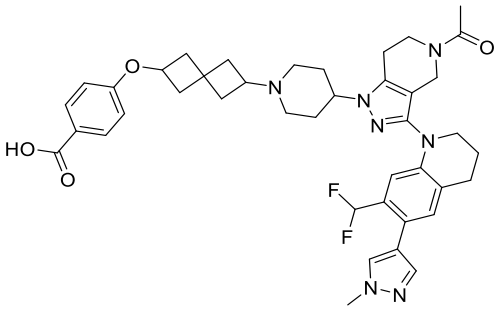
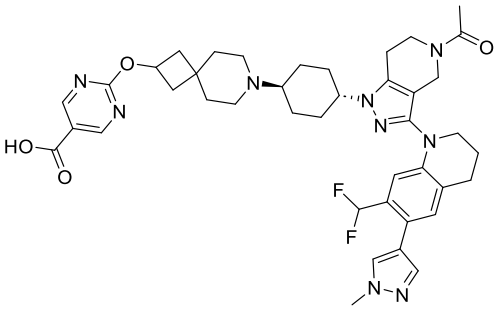
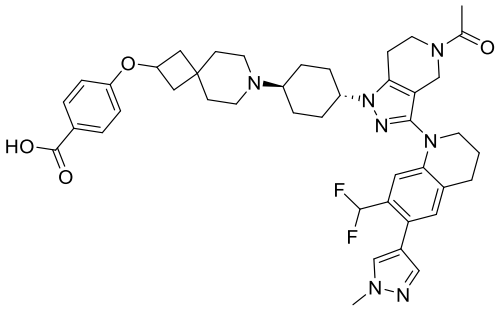
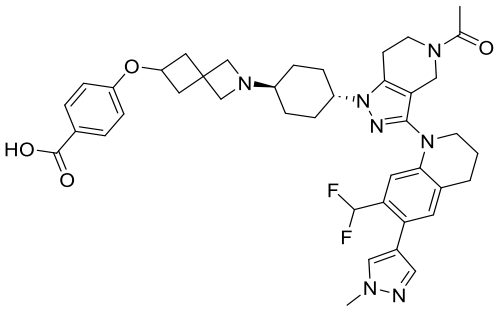
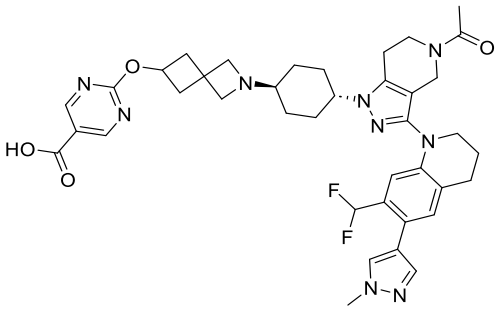
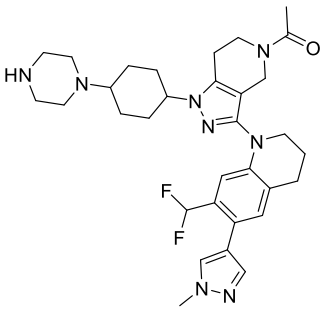
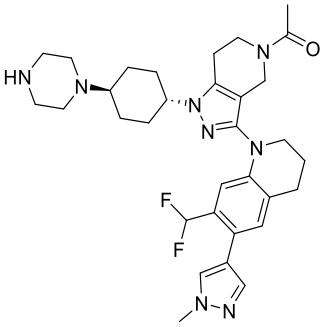
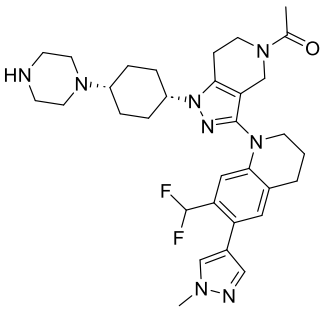
,

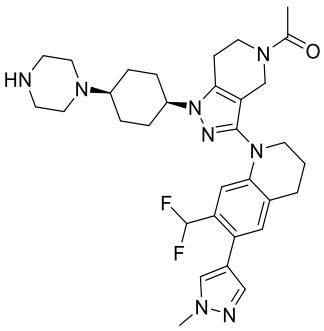
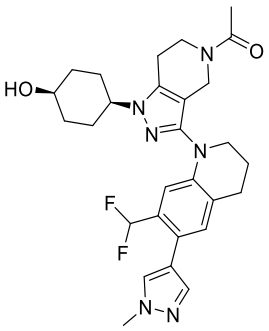
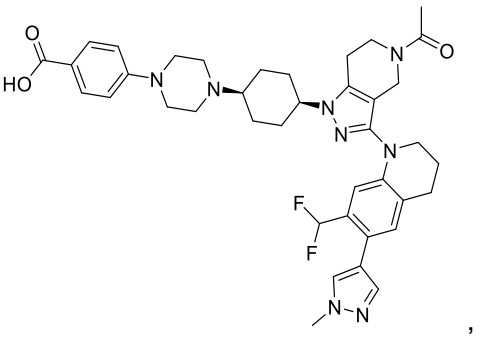
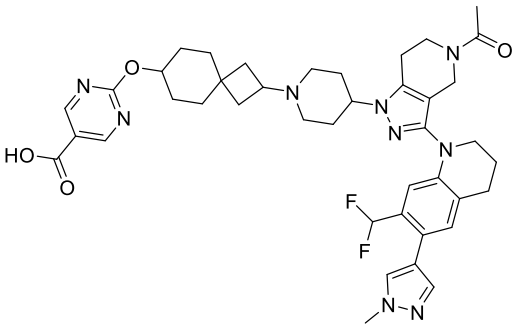
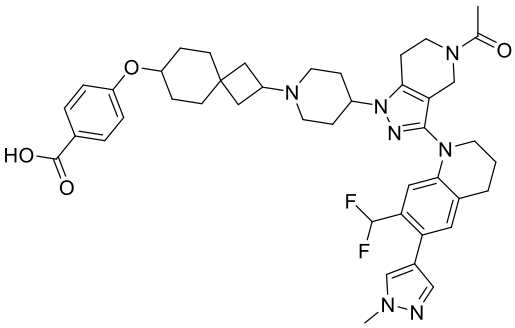
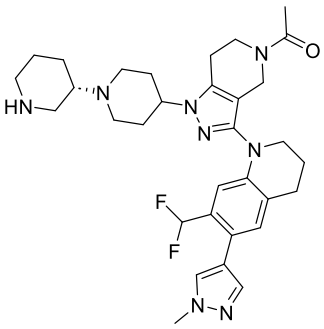
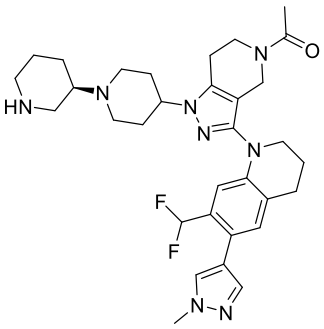
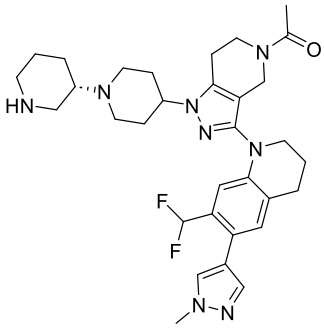
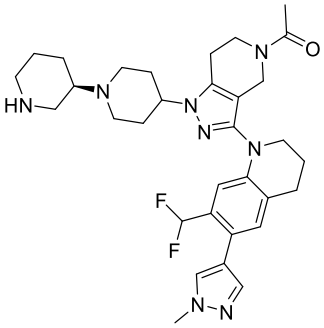
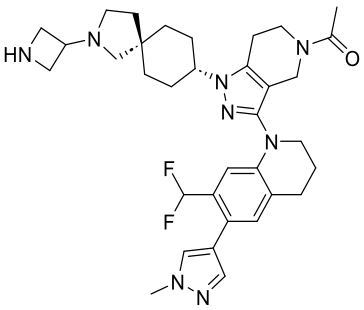
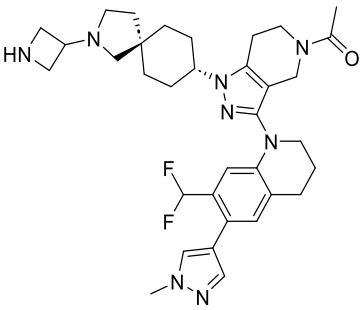
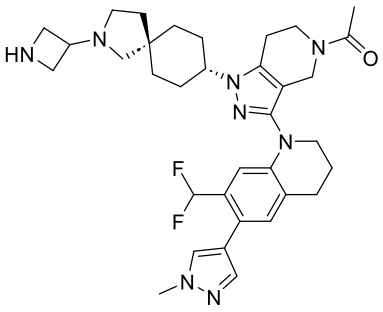
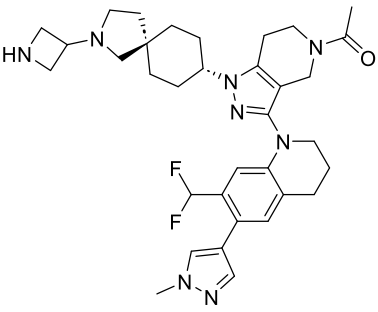
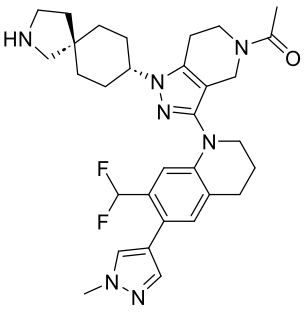

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

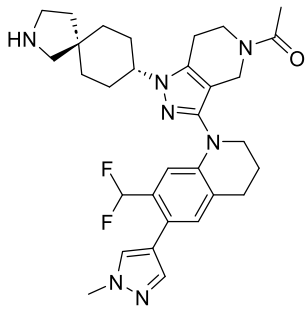
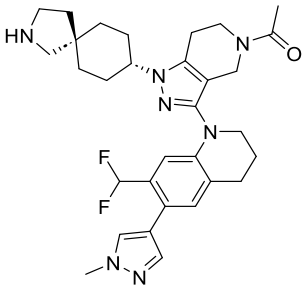
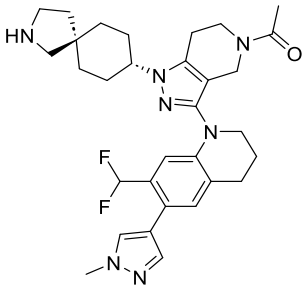
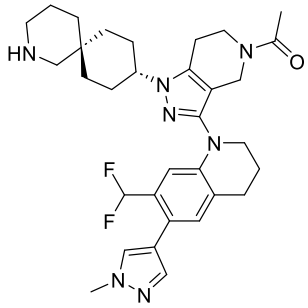
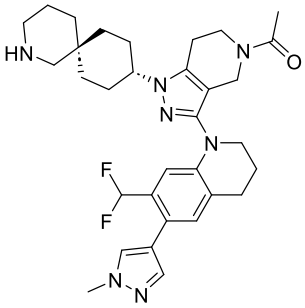
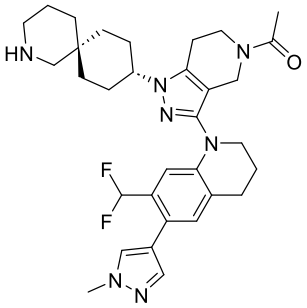
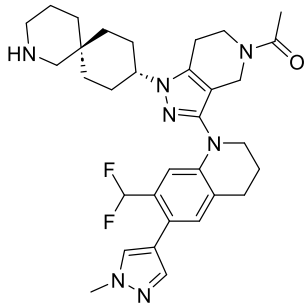
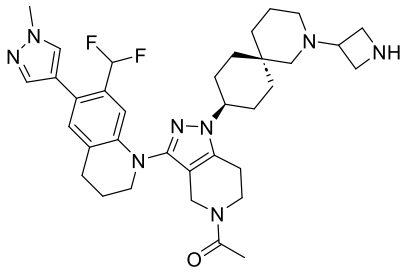
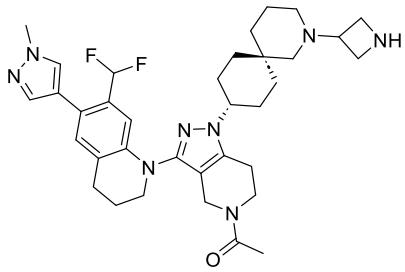
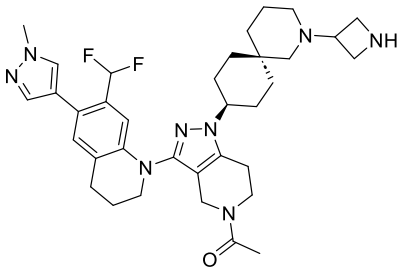
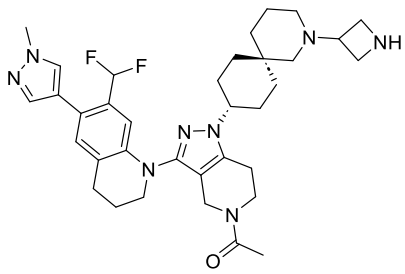
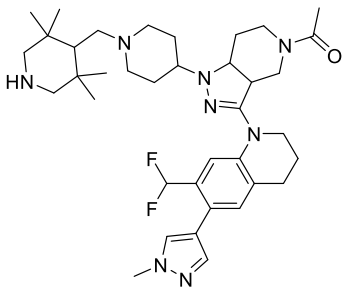
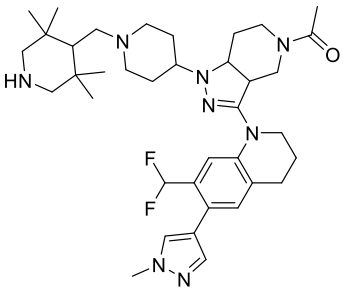

,

,

,

,

,

,

,

,

,

,

,

,

,

,

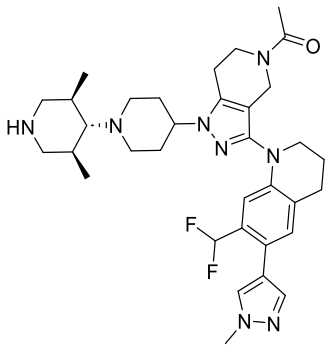
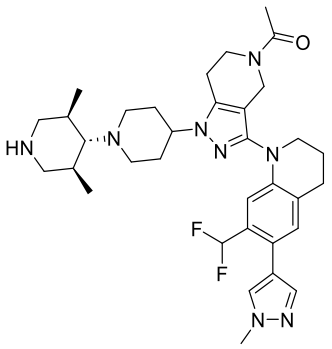
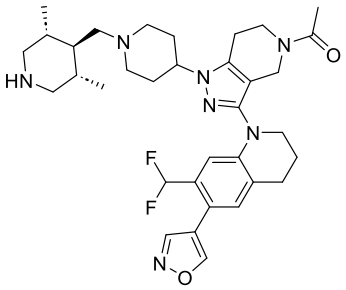
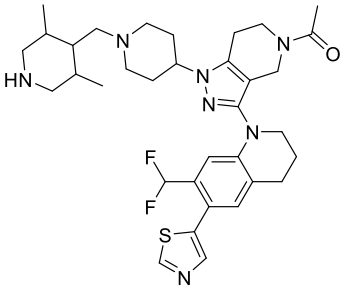
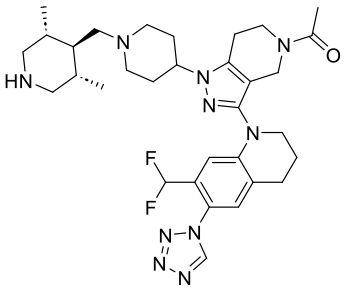
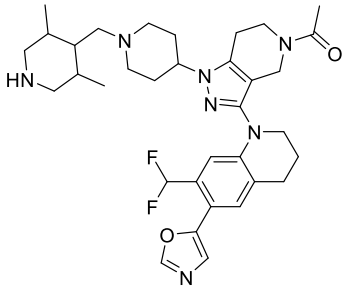
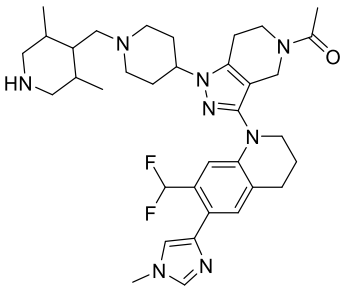
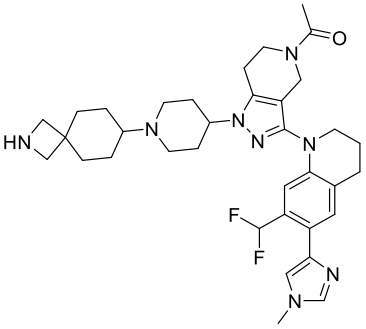
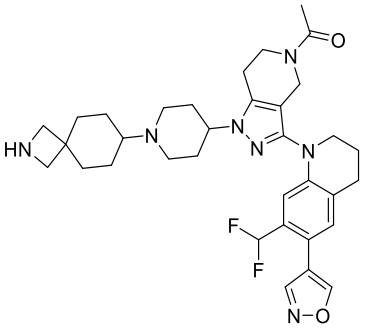
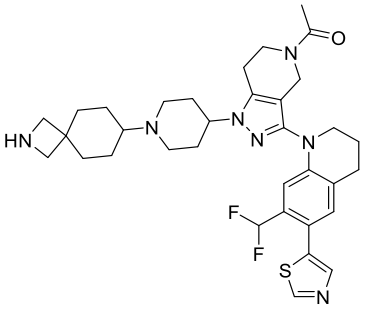
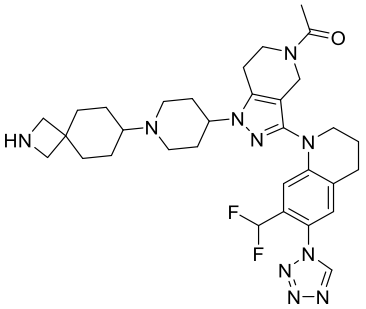
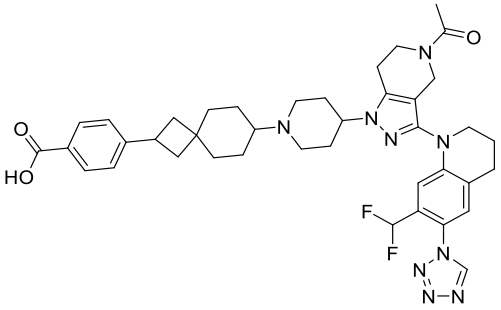
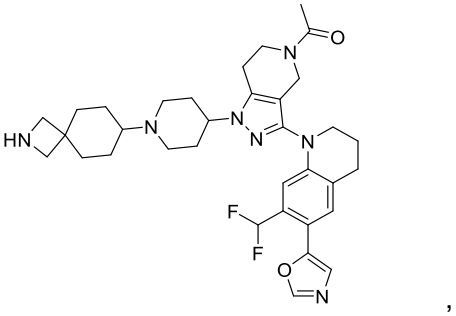

,

,

,

,

,

,

,

,

,

,

,

,

,

,

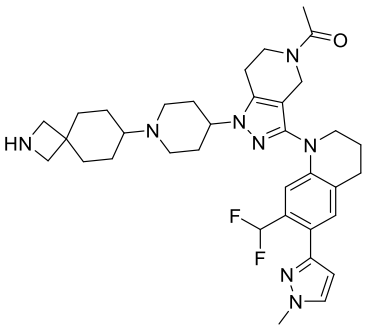
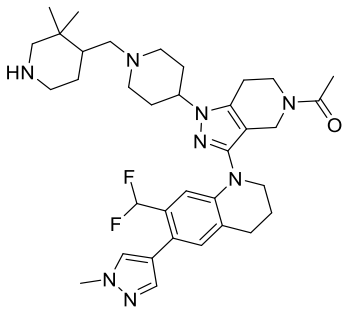
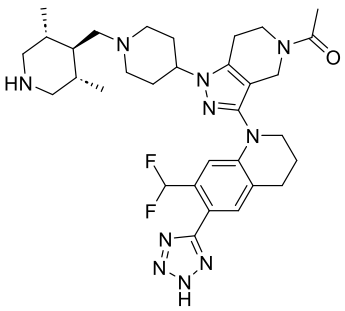
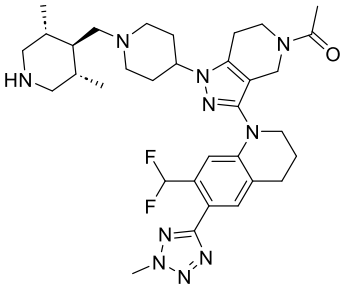
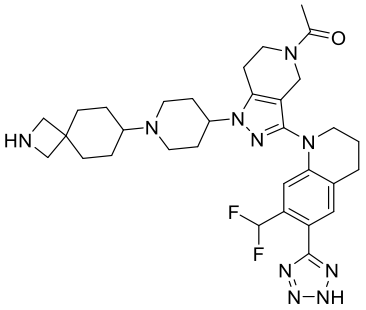
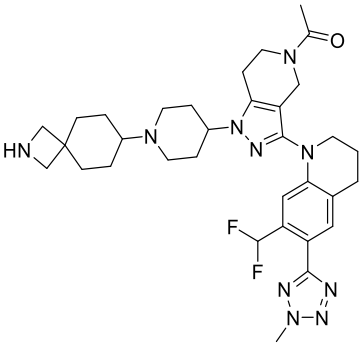
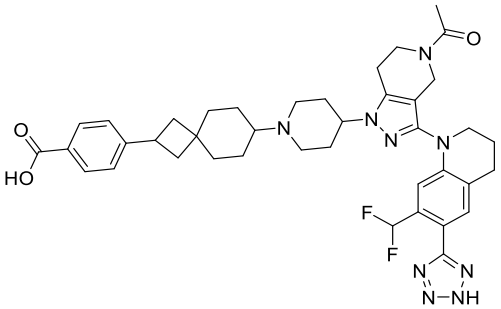
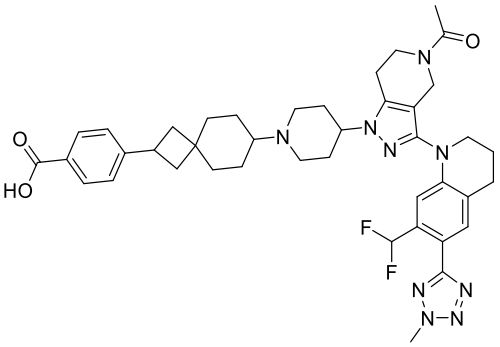
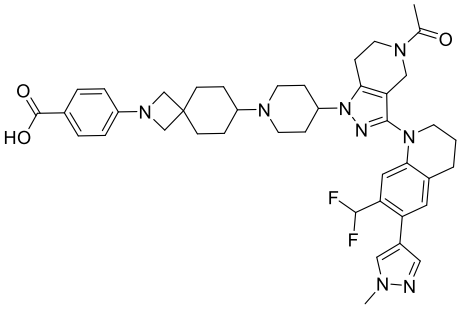
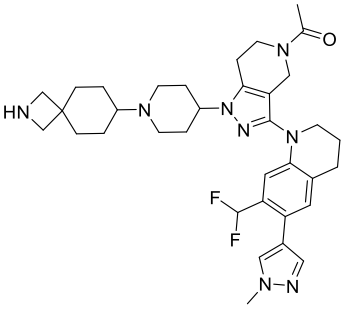
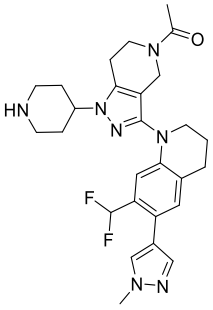
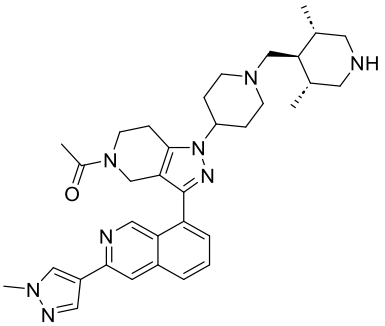
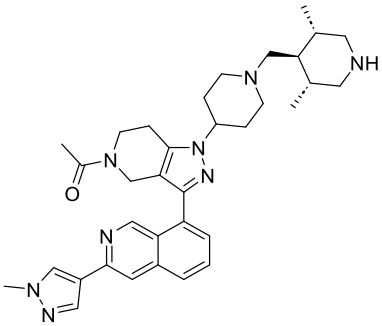

,

,

,

,

,

,

,

,

,

,

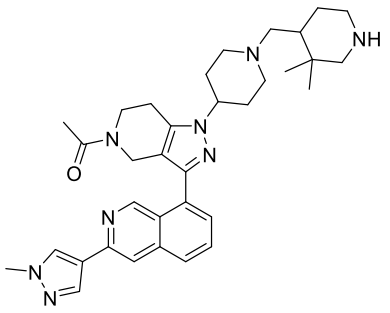
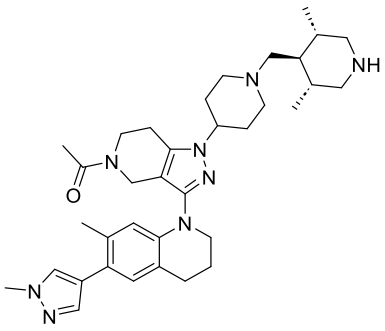
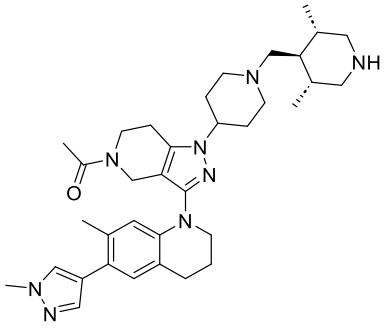
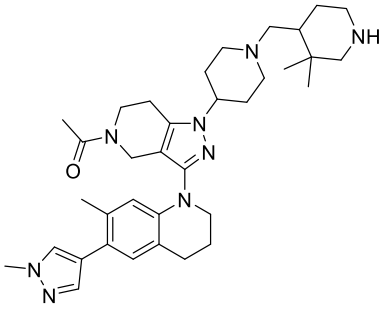
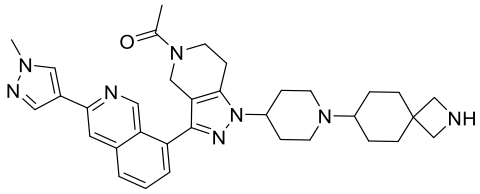
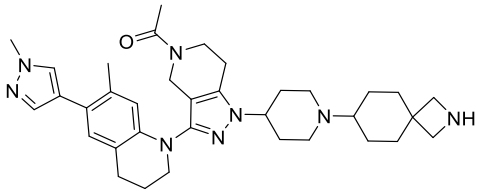
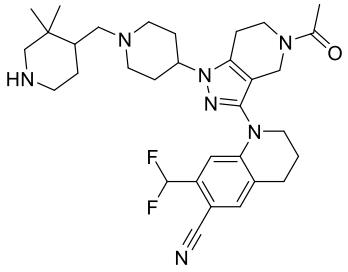
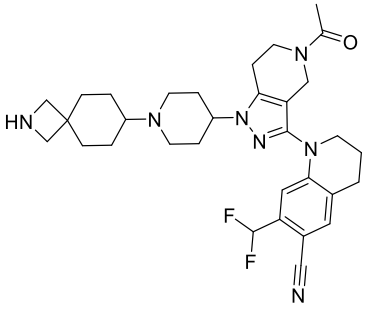
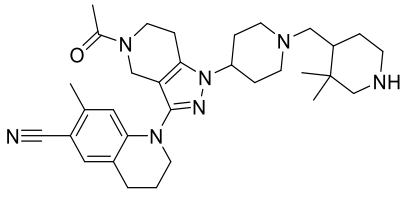
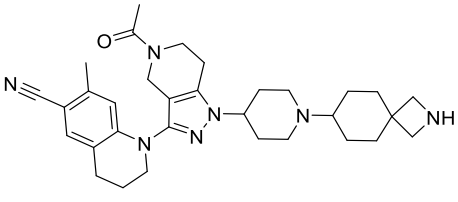

,

,

,

,

,

,

,

,

,

,

,

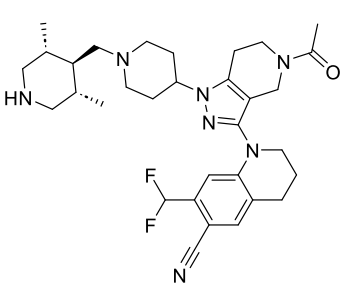
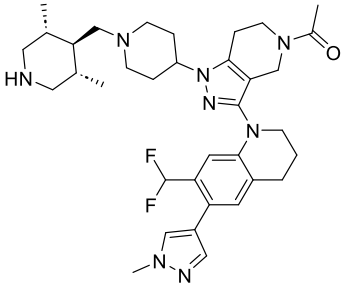
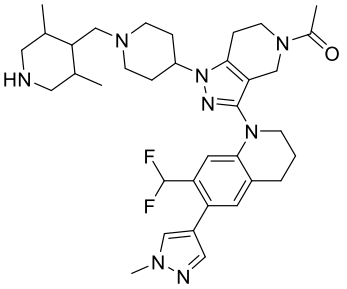
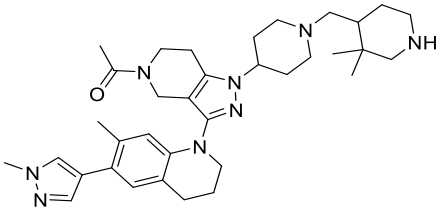
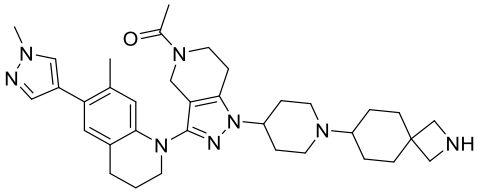

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

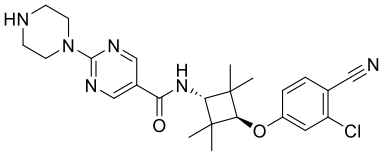
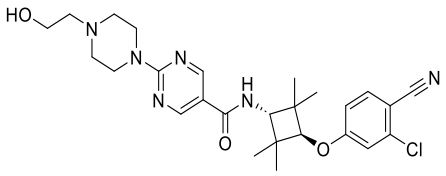
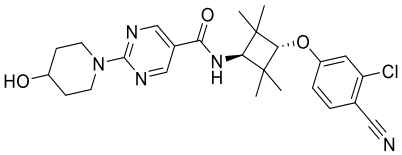
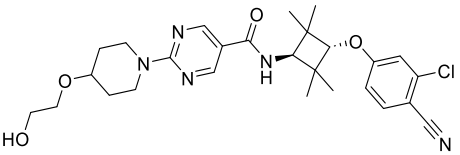
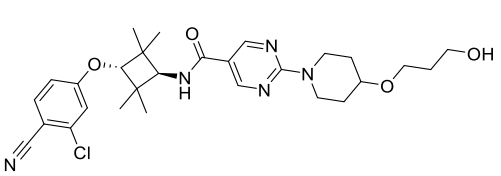
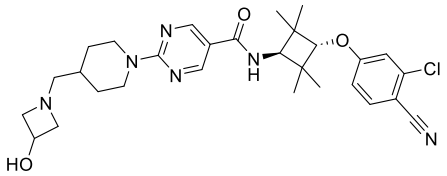
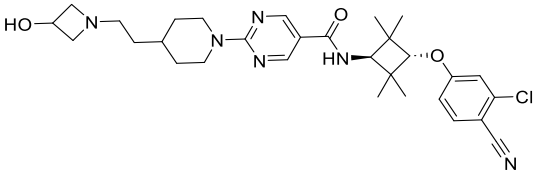
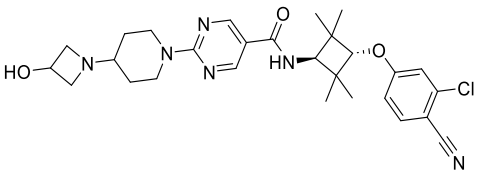
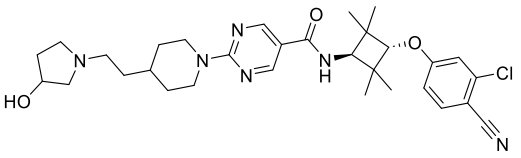
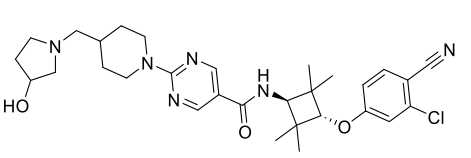

,

,

,

,

,

,

,

,

,

,

,

,

,

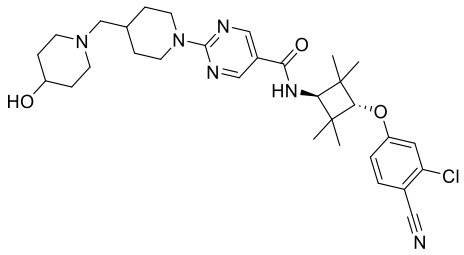
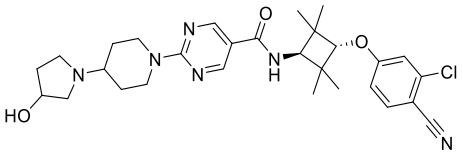
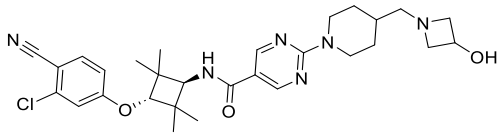
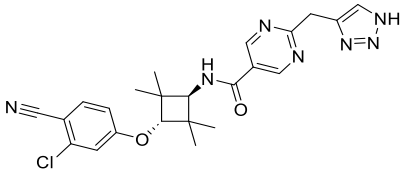
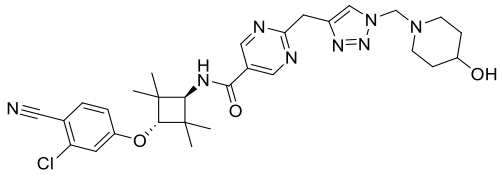
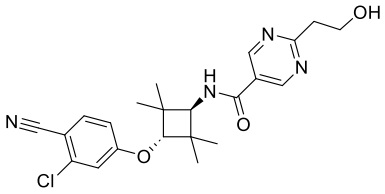
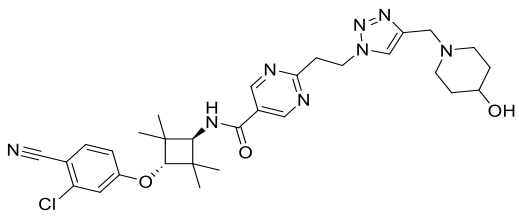
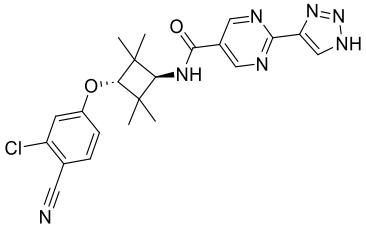
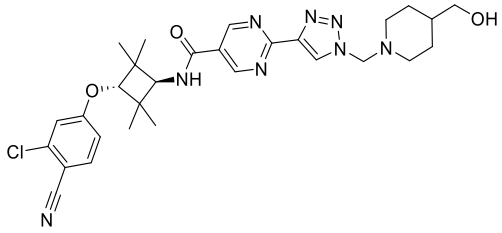
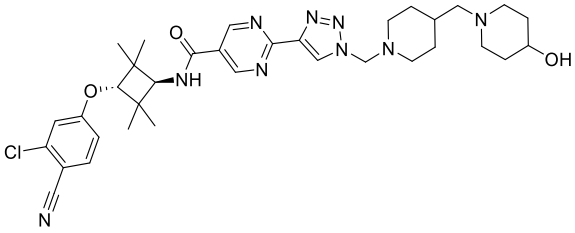
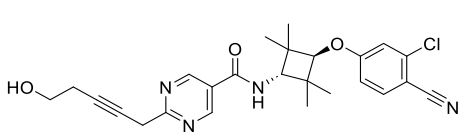
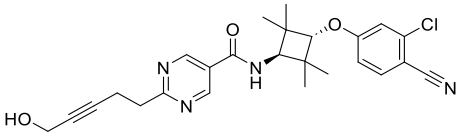
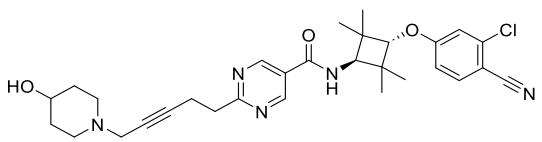
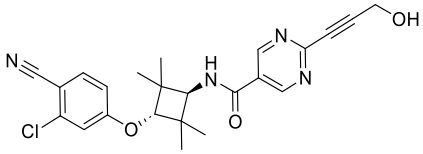
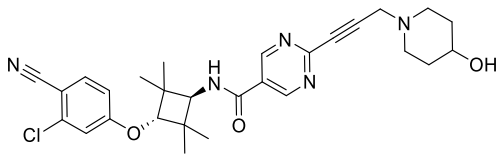
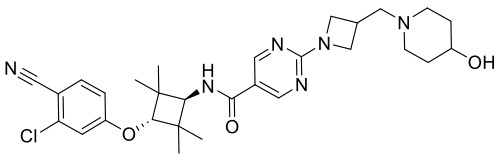

,

,

,

,

,

,

,

,

,

,

,

,

,

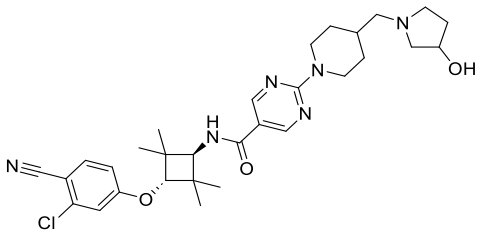
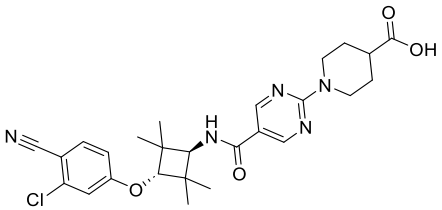
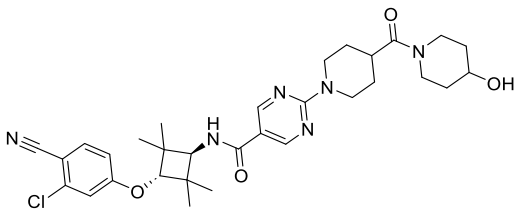
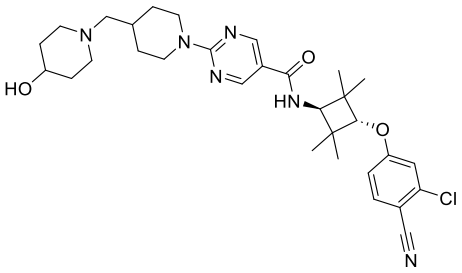
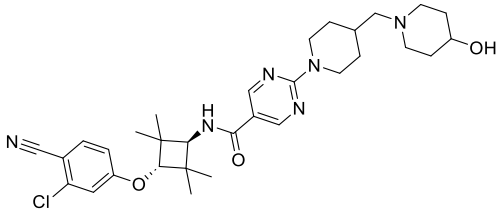
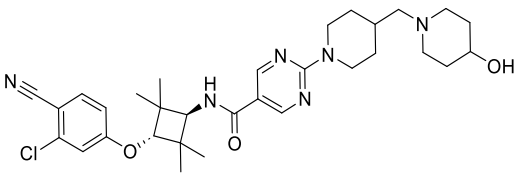
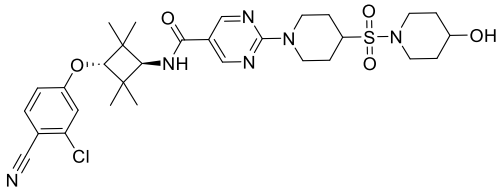
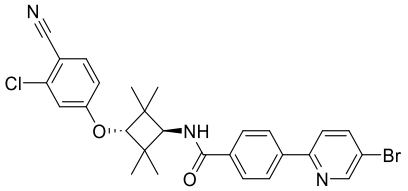
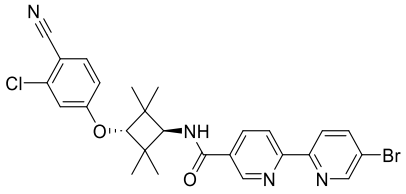
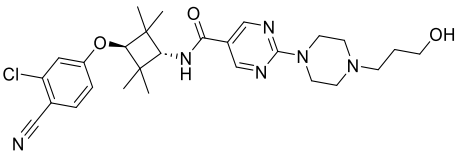
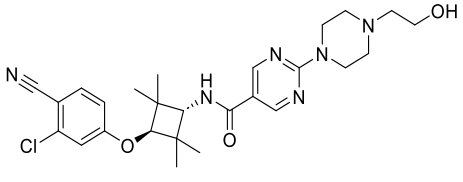
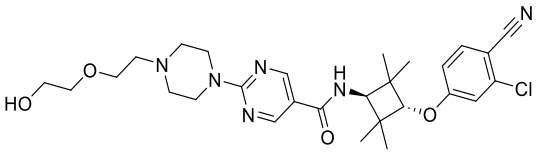
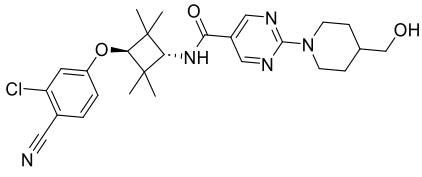
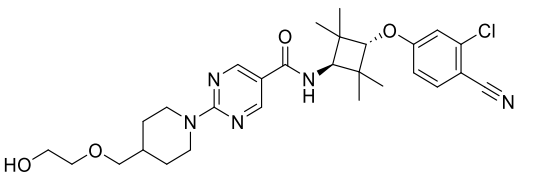

,

,

,

,

,

,

,

,

,

,


,

,

,

, o

.

[00318] Forma de realización 125. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:

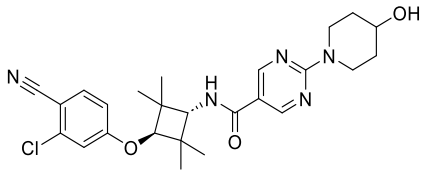
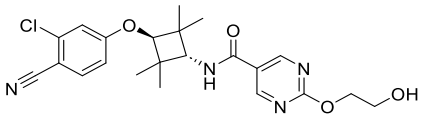
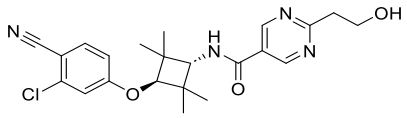
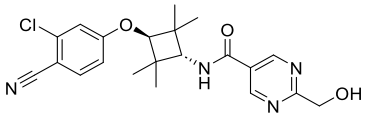
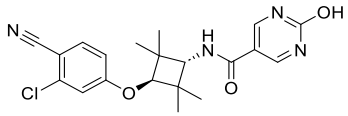
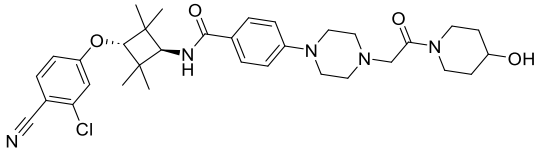
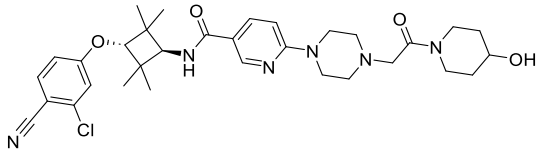
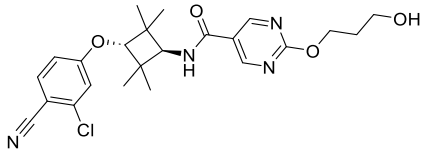
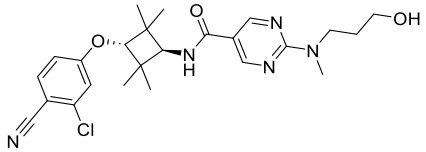
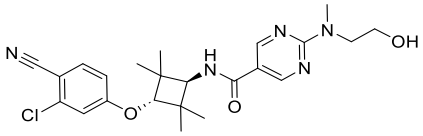
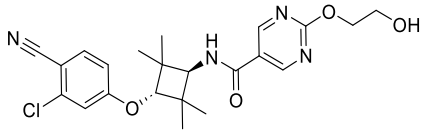
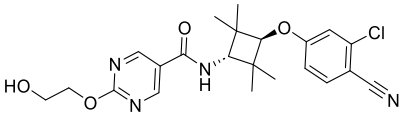
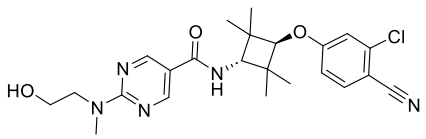
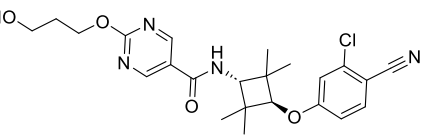
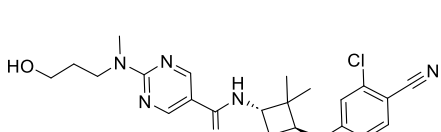
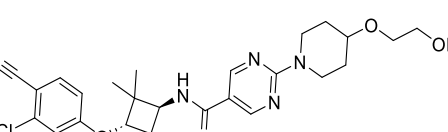
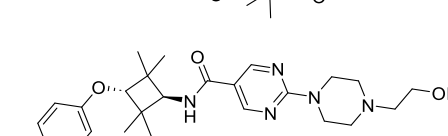
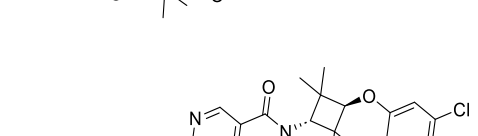
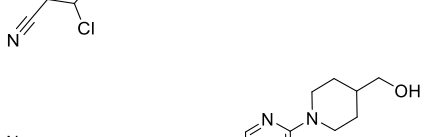
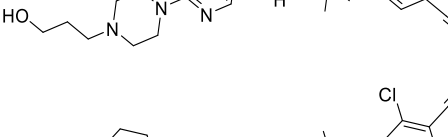
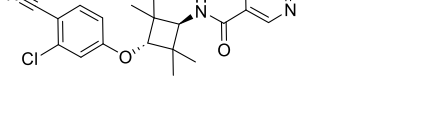
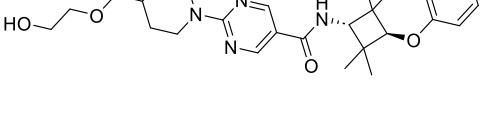

,

,

,

,

,

,

,

,

,

,

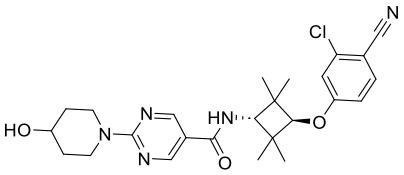
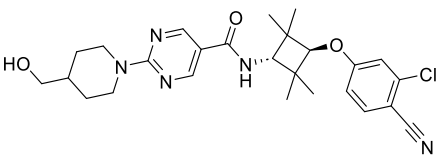
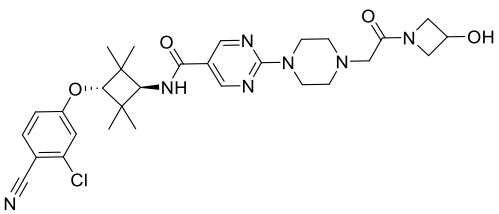
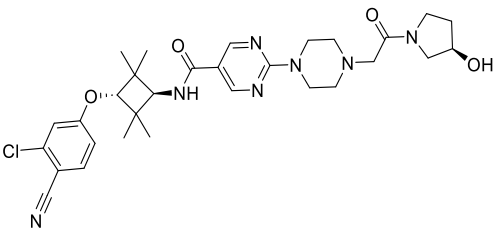
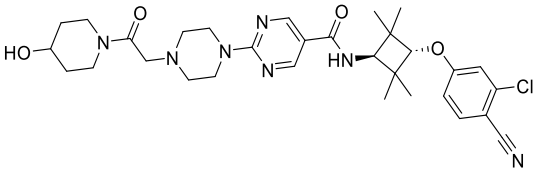
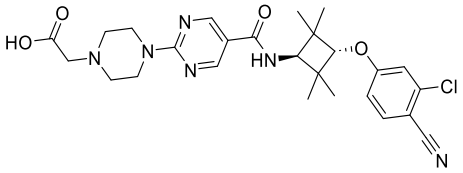
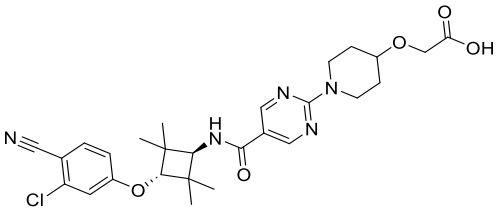
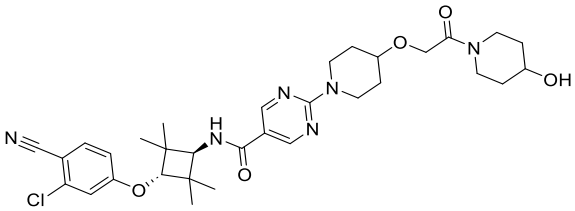
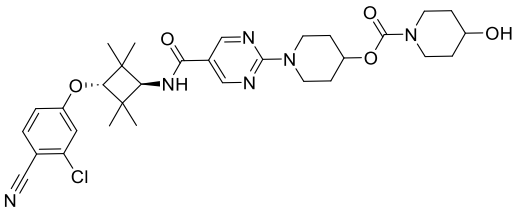
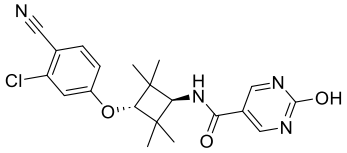
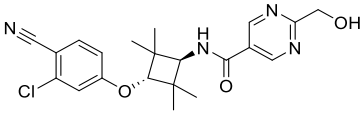
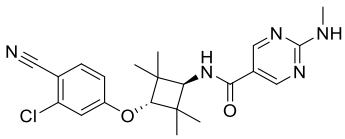
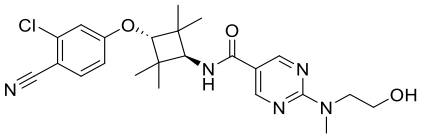
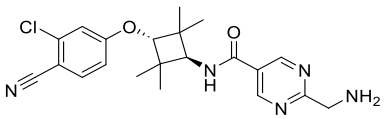
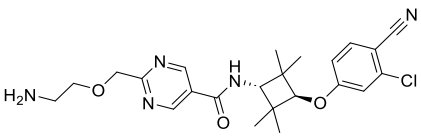
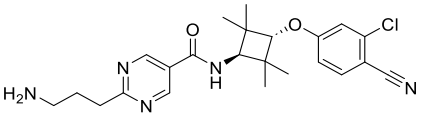
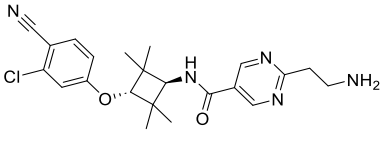
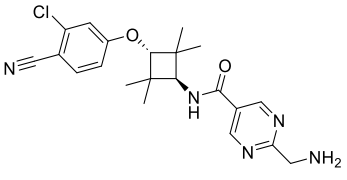

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

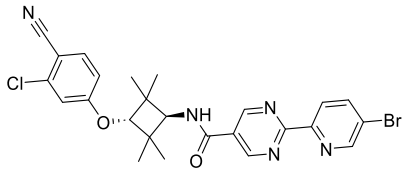
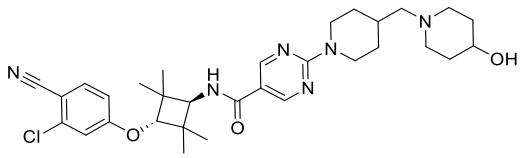
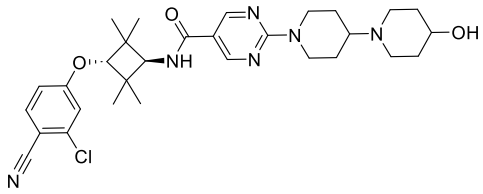
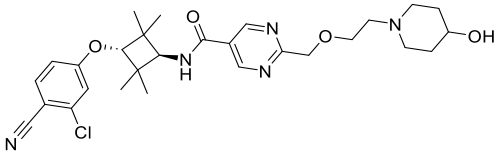
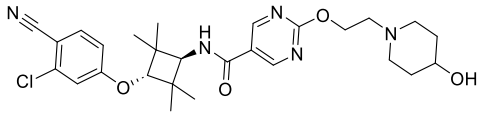
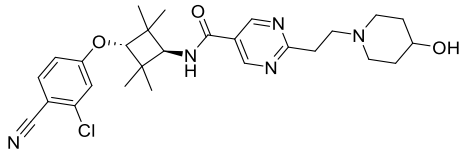
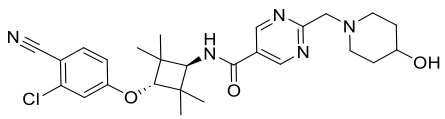
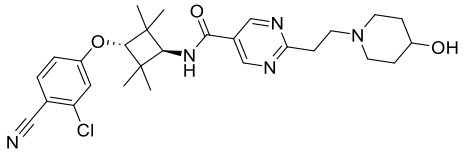
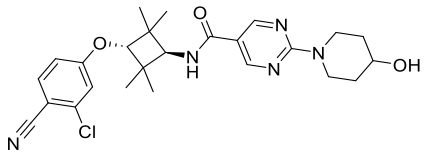
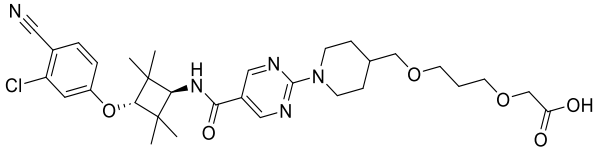
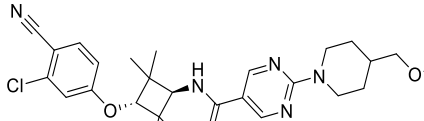
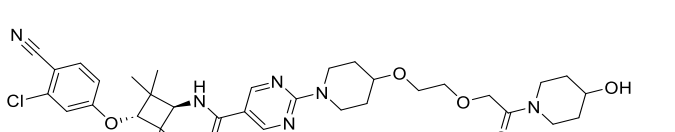

,

,

,

,

,

,

,

,

,

,

,

,

,

,

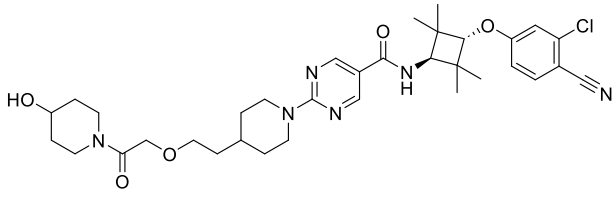
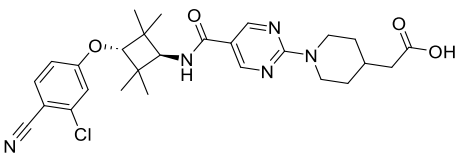
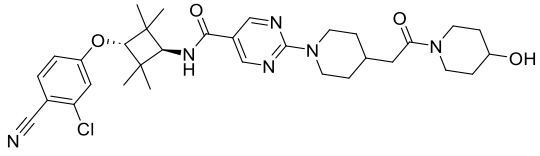
,

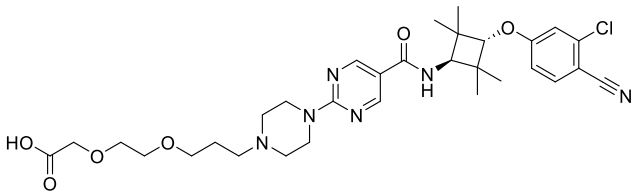
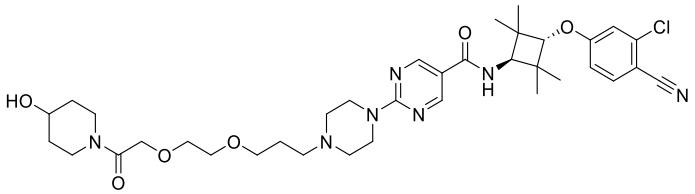
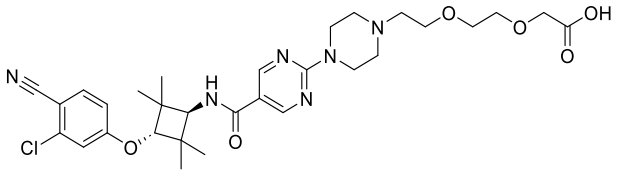
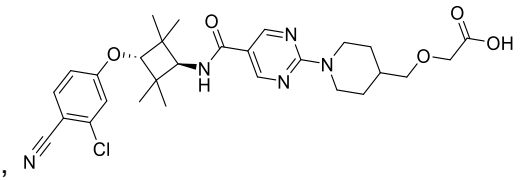
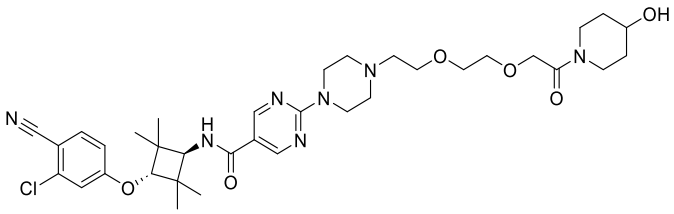
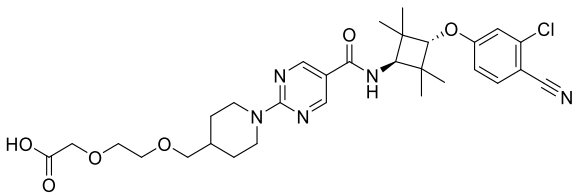
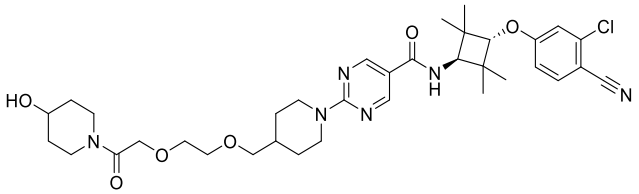
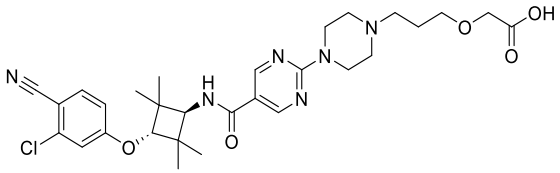
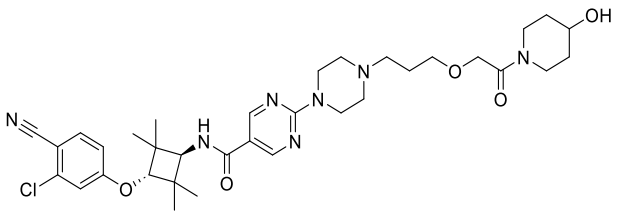
,

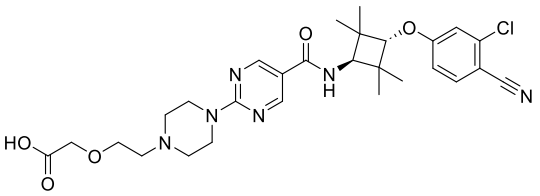
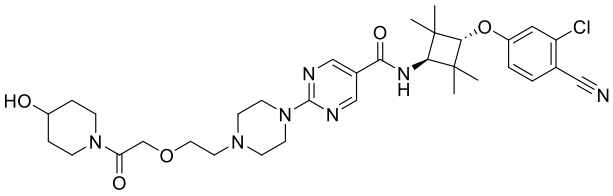
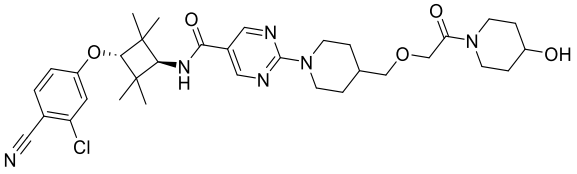
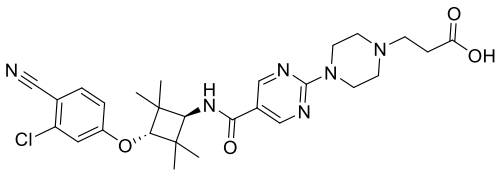
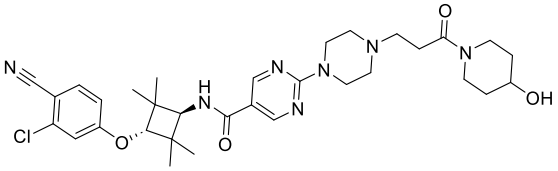
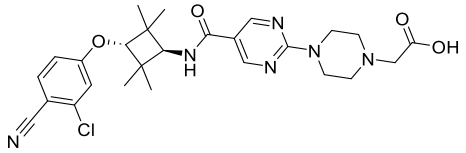
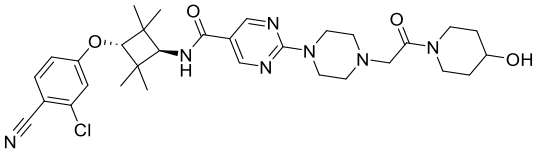
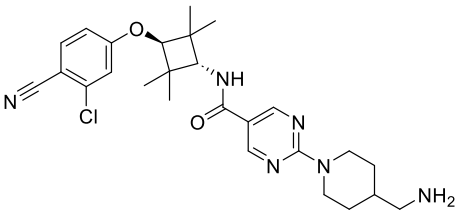
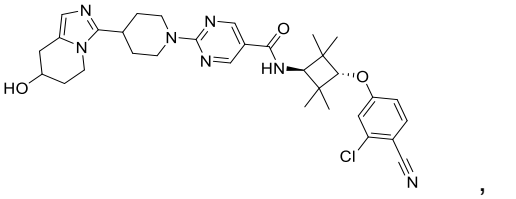
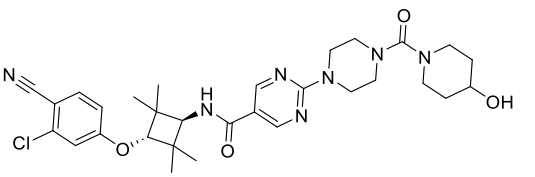
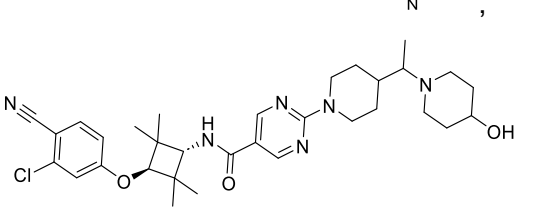
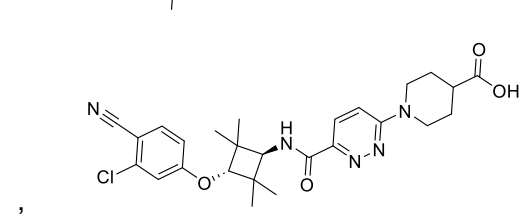
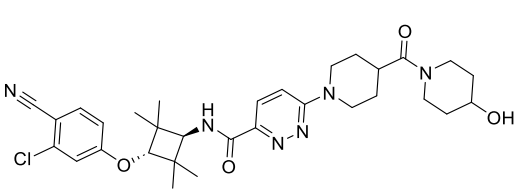
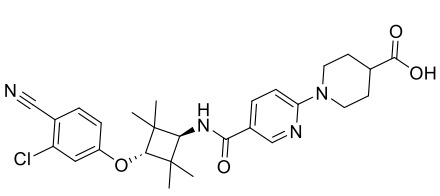

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

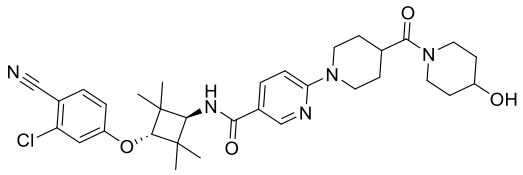
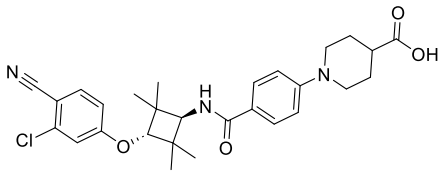
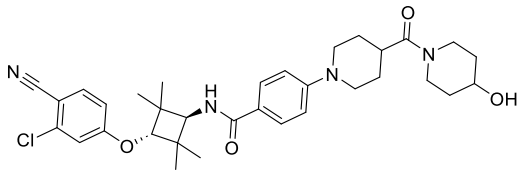
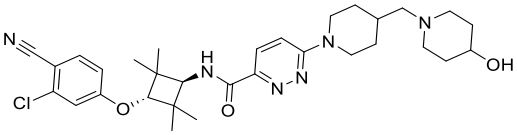
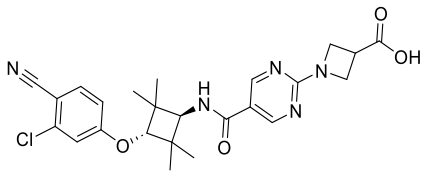
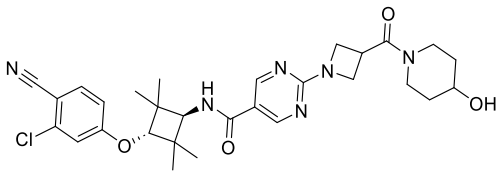
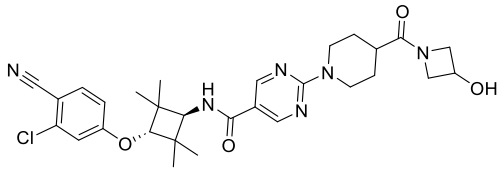
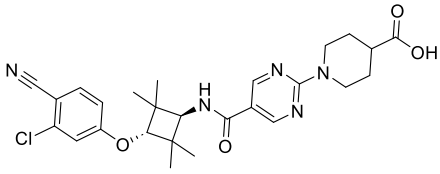
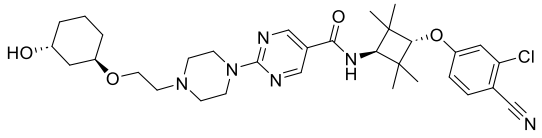
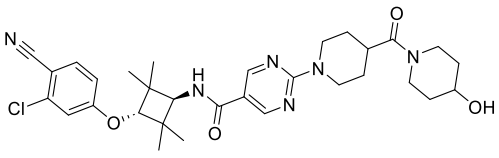
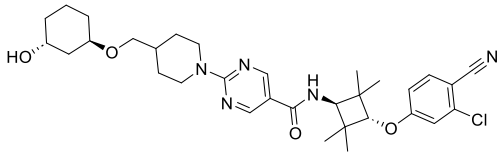
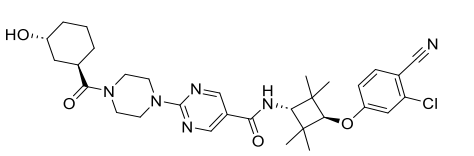
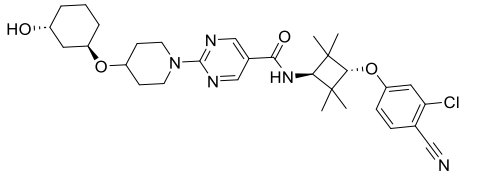
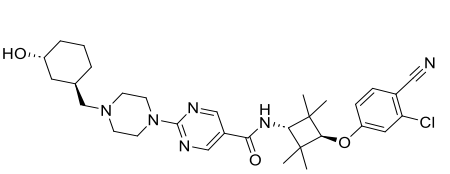
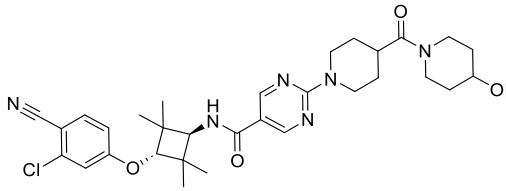
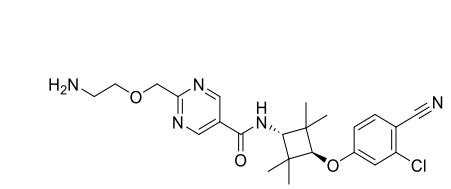
,

,

,

,


,

,

,

,

,
,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

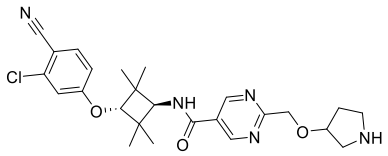
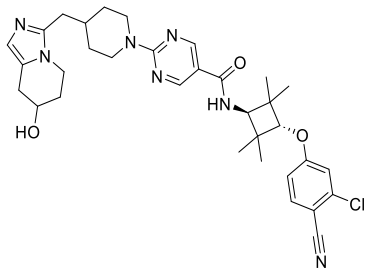
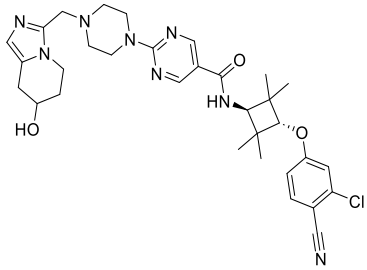
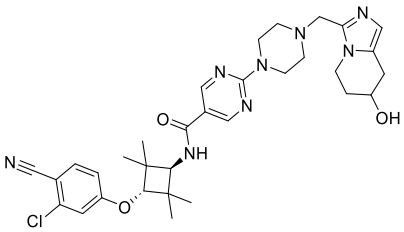
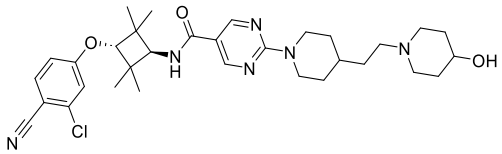
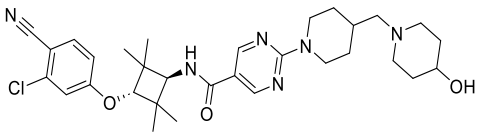
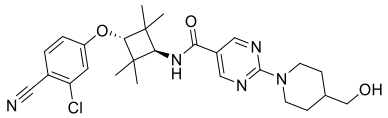
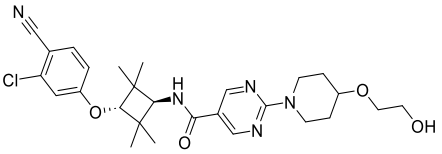
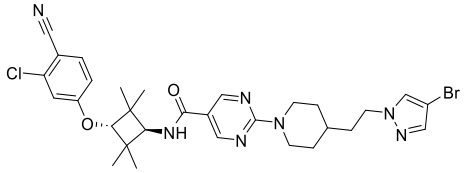
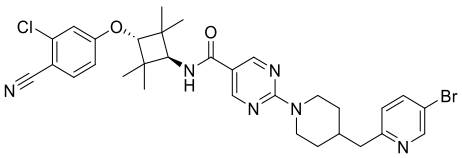
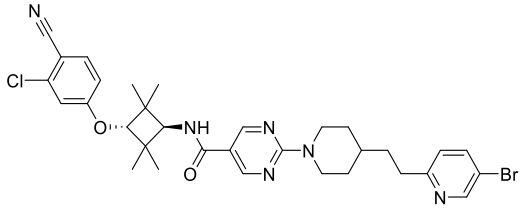
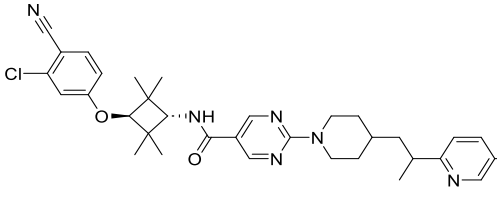
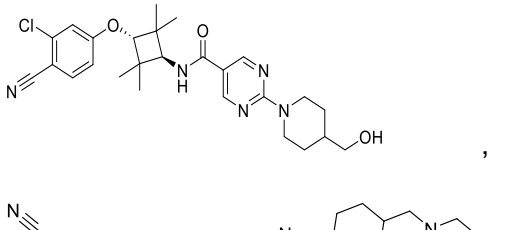
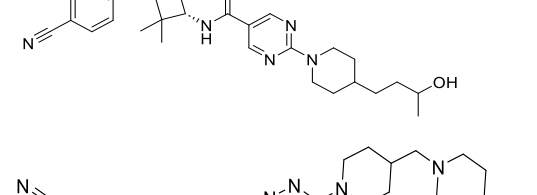
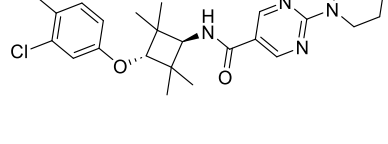
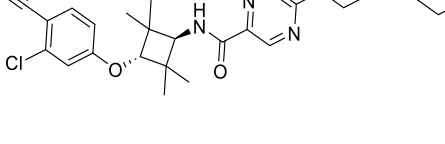

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

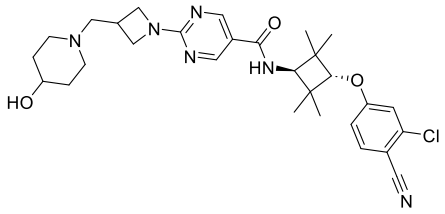
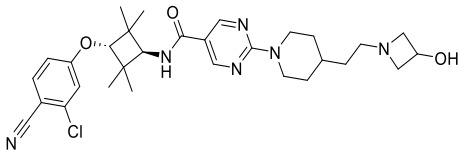
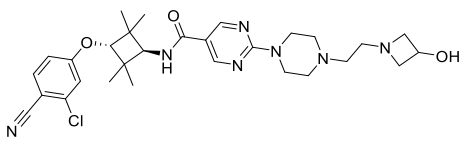
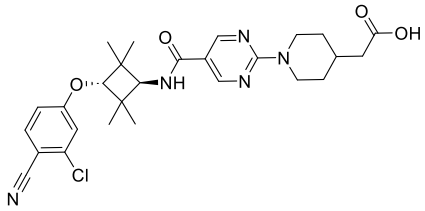
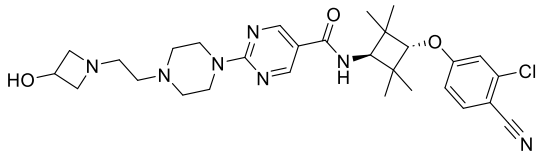
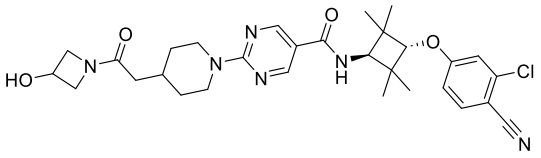
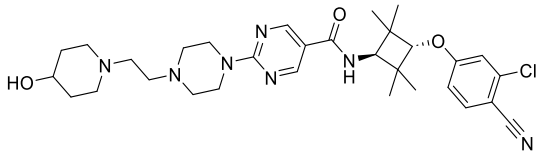
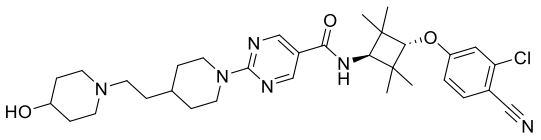
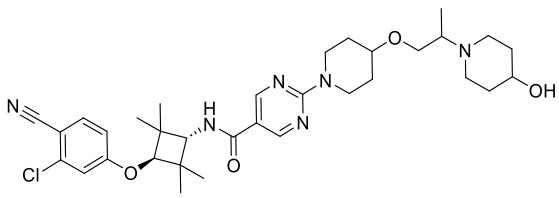
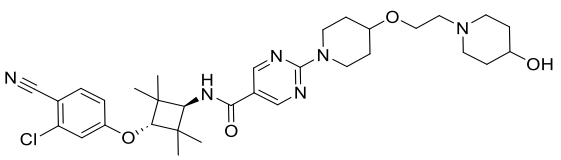
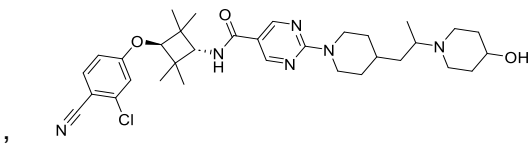
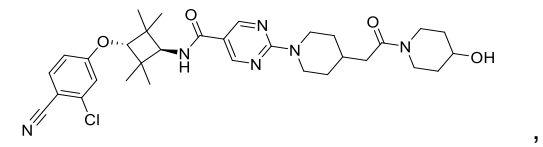
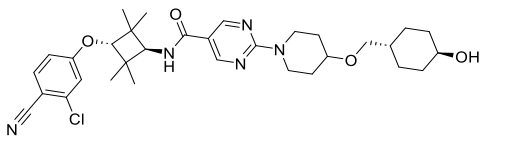
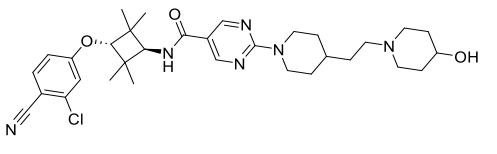
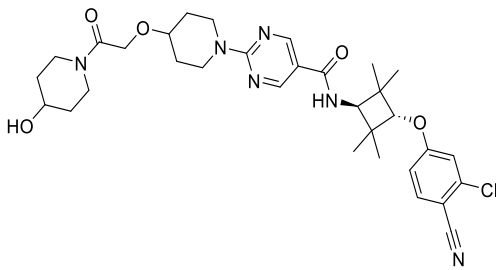
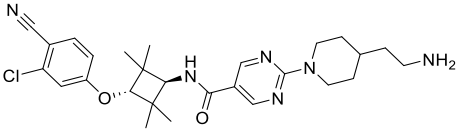
,

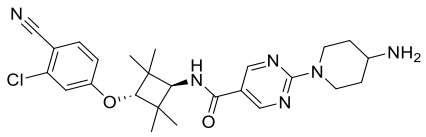
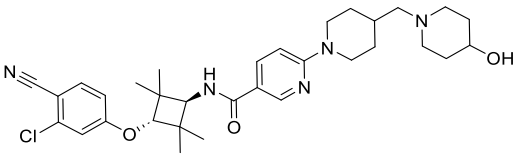
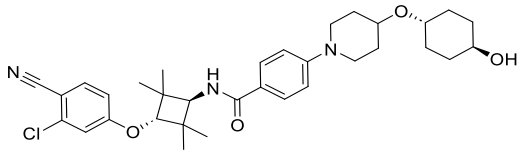
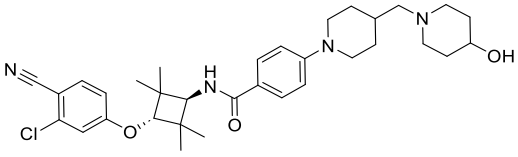
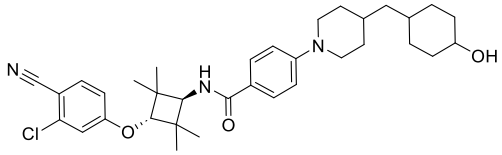
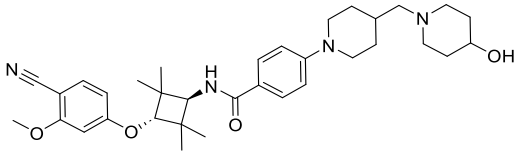
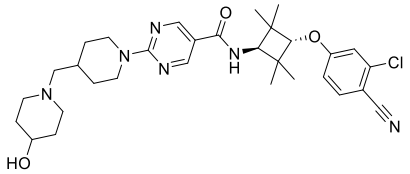
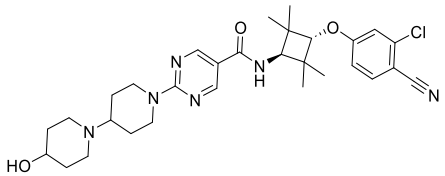
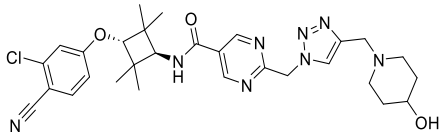
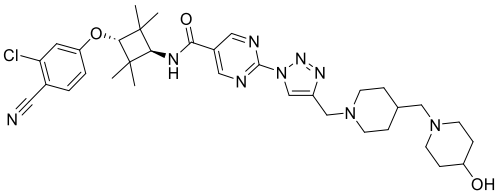
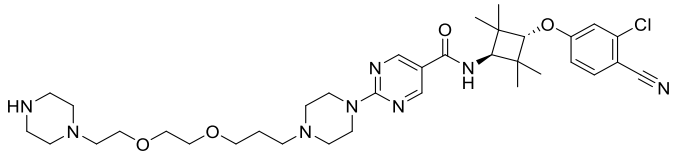
,

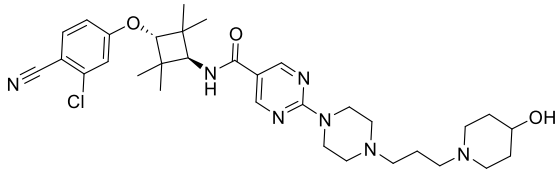
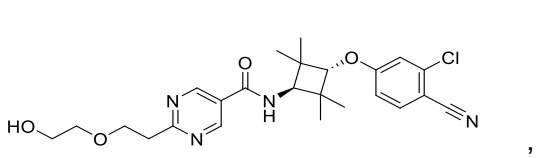
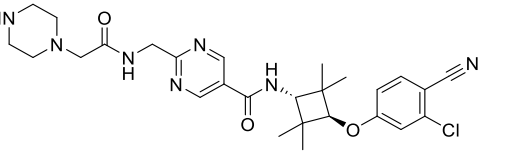
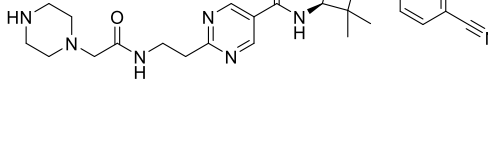
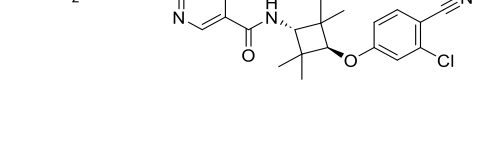

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

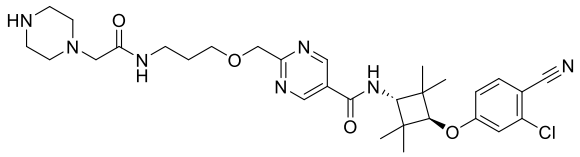
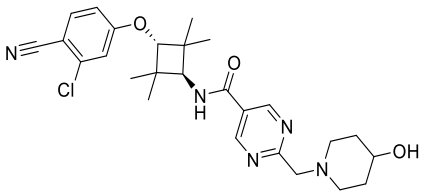
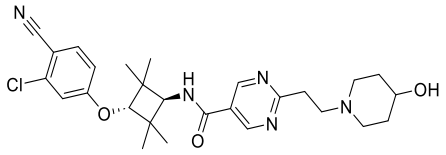
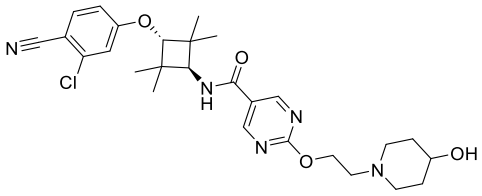
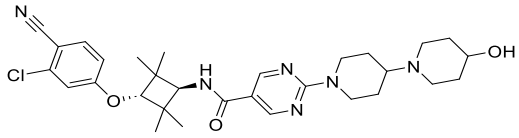
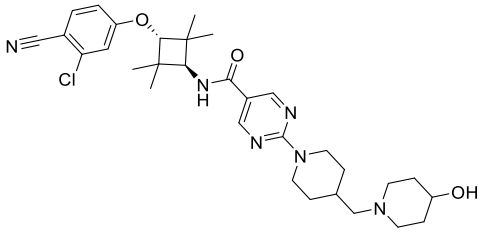
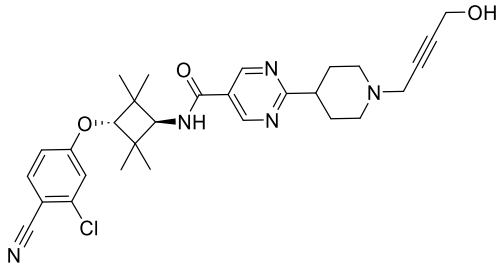
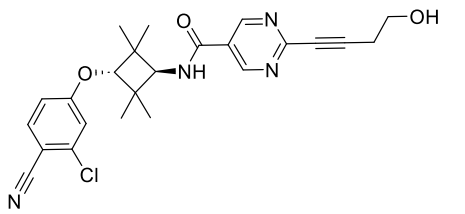
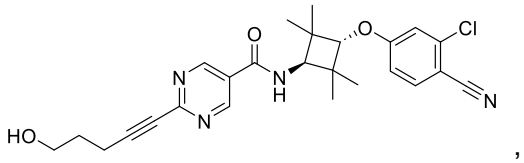
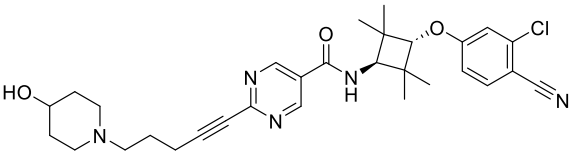
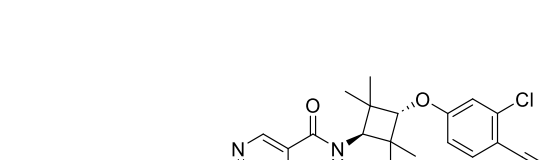
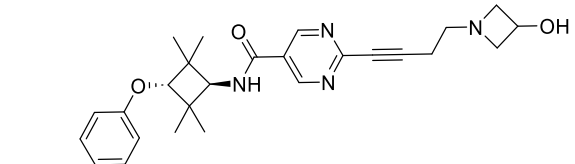
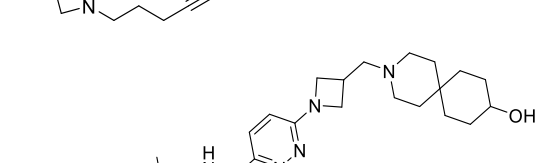

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

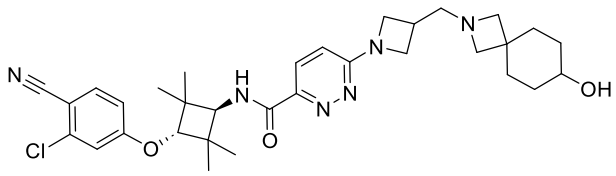
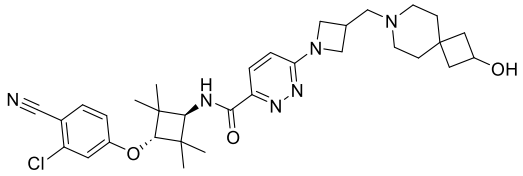
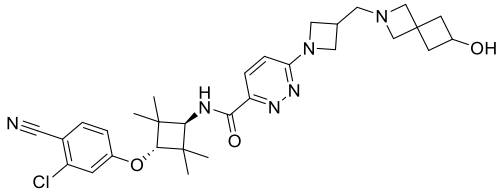
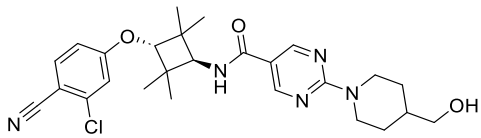
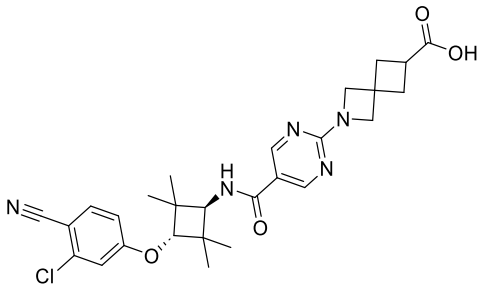
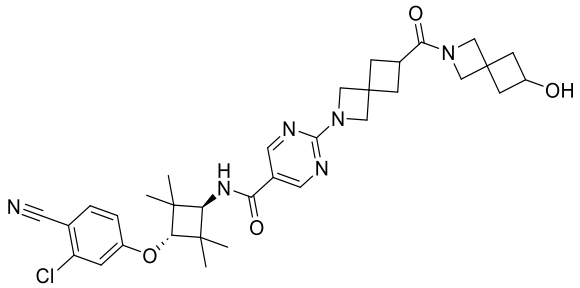
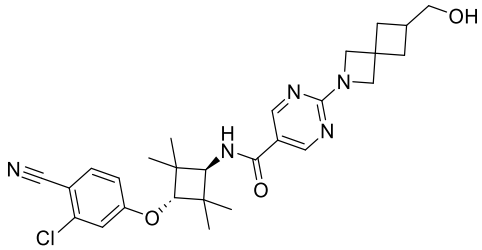
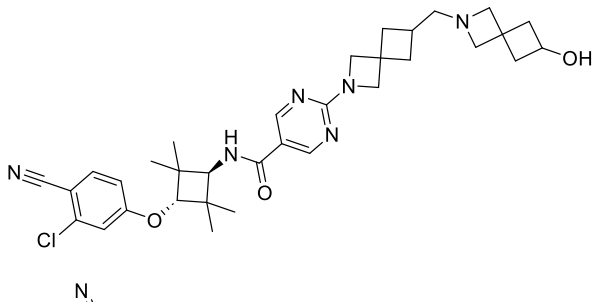
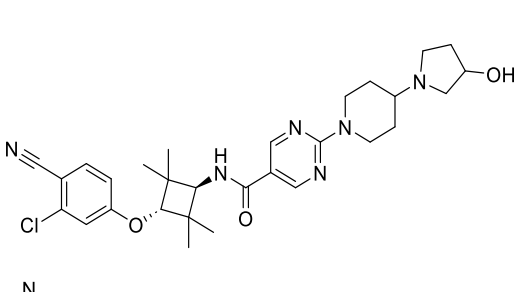
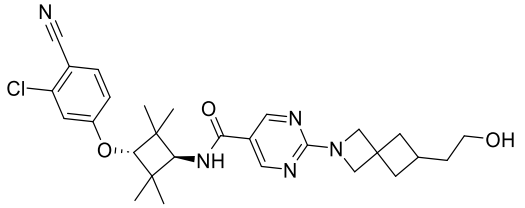
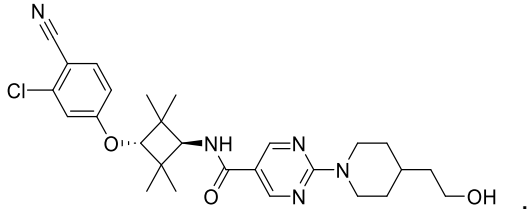
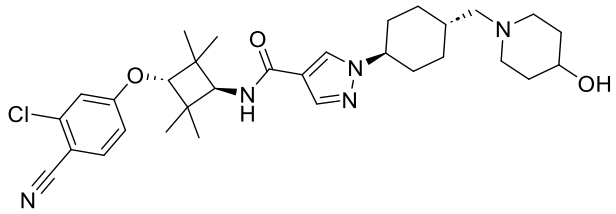
,

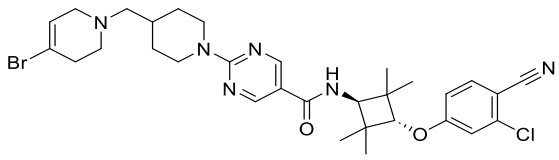
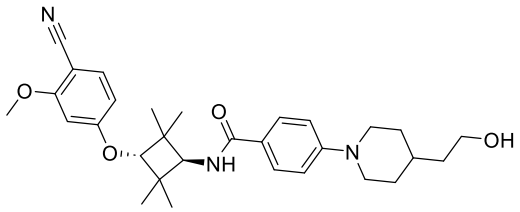
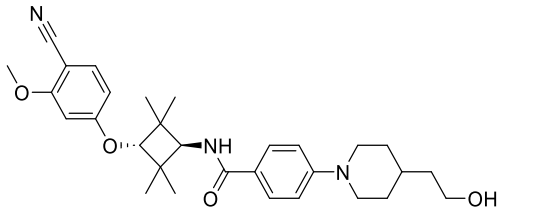
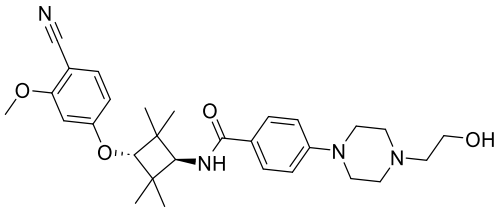
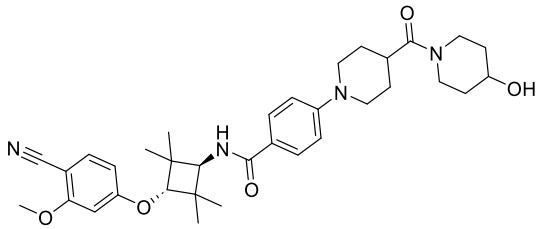
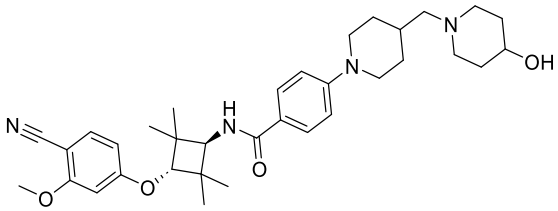
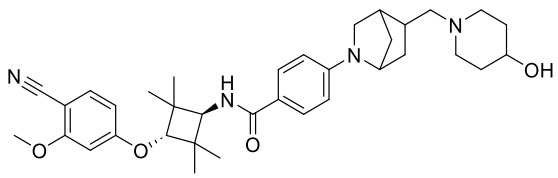
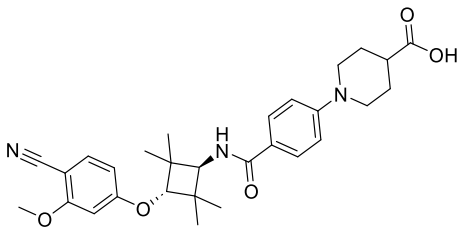
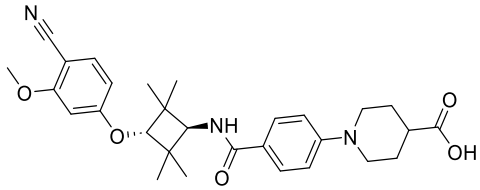
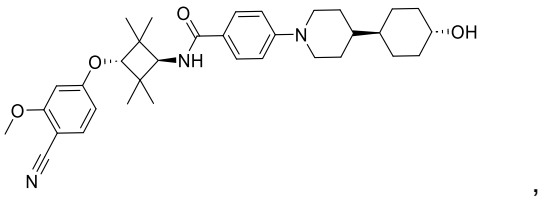
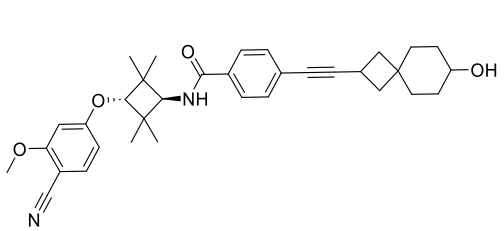
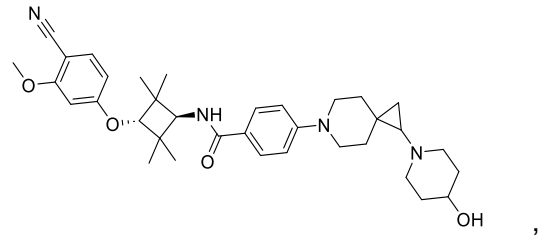
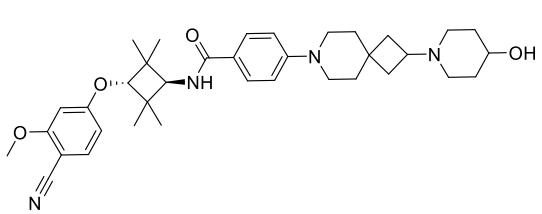
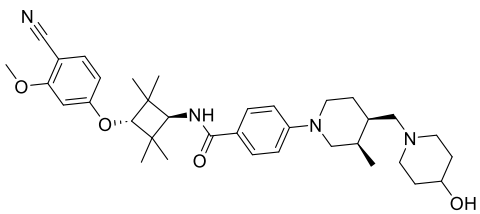
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

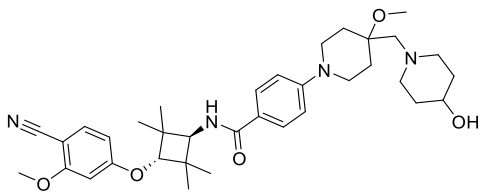
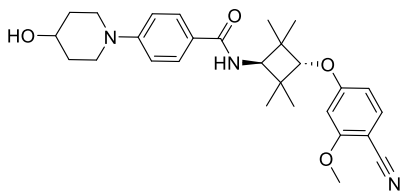
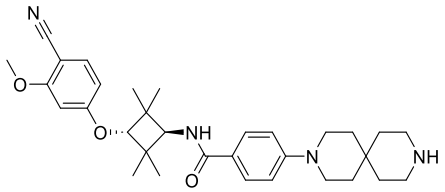
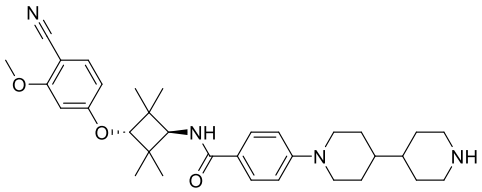
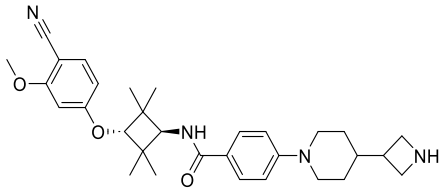
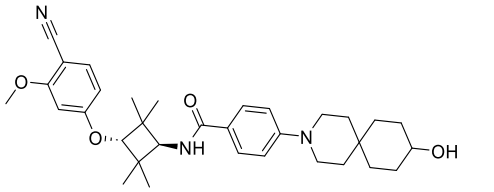
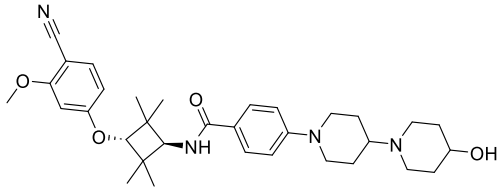
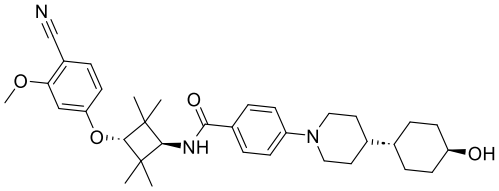
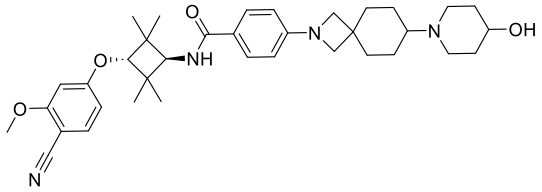
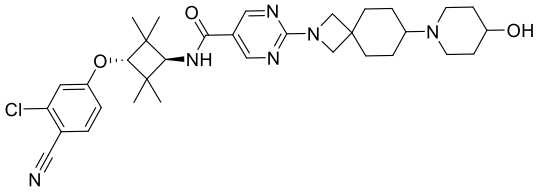
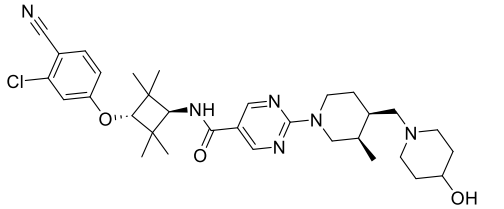
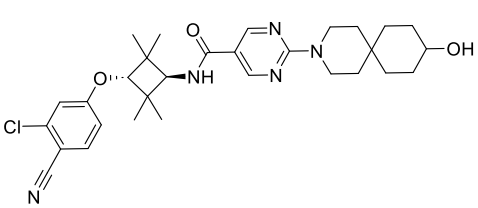
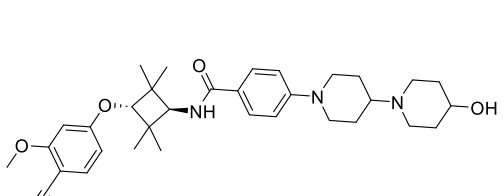
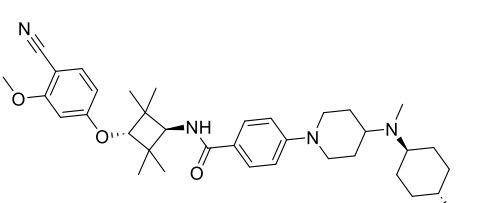
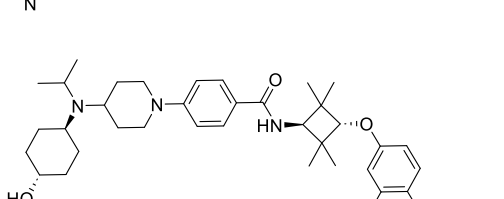
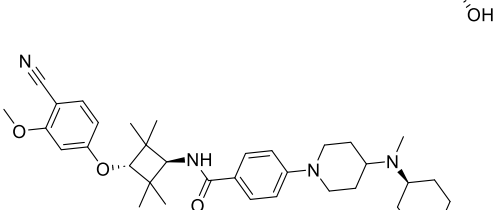
,


,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

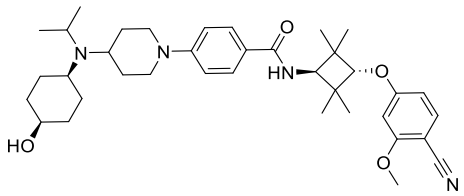
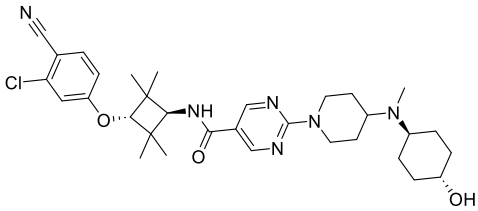
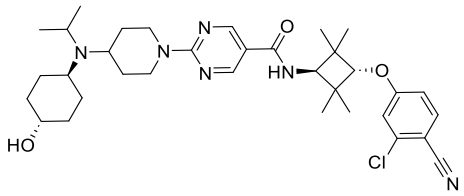
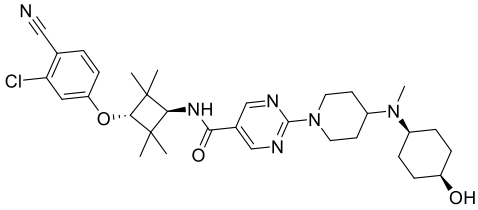
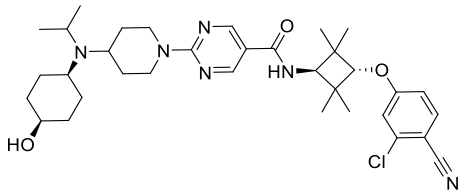
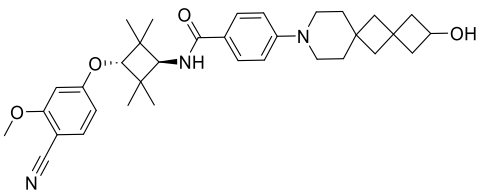
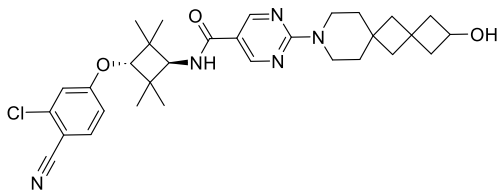
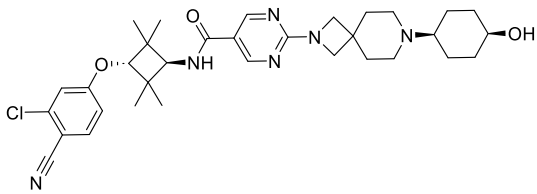
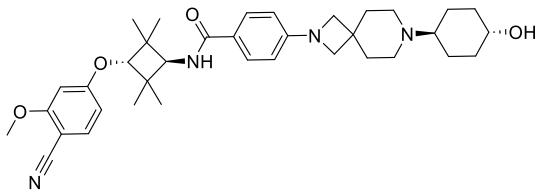
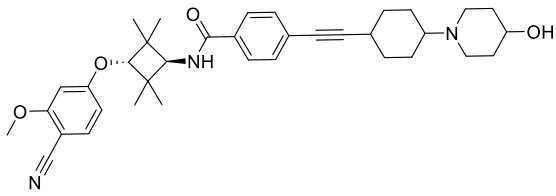
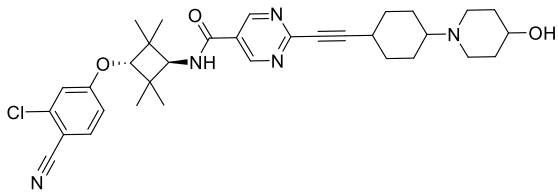
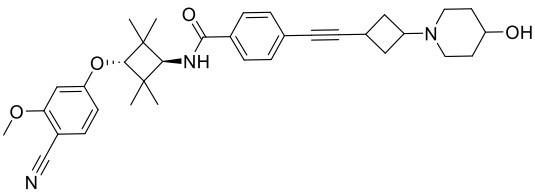
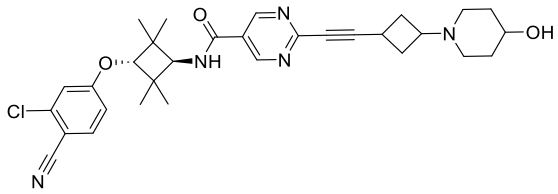
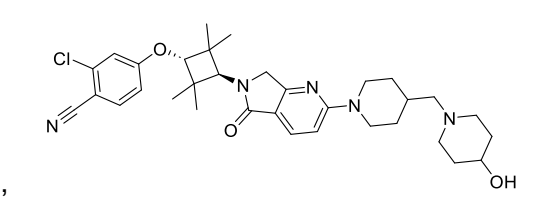
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

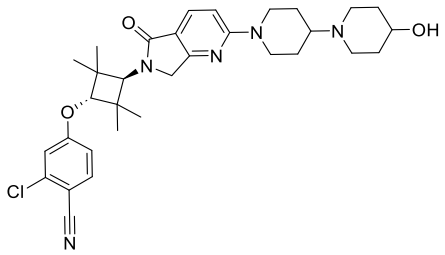
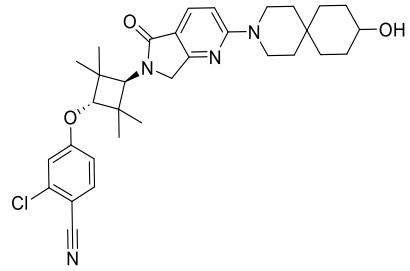
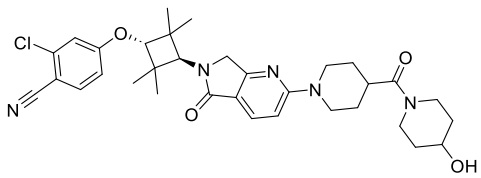
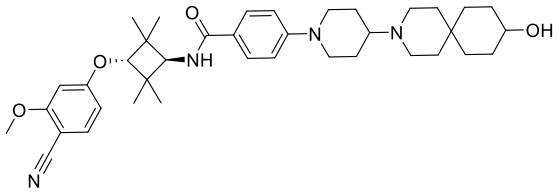
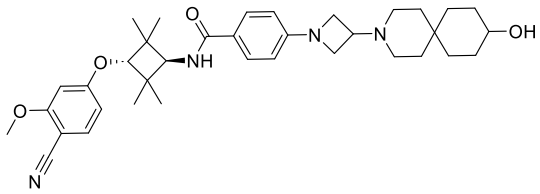
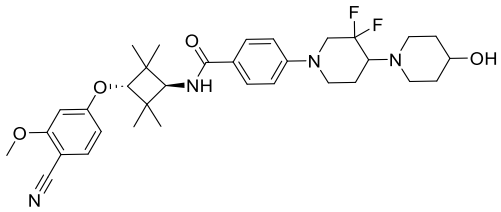
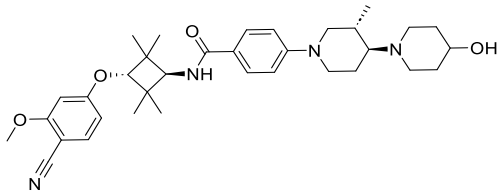
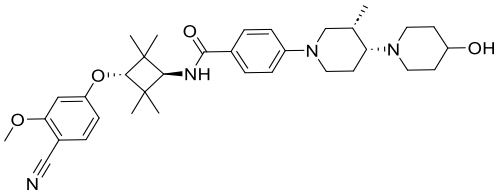
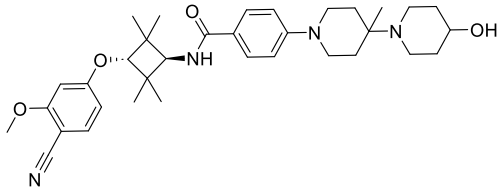
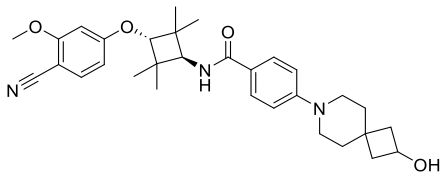
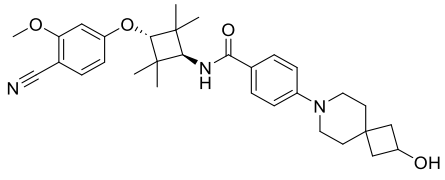
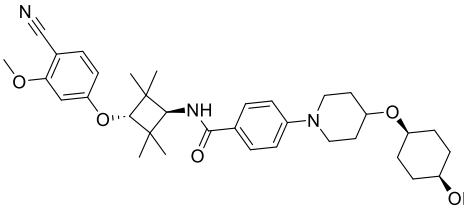
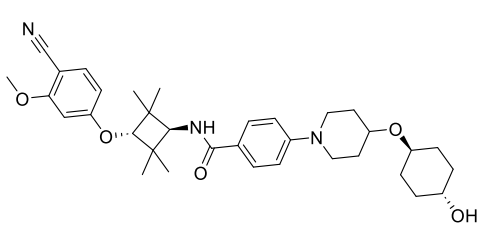
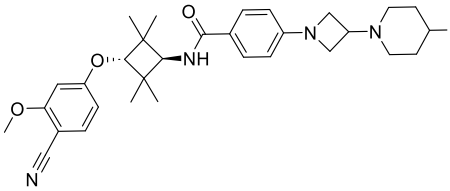
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

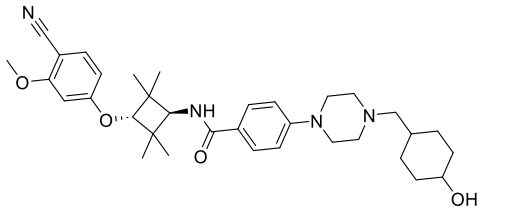
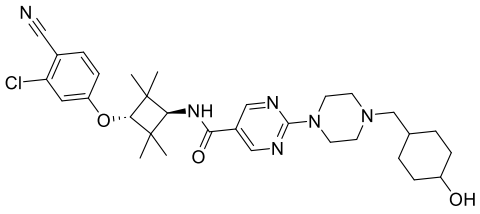
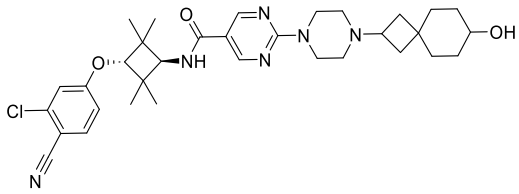
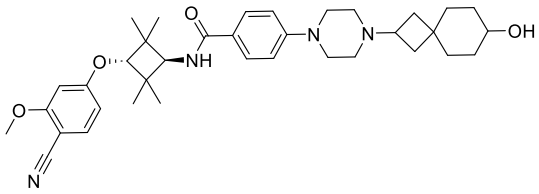
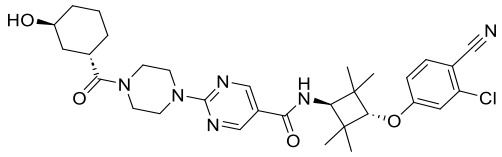
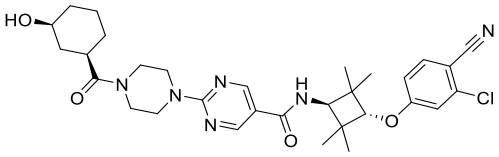
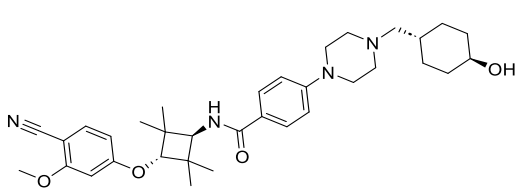
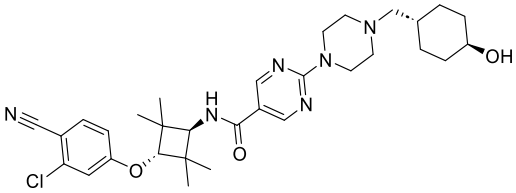
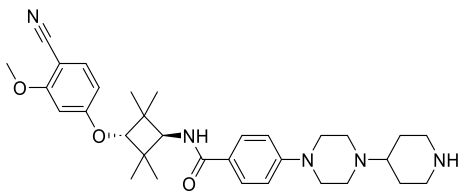
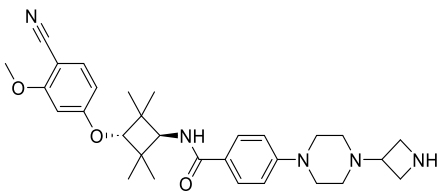
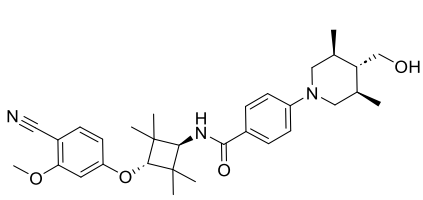
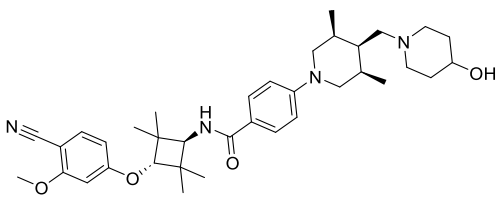
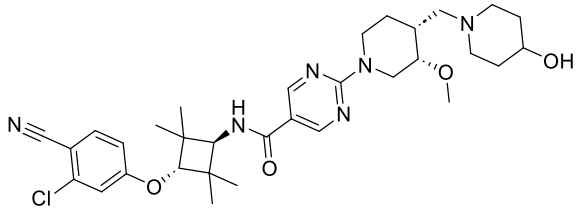
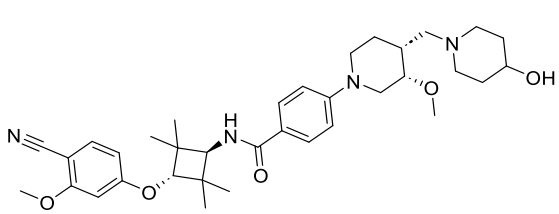
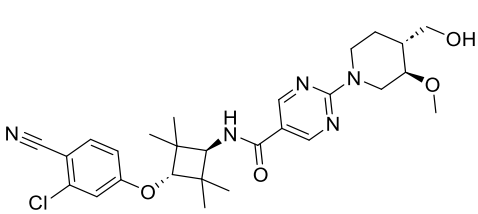
,

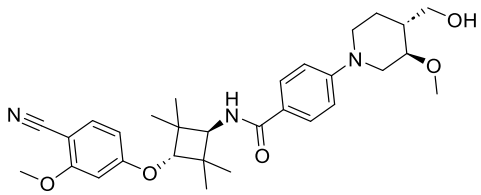
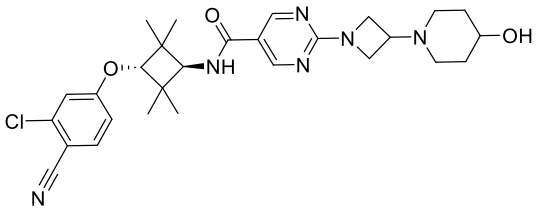
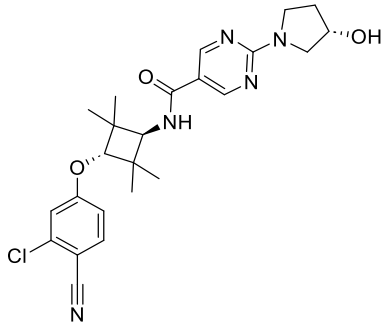
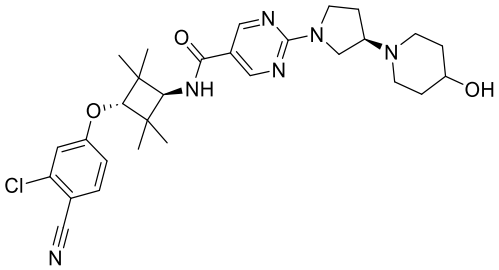
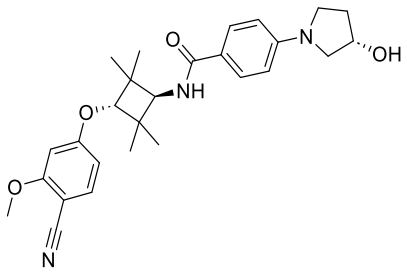
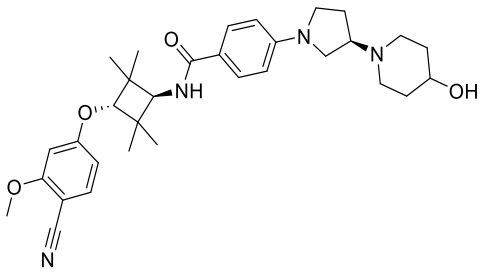
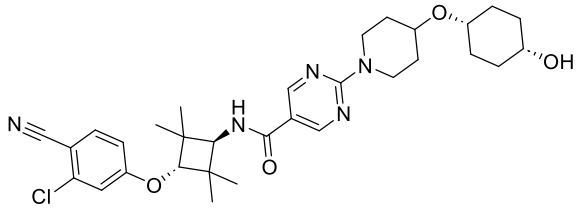
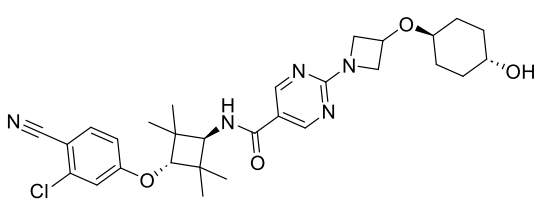
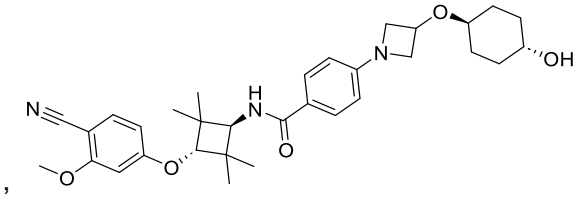
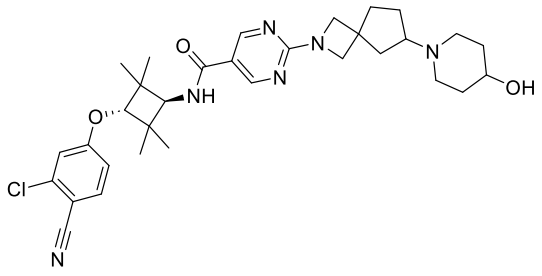
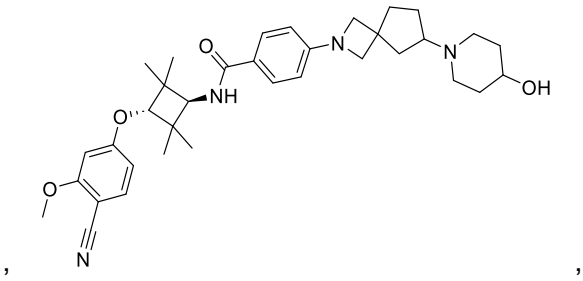
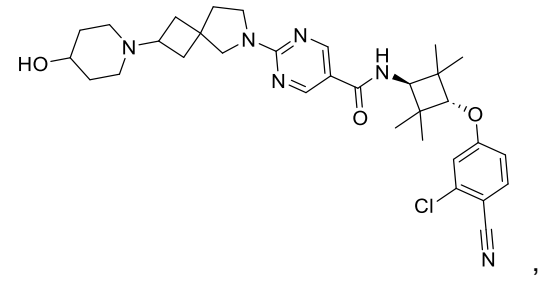
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

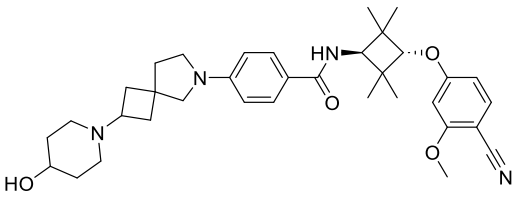
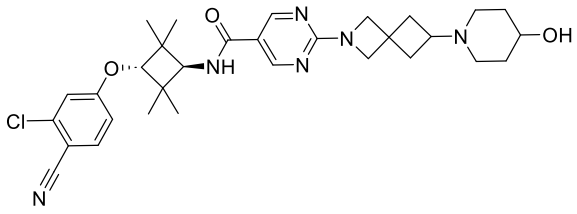
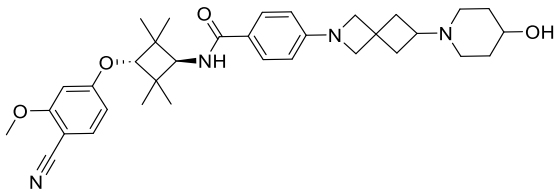
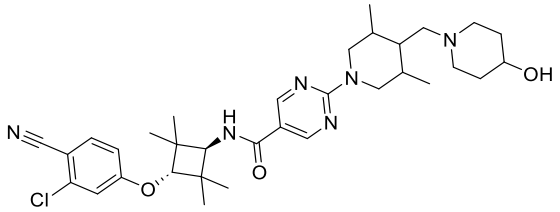
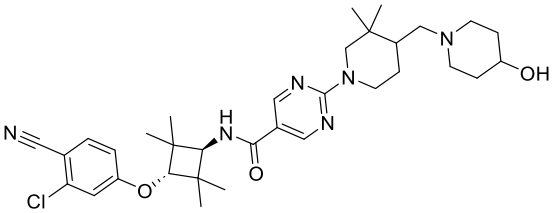
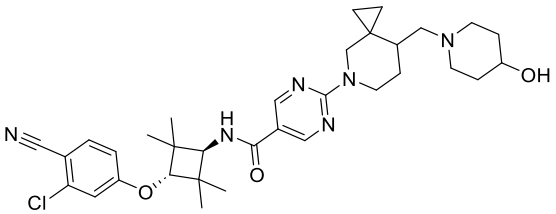
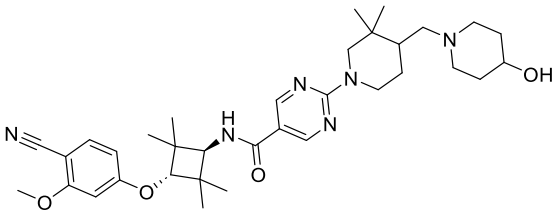
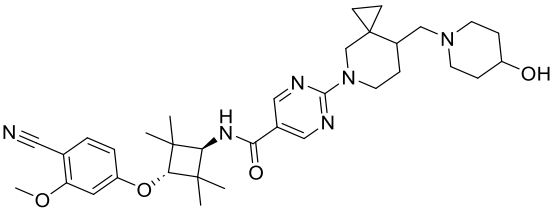
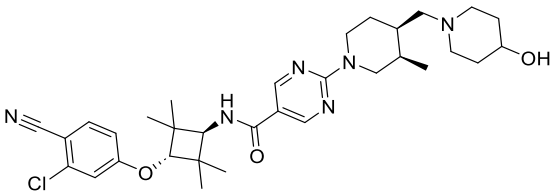
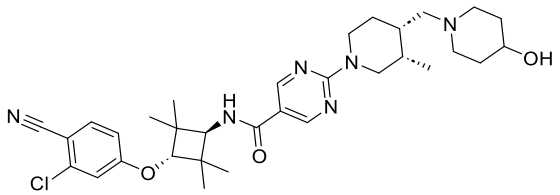
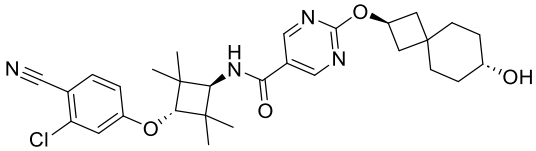
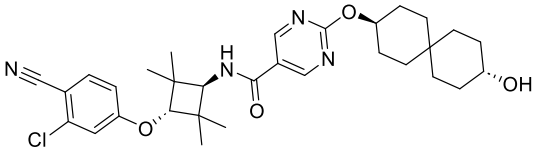
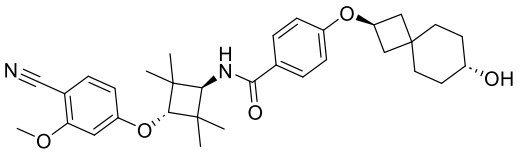
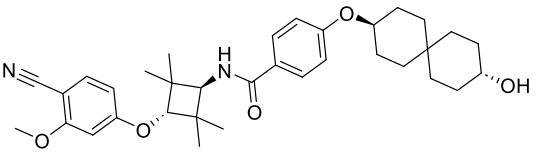
,

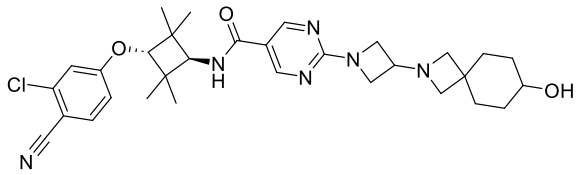
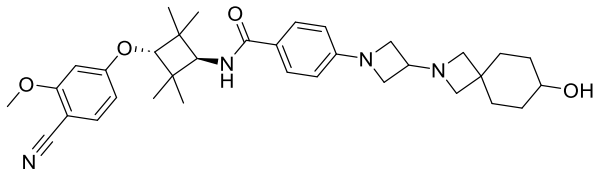
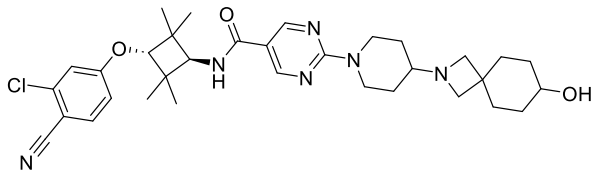
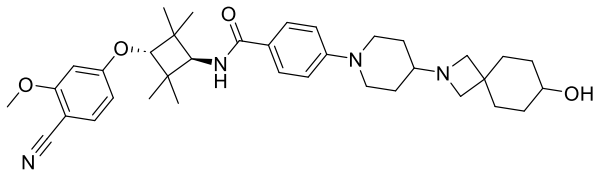
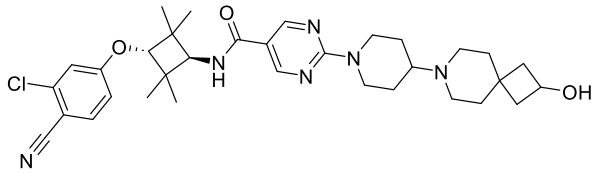
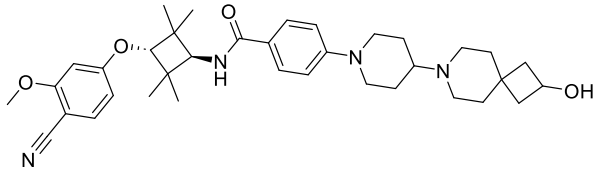
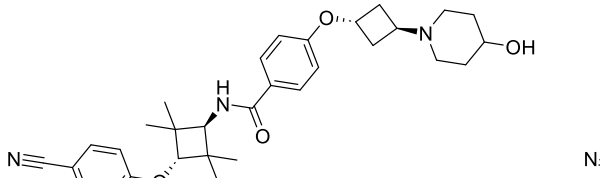

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

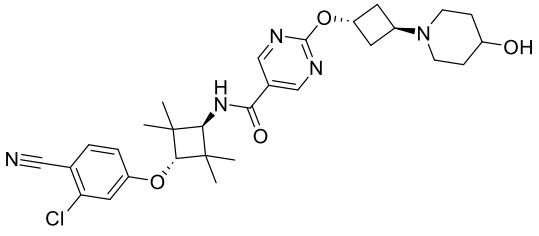
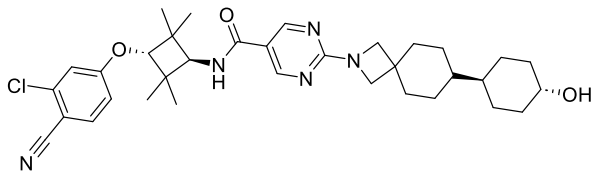

,

,

,

,

,

,

,

,

,

,

,

,

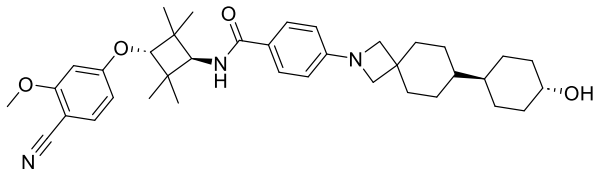
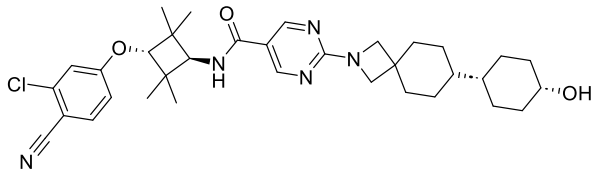
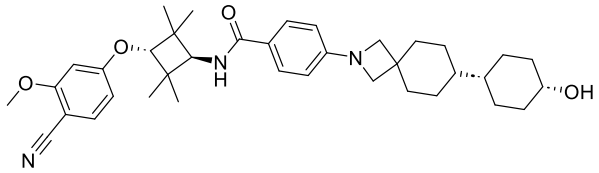
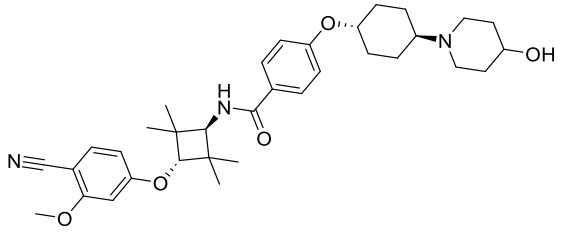
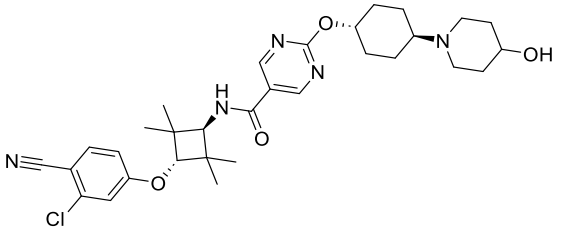
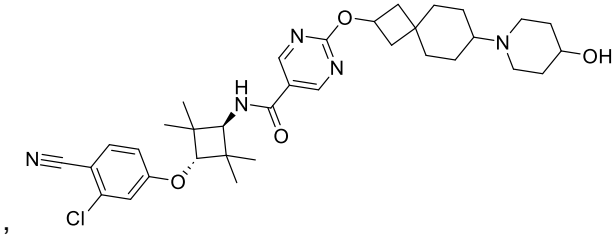
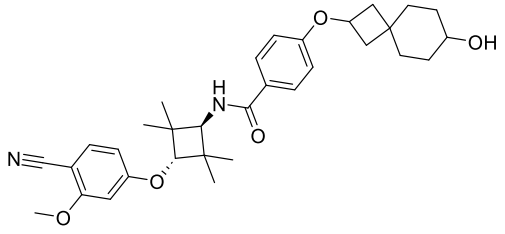
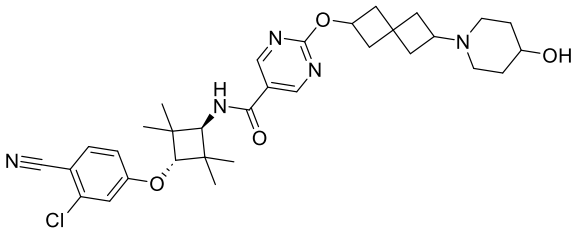
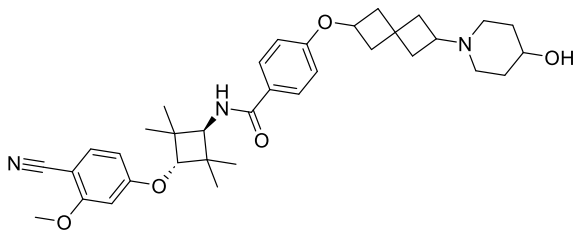
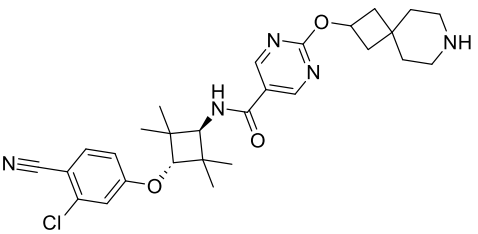
,

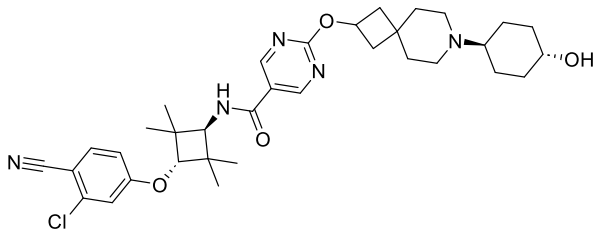
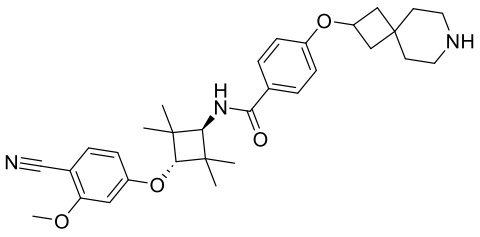
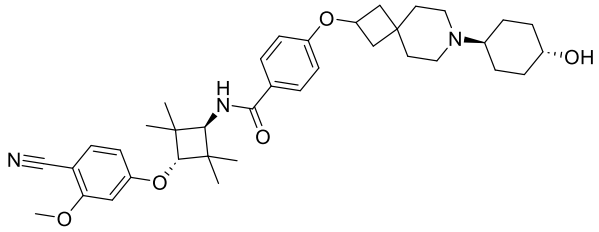
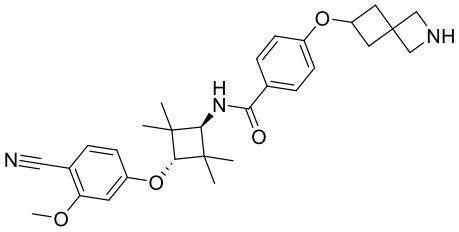
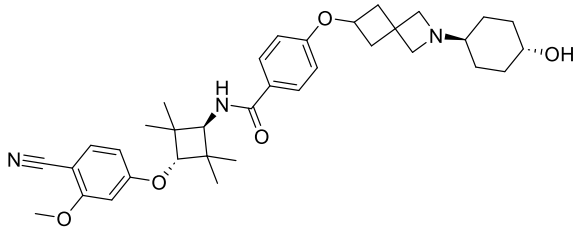
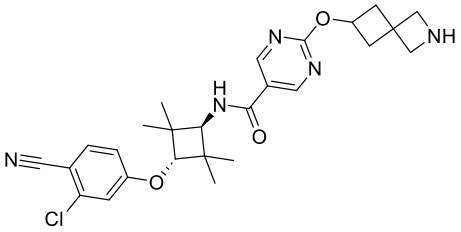
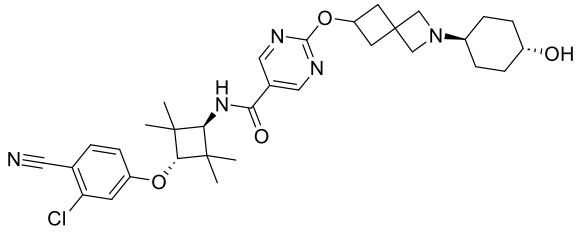
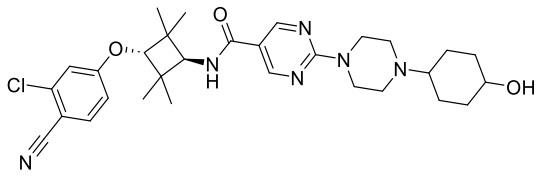
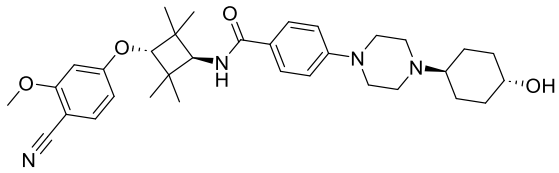
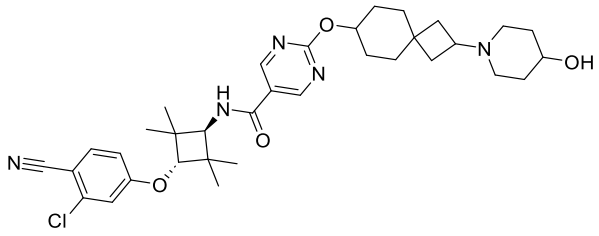
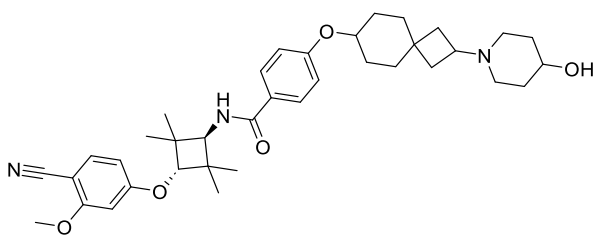
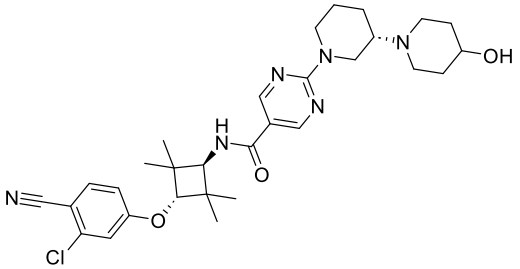
,

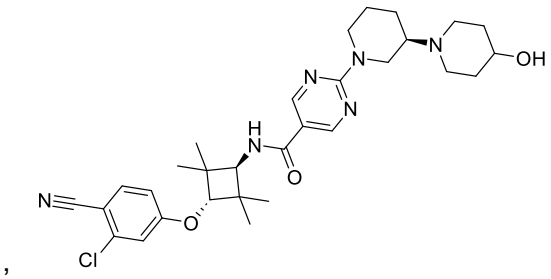
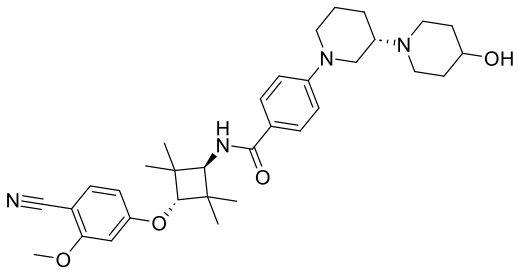
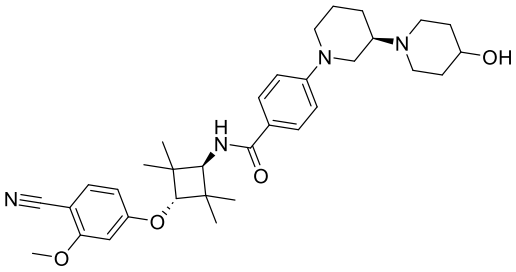
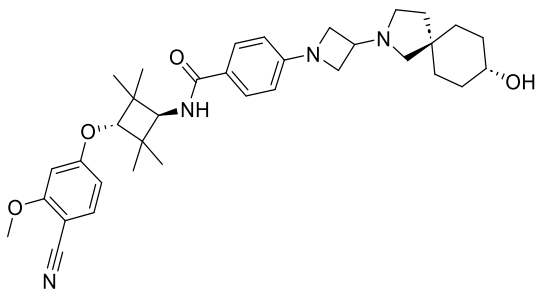
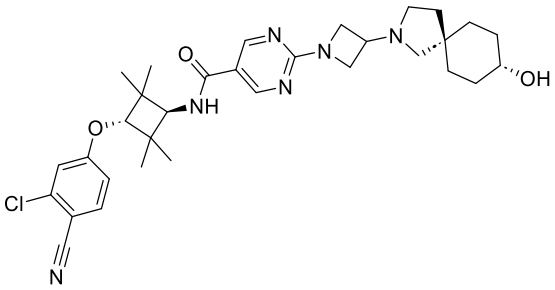
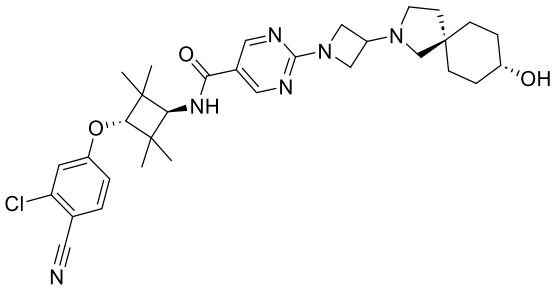
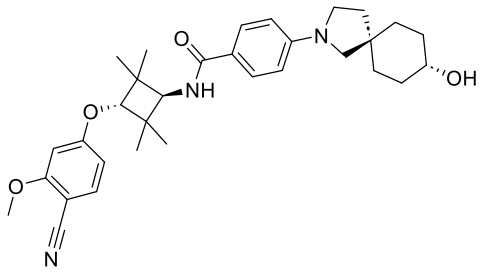
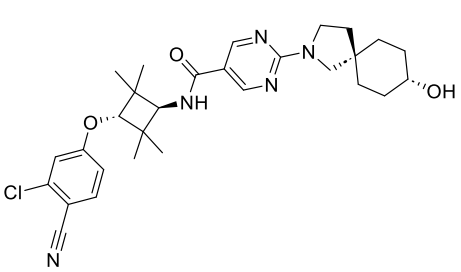
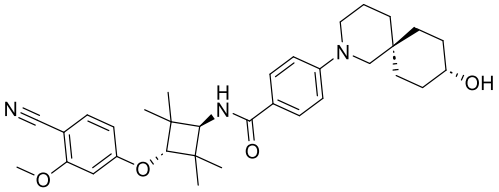
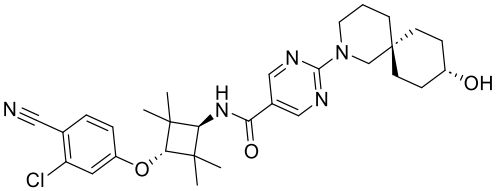
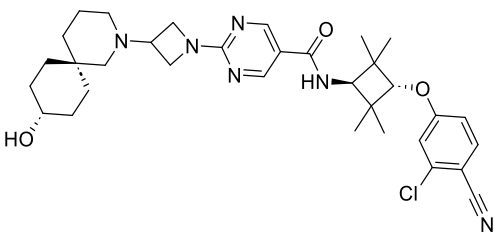
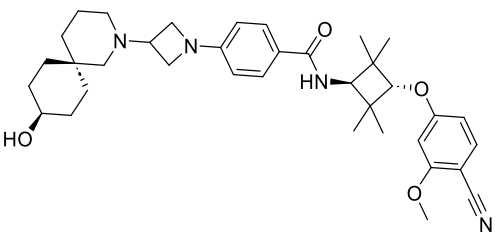

,

,

,

,

,
,

,

,

,
,

,

,

,

,
,

,

,

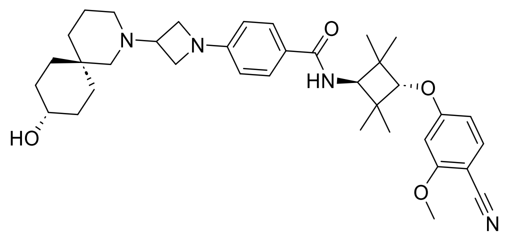
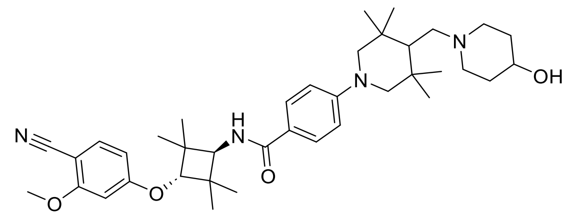
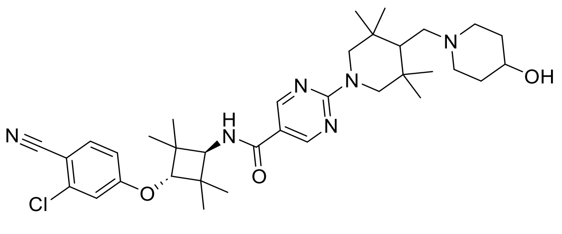
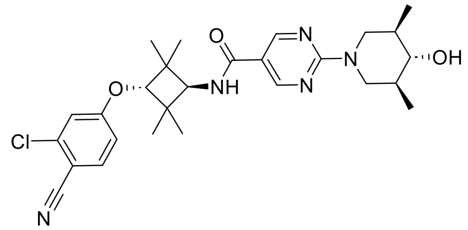
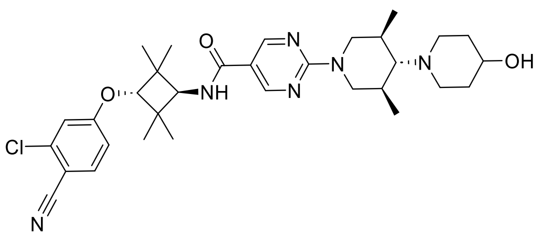
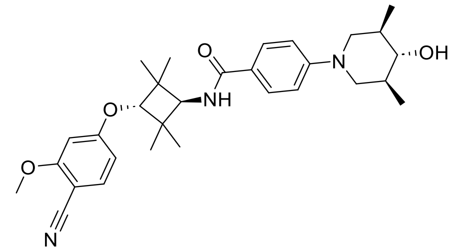
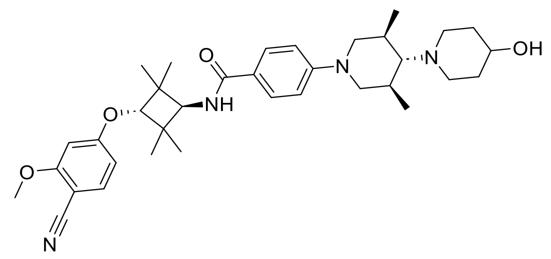
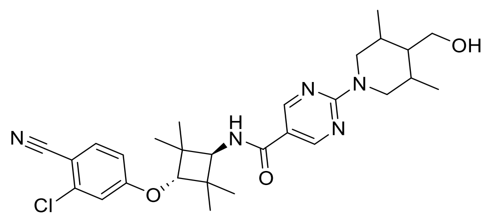
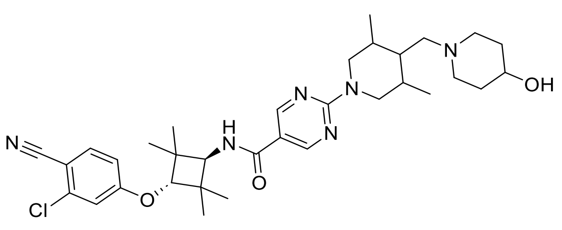
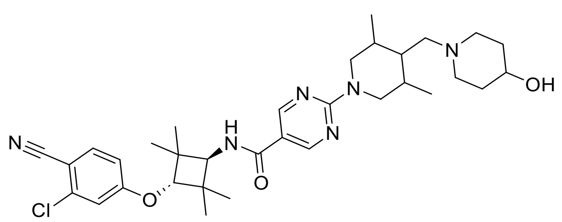
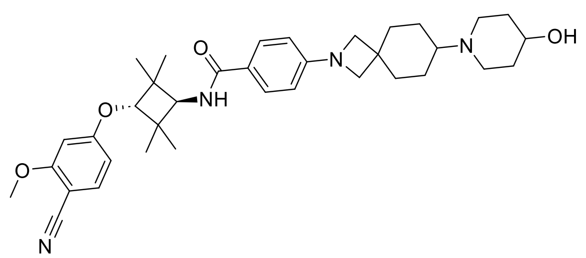

,

,

,

,

,

,

,

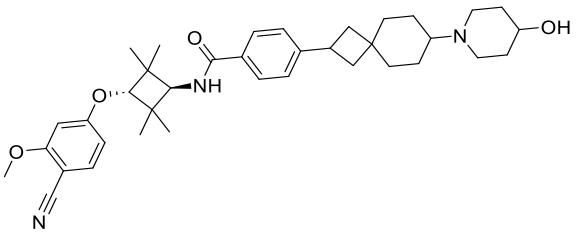
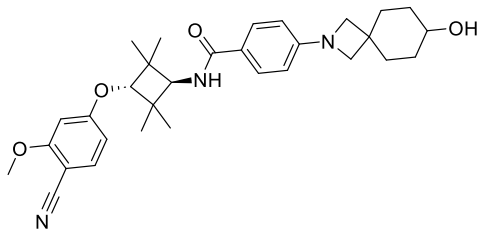
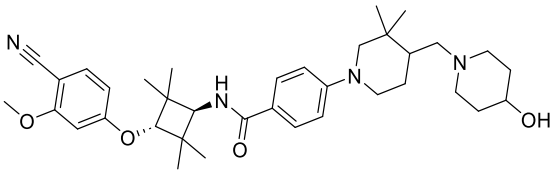
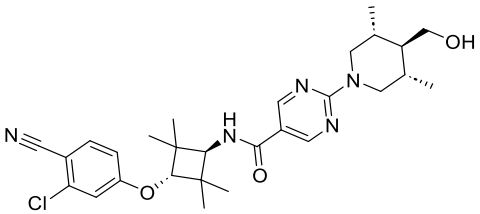
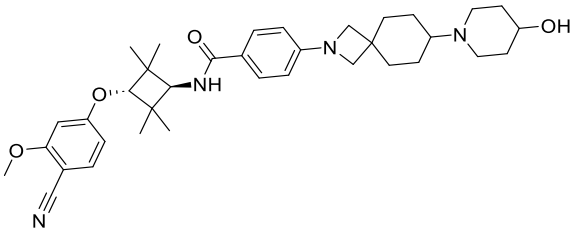
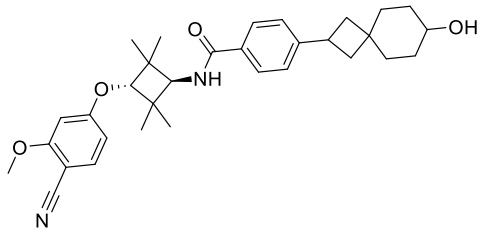
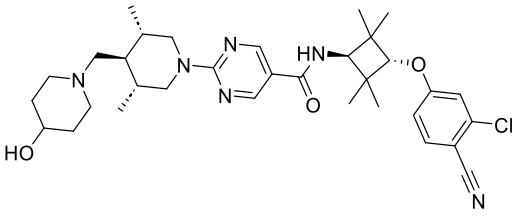
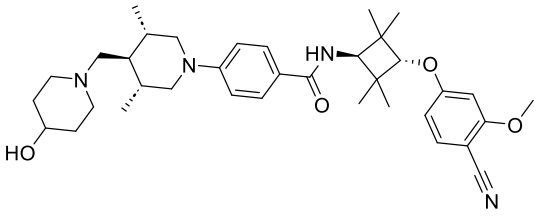
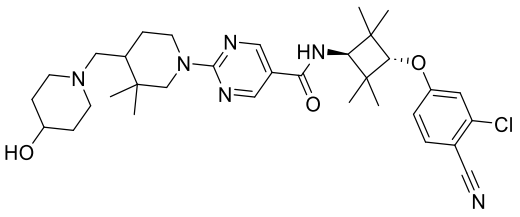
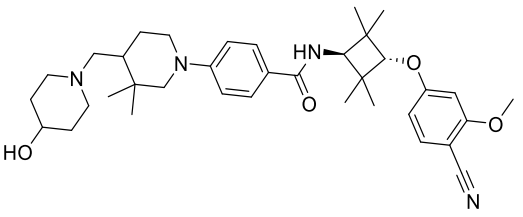
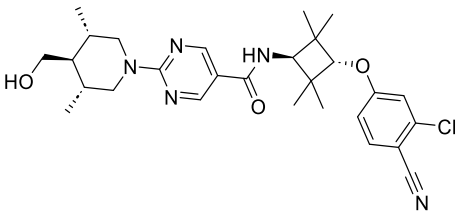
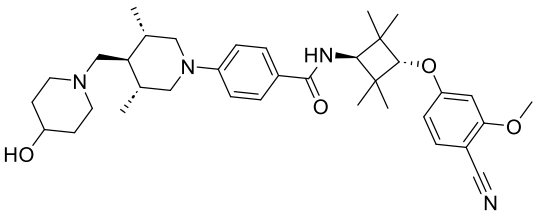
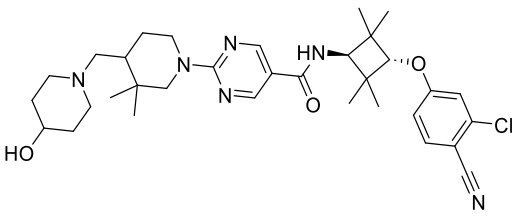
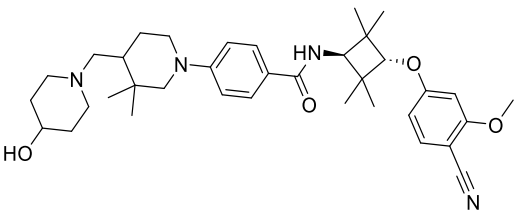
,

,

,

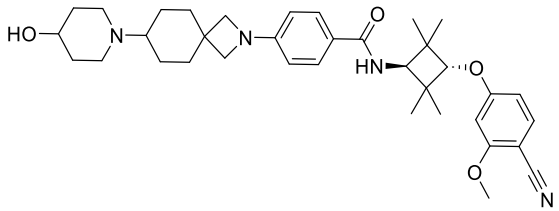
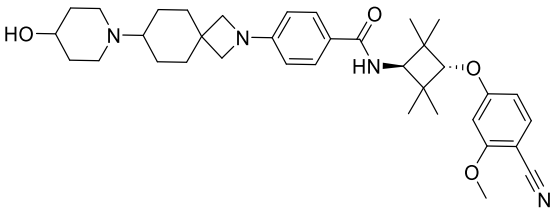
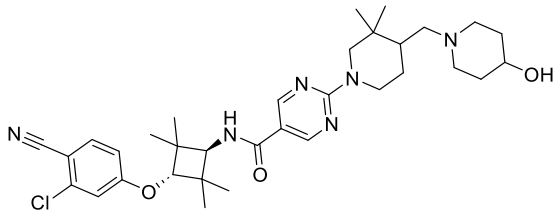
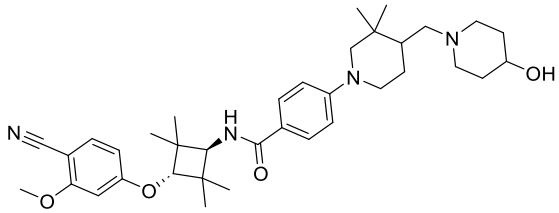
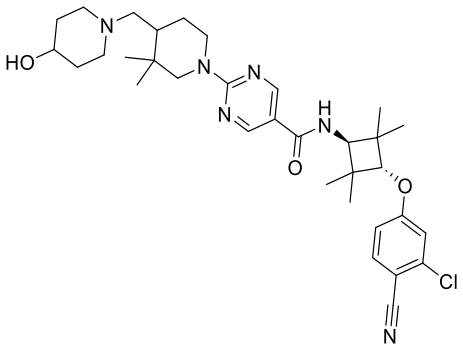
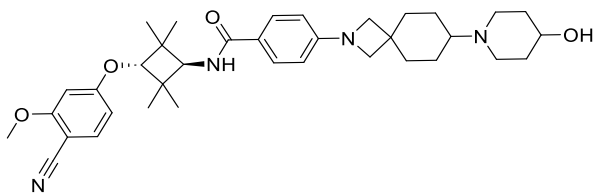
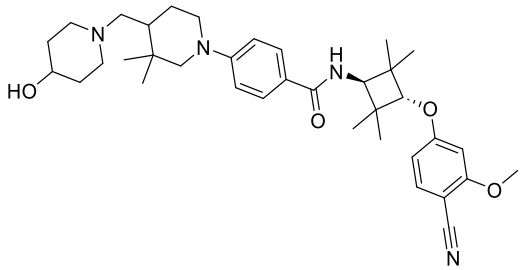
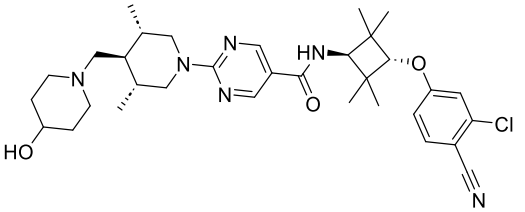
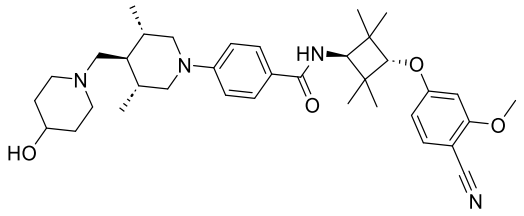
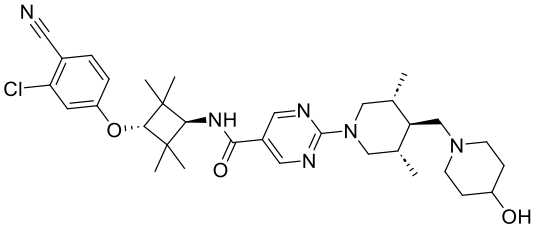

,

,

,

,

,

,

,

,

,

,

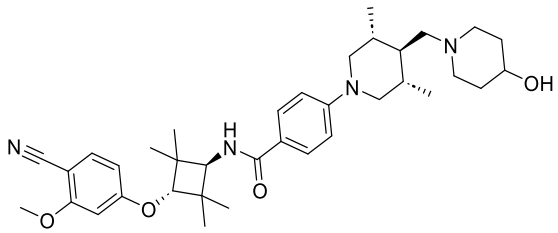
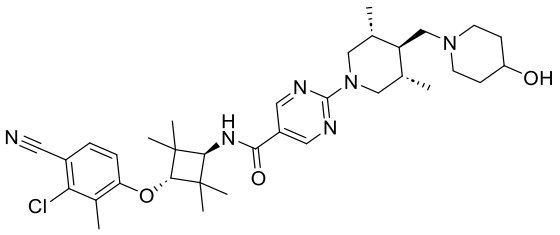
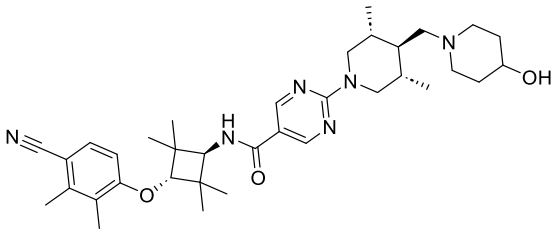
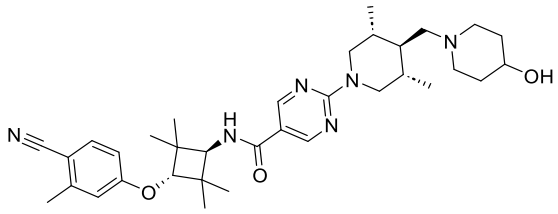
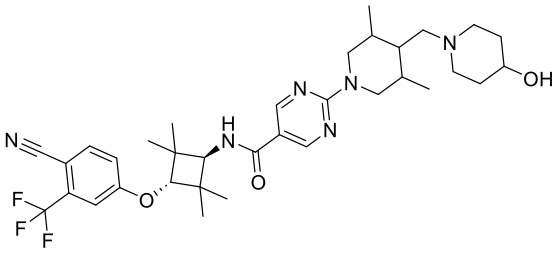
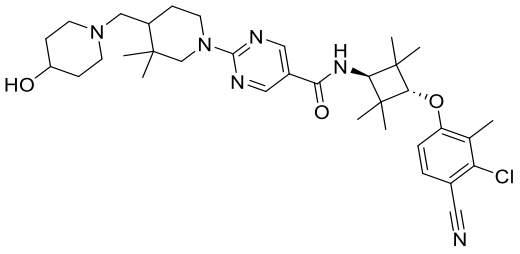
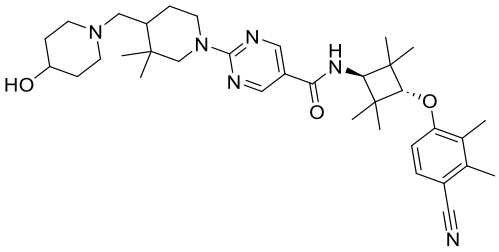
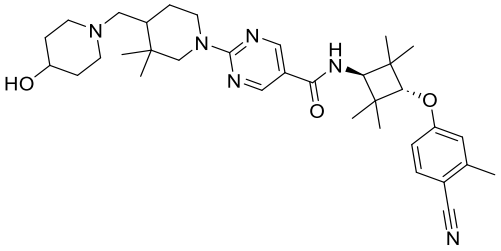
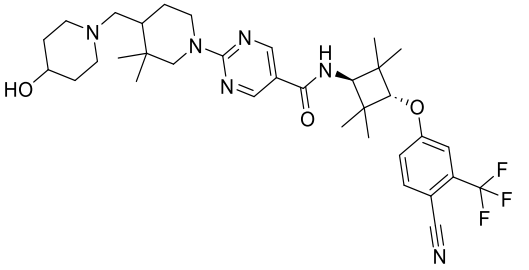
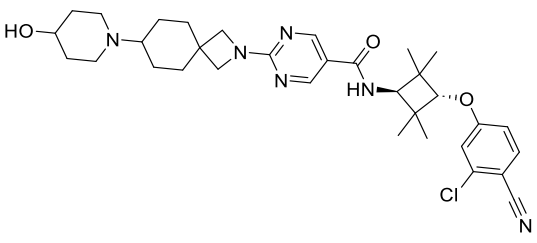
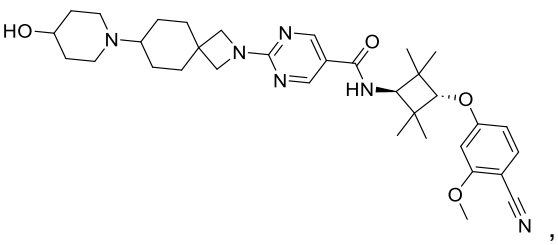













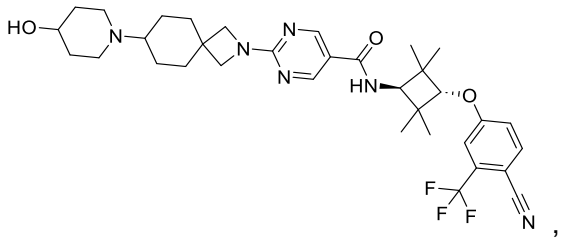
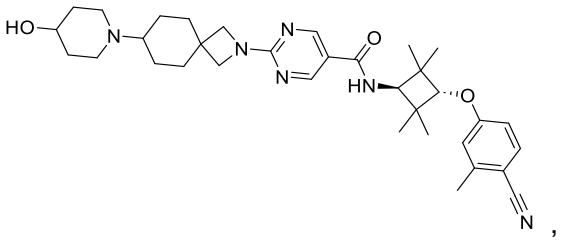
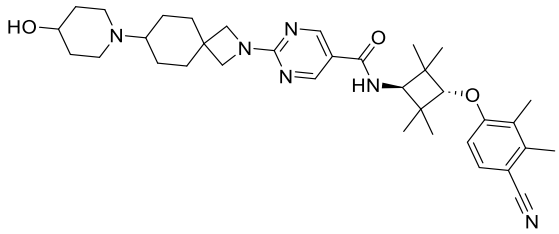
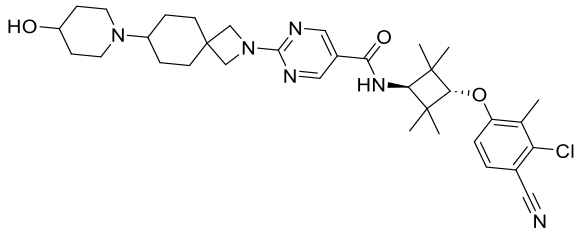














,

,

,

,

,

,

,

,

,

,

,

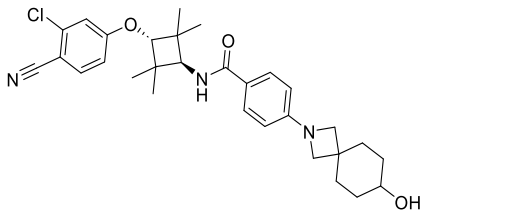
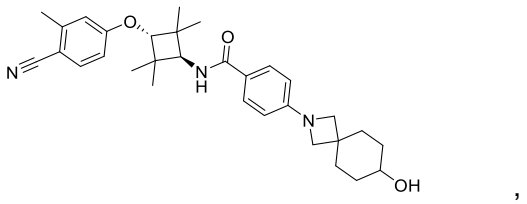
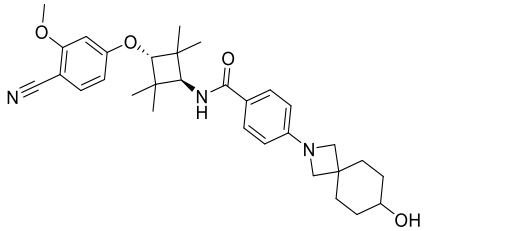
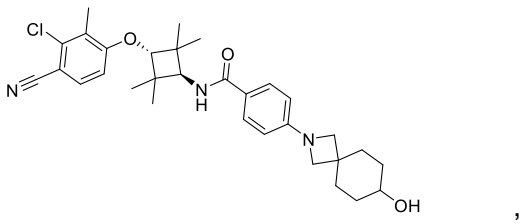
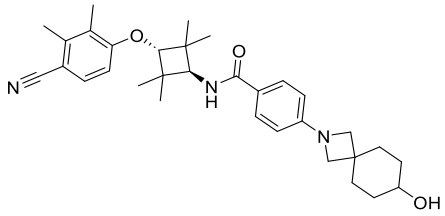
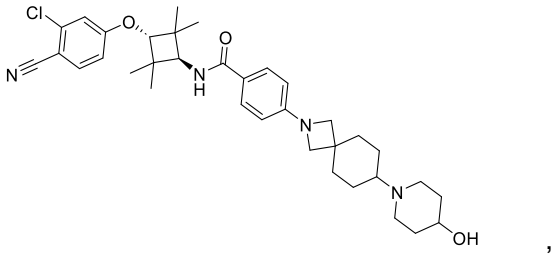















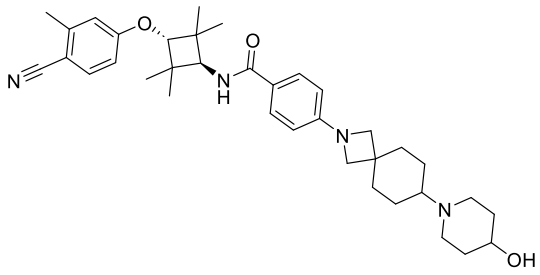
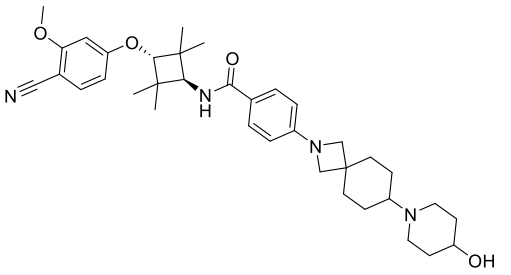
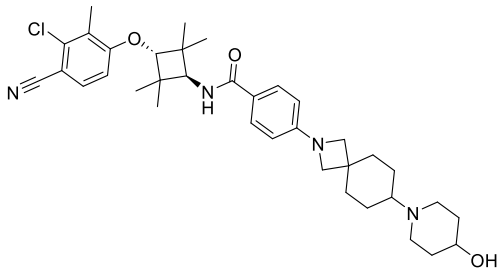
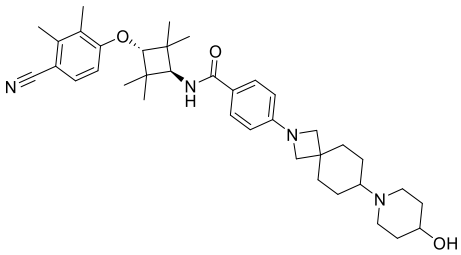
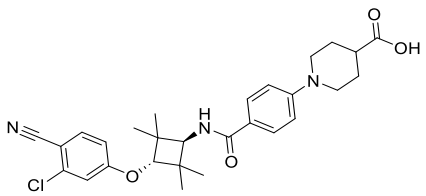
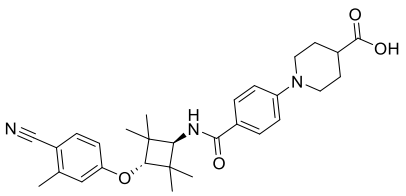
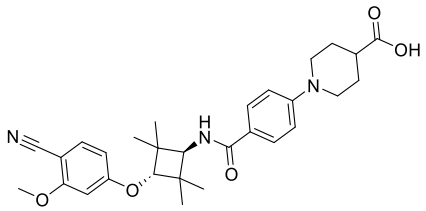
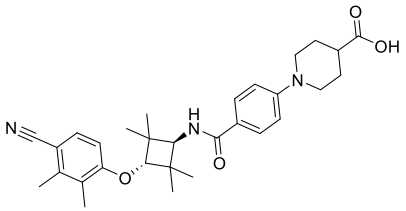
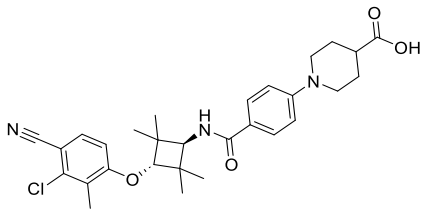
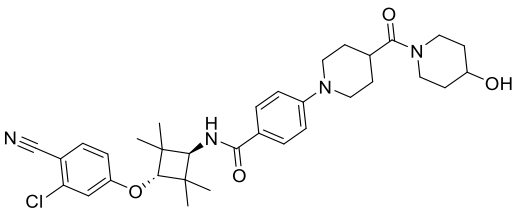
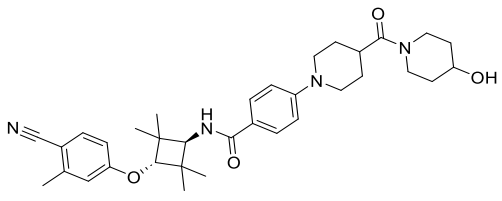
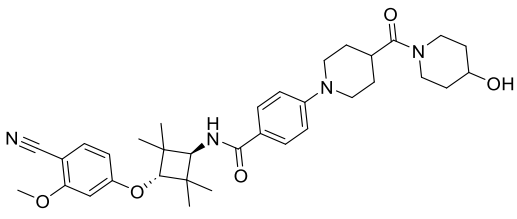
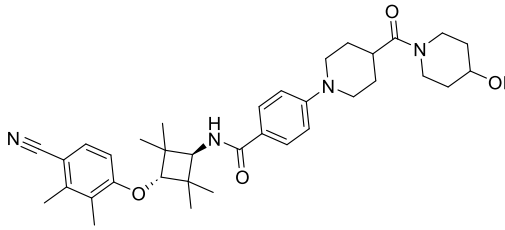
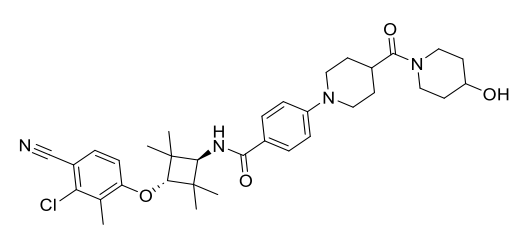

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,




o


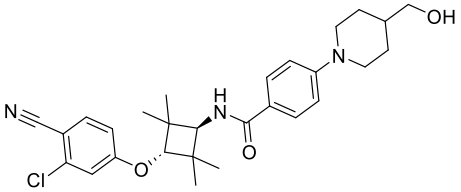
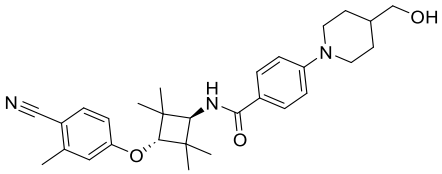
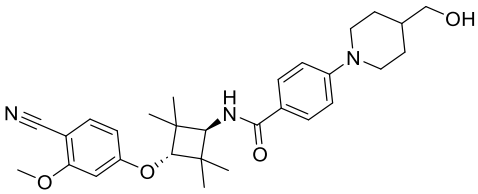
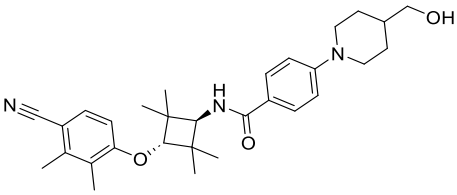
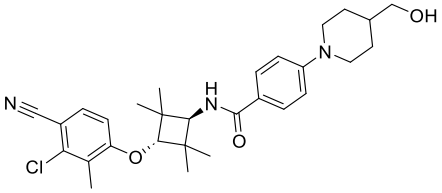
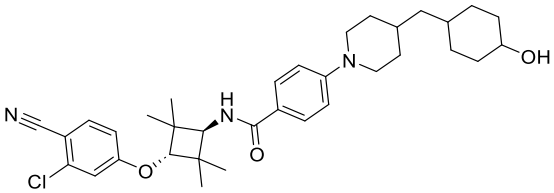
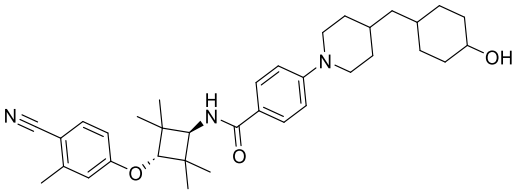
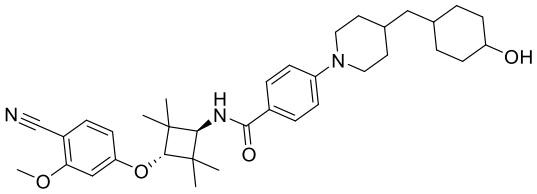
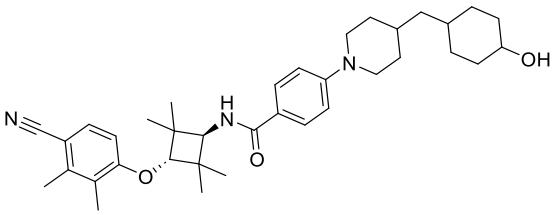
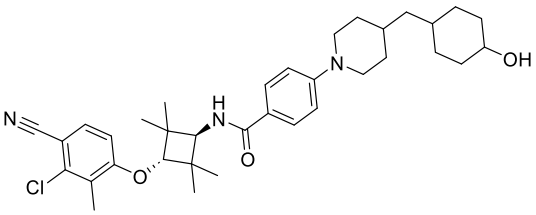
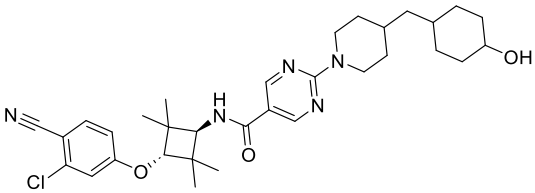
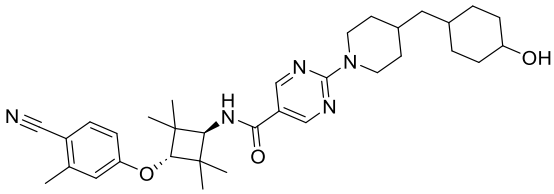
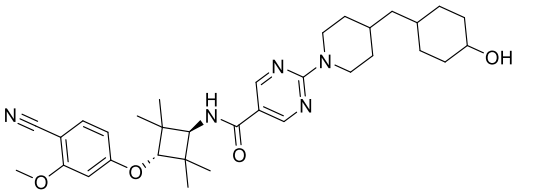
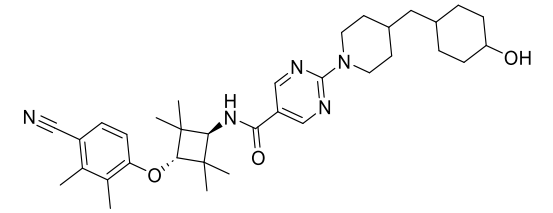
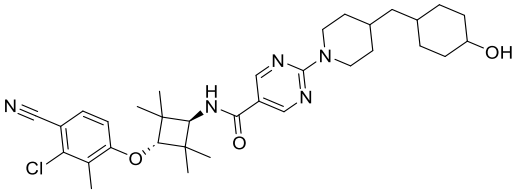
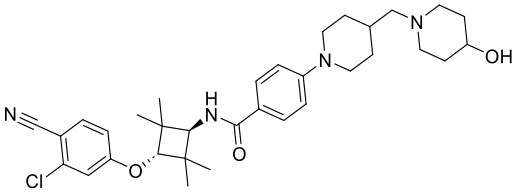
[00319] Forma de realización 126. Un compuesto, o una sal o solvato farmacéuticamente aceptable de este, que tenga una de las siguientes estructuras:


,

,

,

,

,

,

,

,

,

,

,

,

,

,

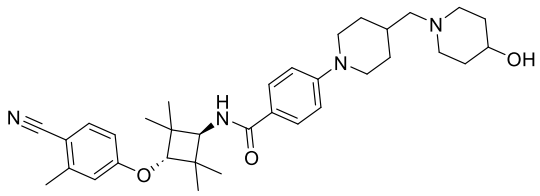
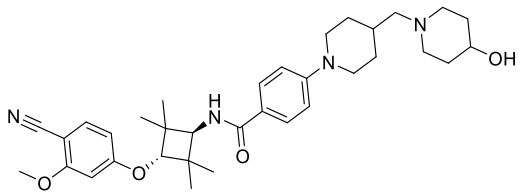
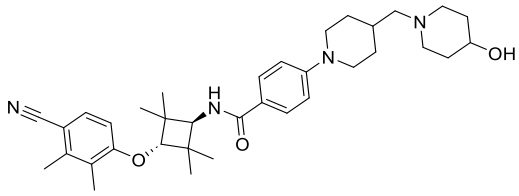
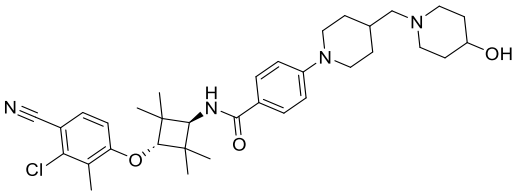
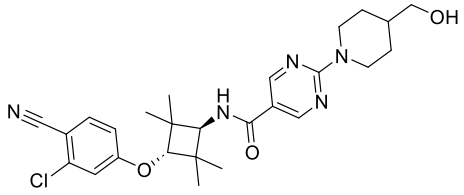
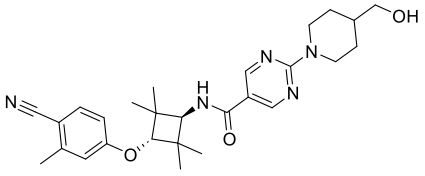
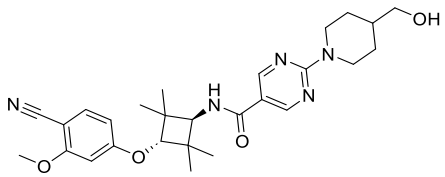
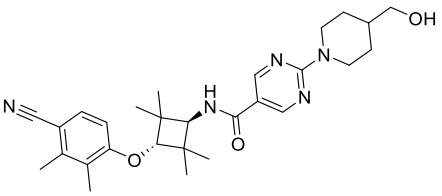
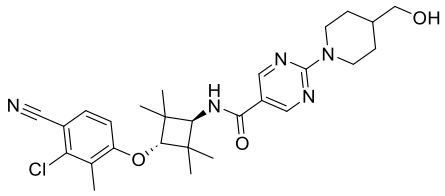
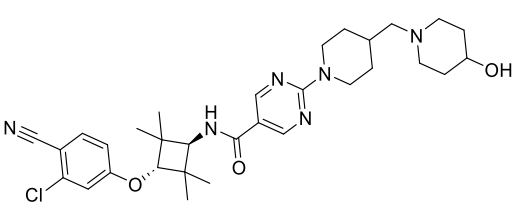
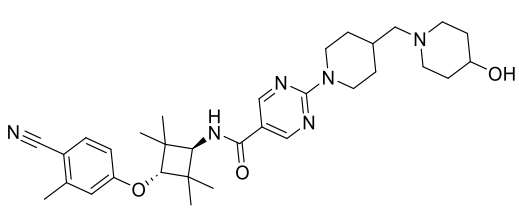
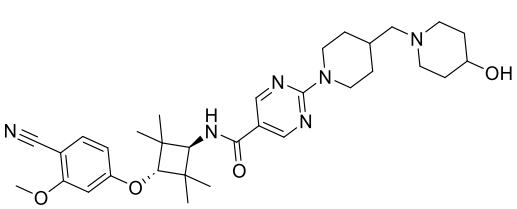
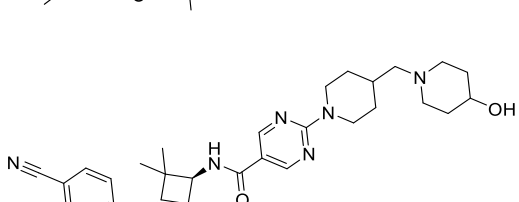
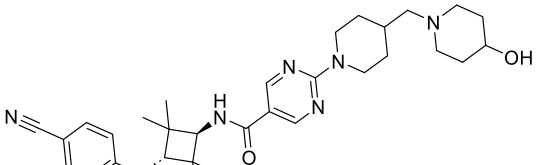
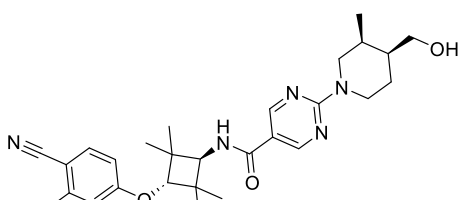
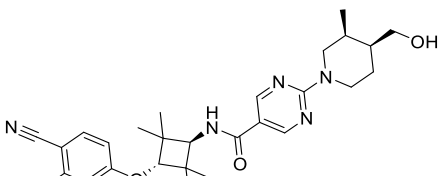
,

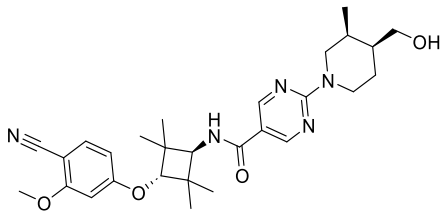
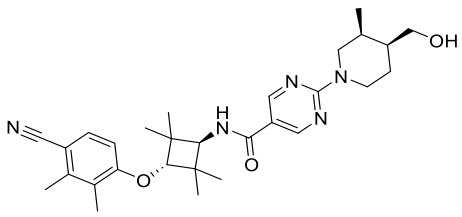
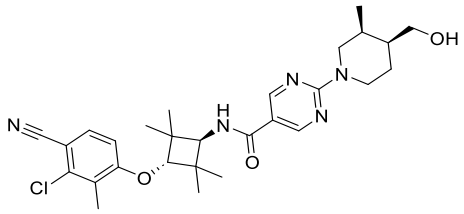
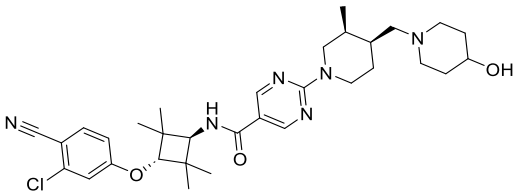
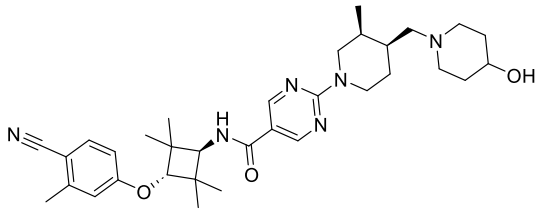
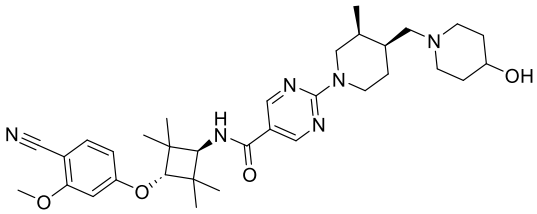
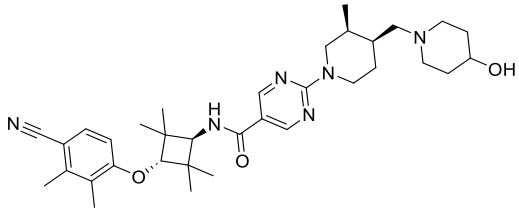
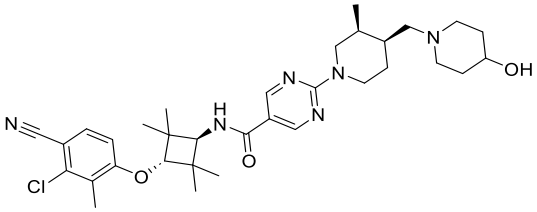
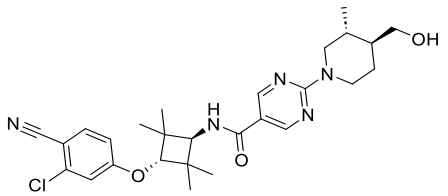
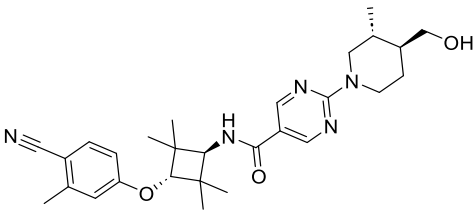
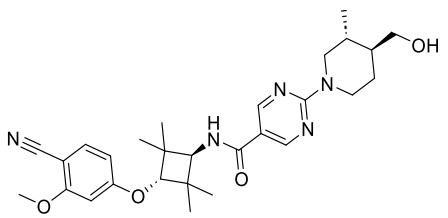
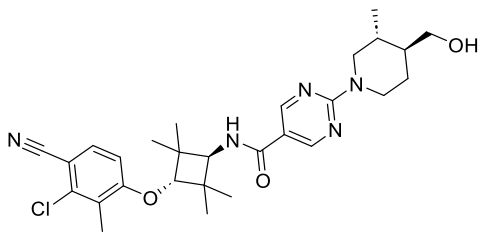
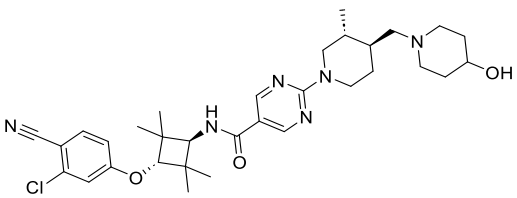
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

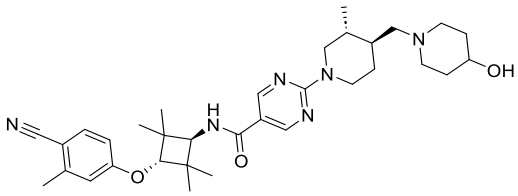
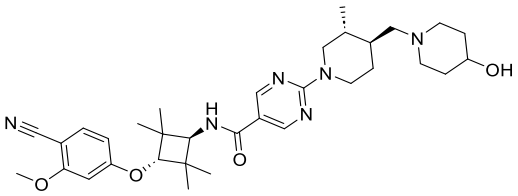
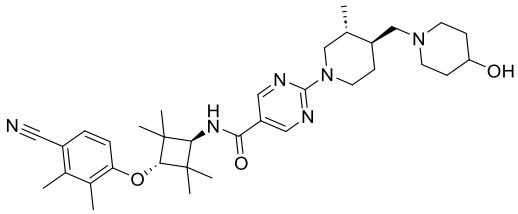
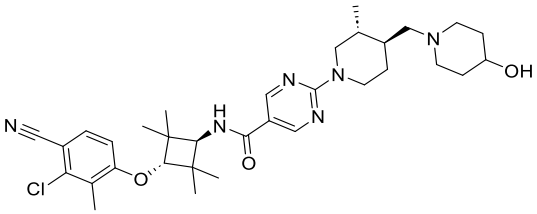
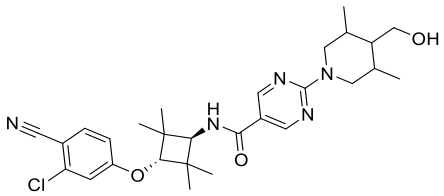
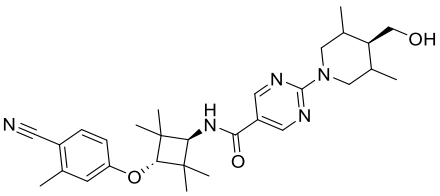
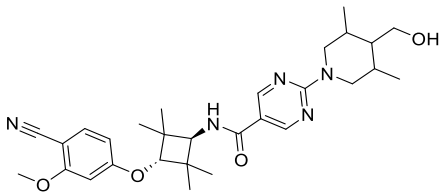
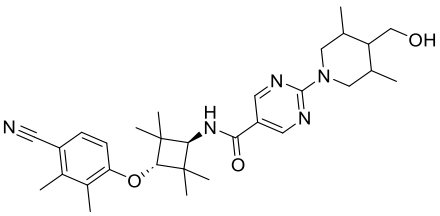
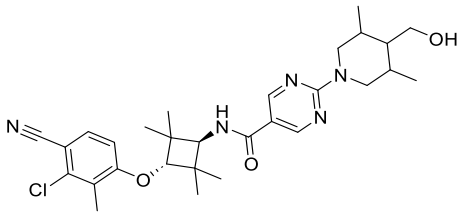
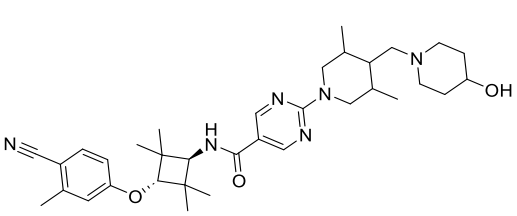
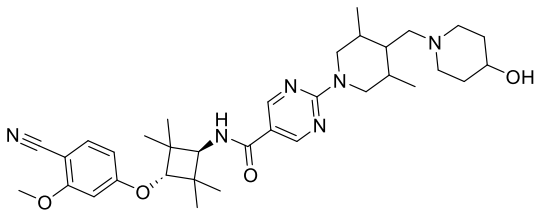
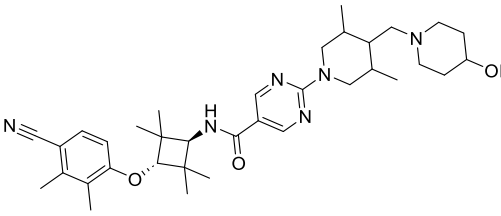
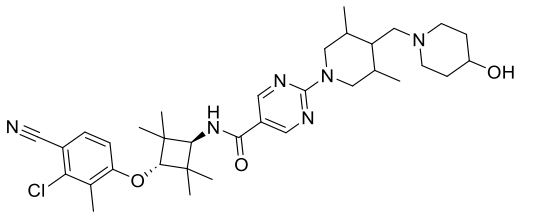
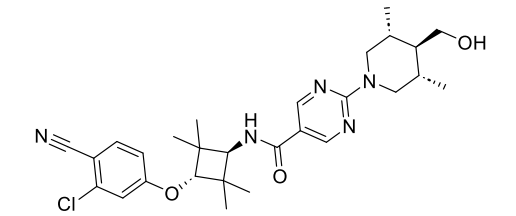
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

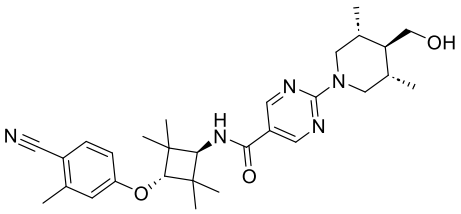
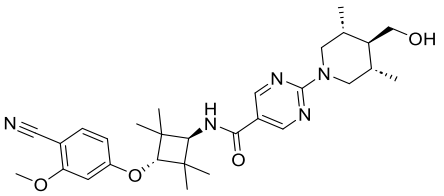
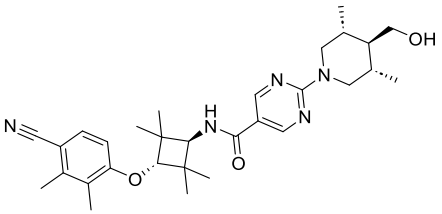
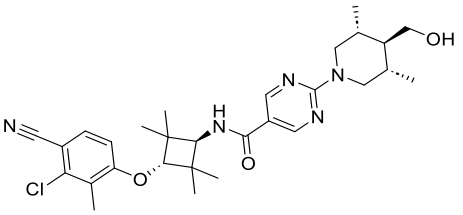
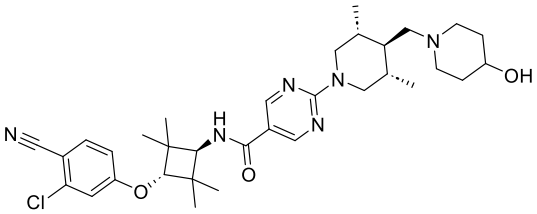
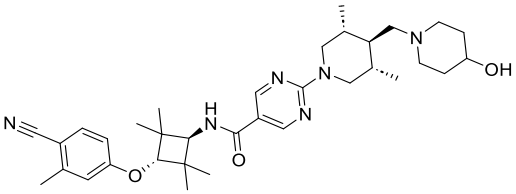
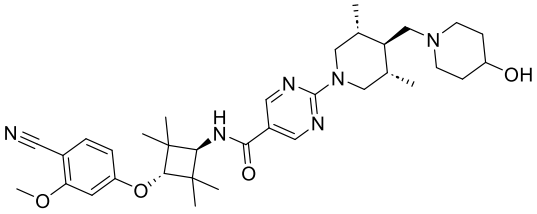
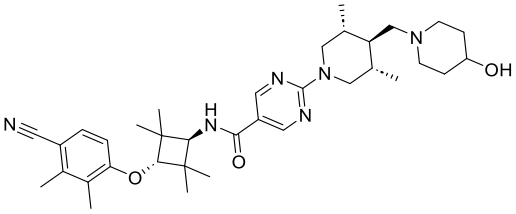
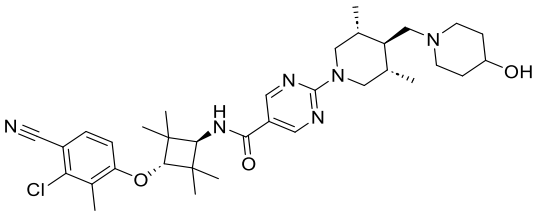
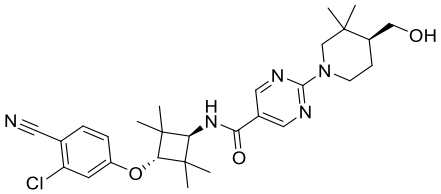
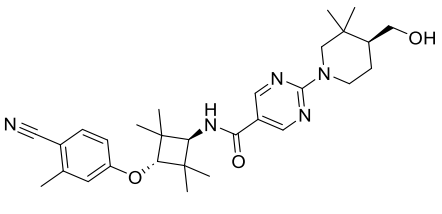
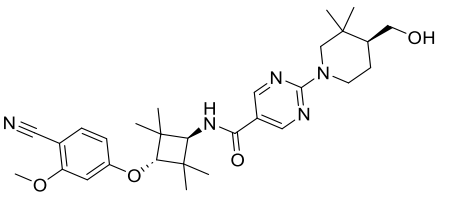
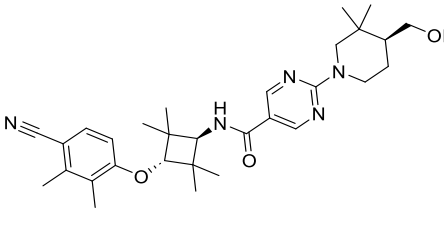
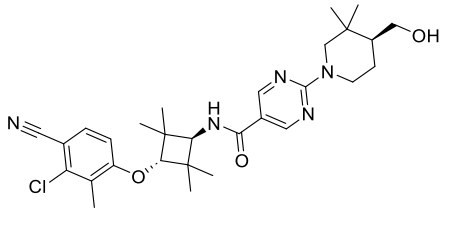
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

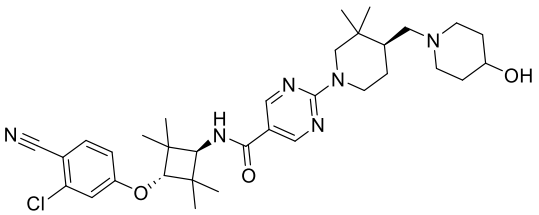
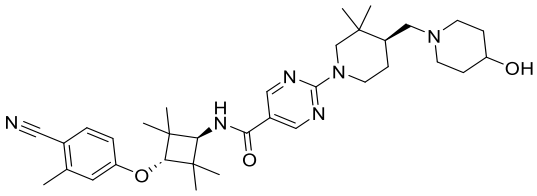
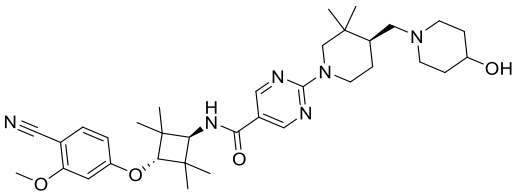
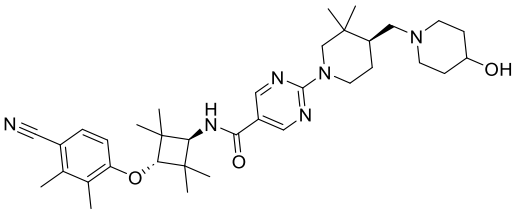
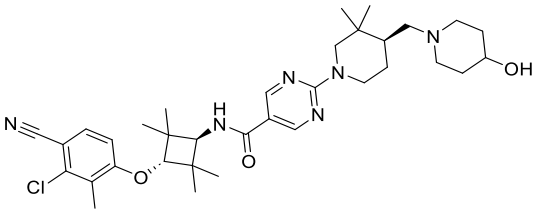
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

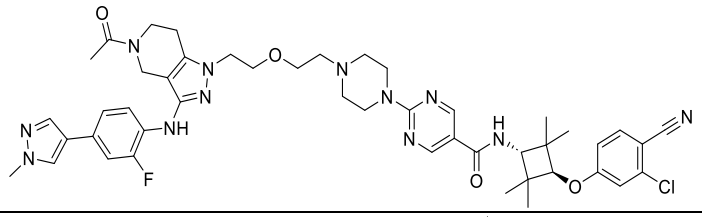
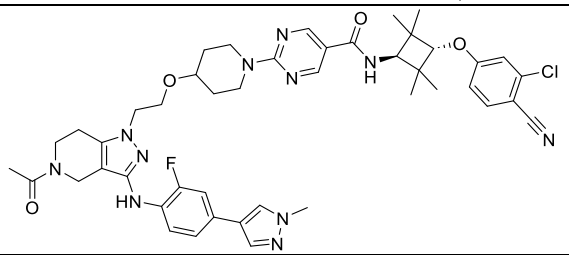
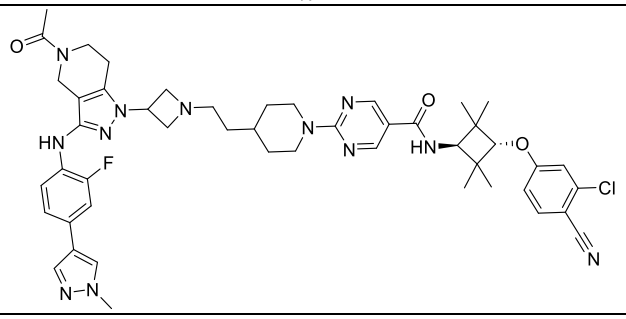
,

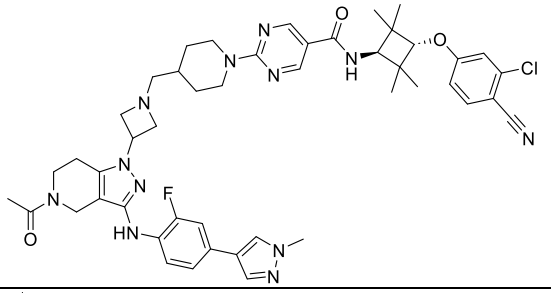
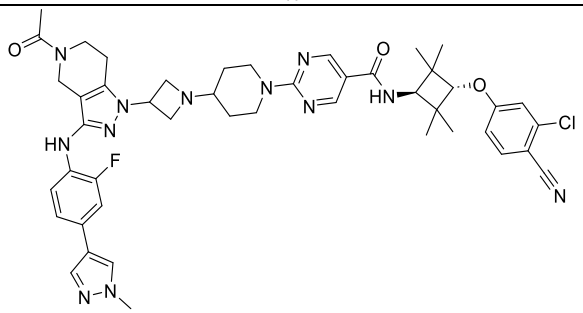
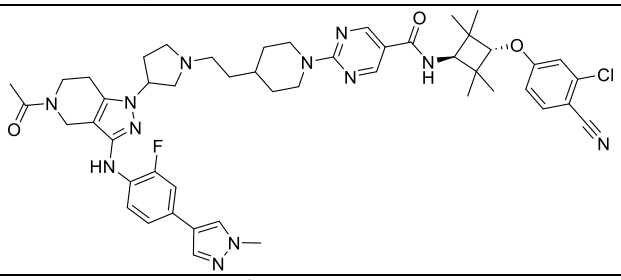
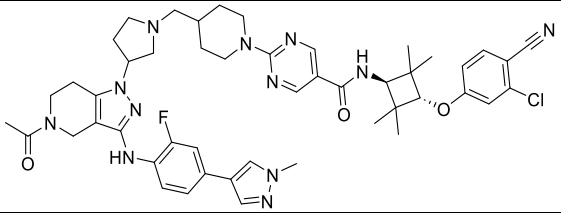
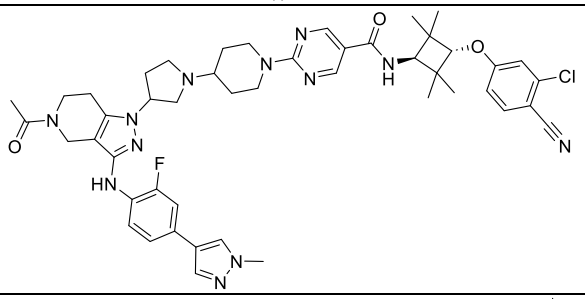
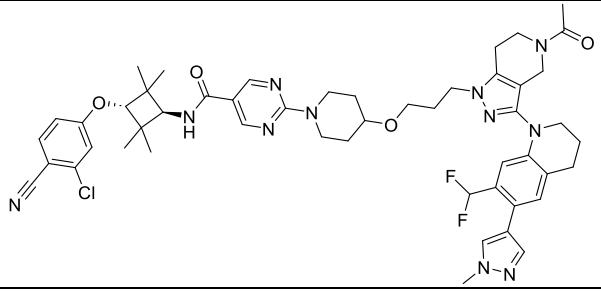
,

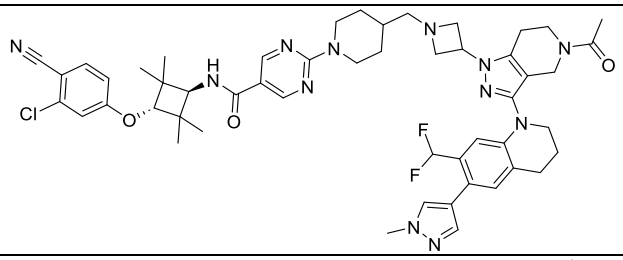
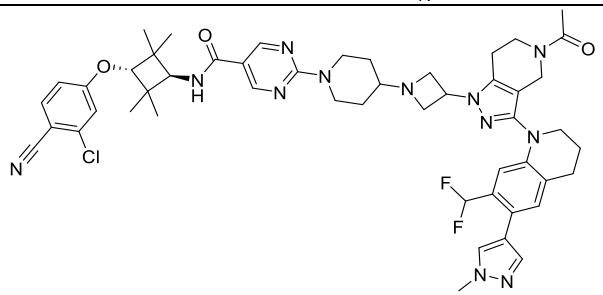
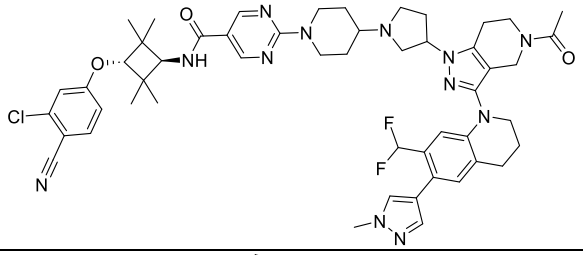
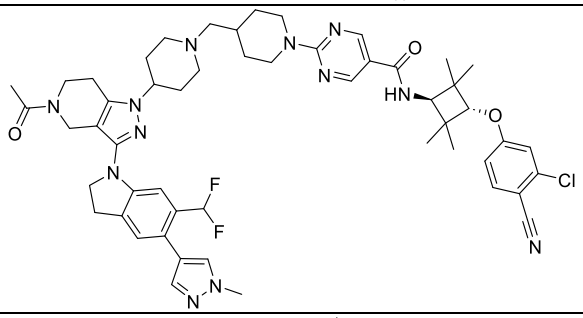
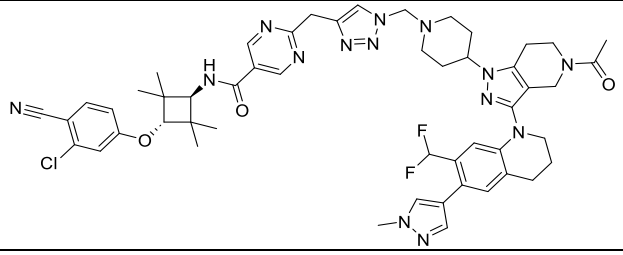
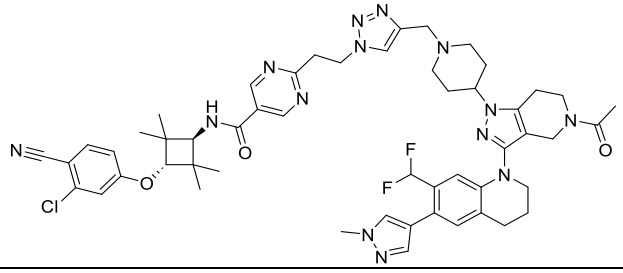

,

,

,

,o

.

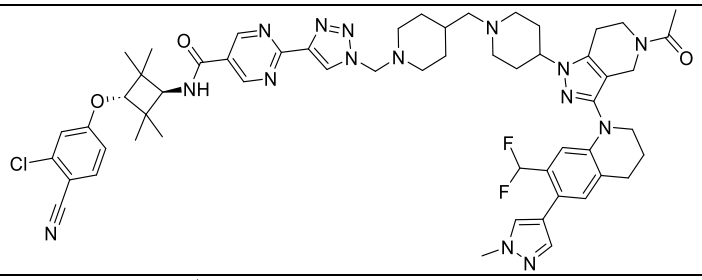
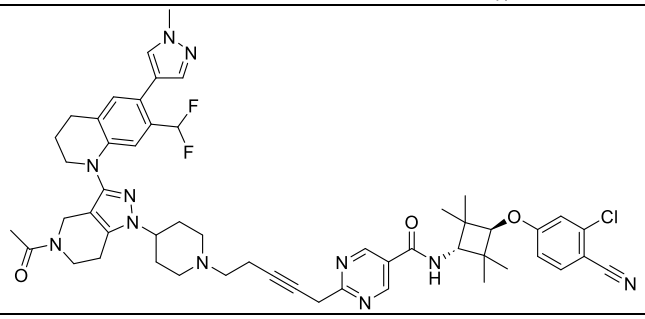
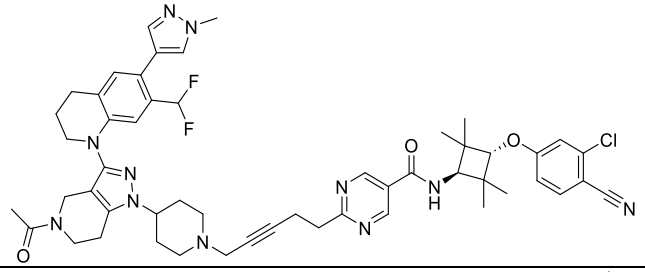
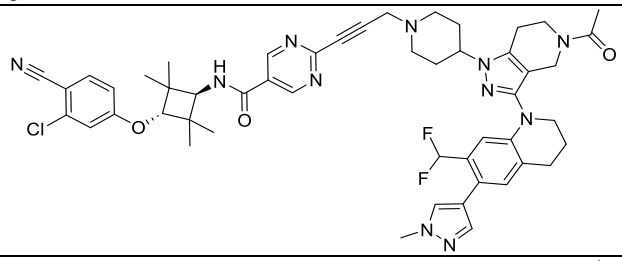
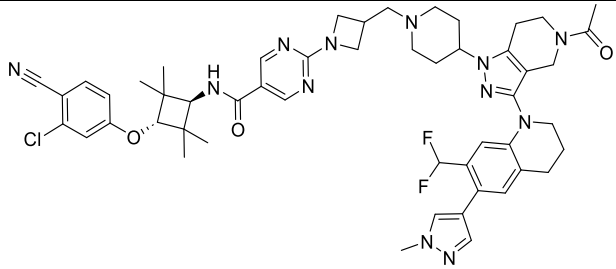
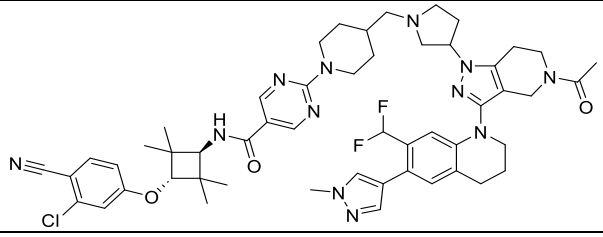
[00320] En algunas formas de realización, el compuesto de fórmula I es un compuesto de la tabla 1, o una sal o solvato farmacéuticamente aceptable de este.

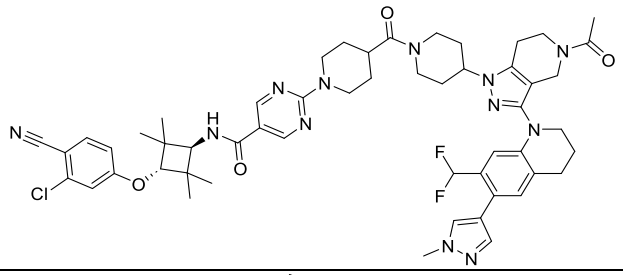
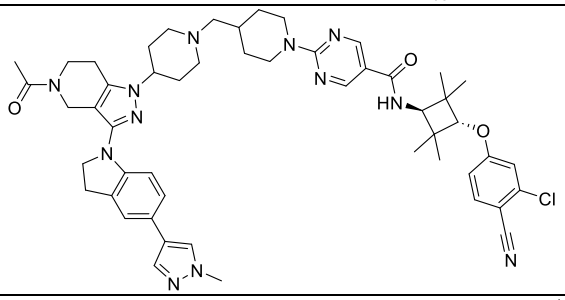
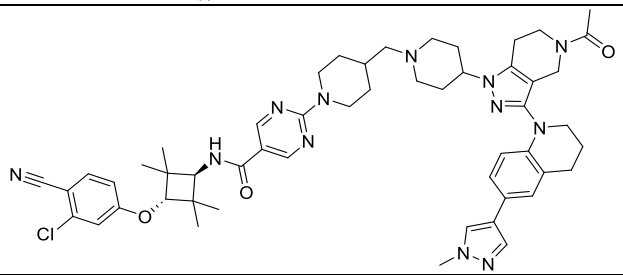
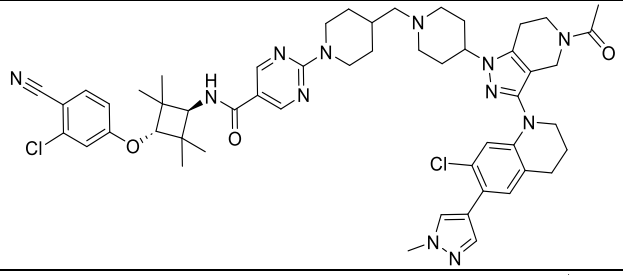
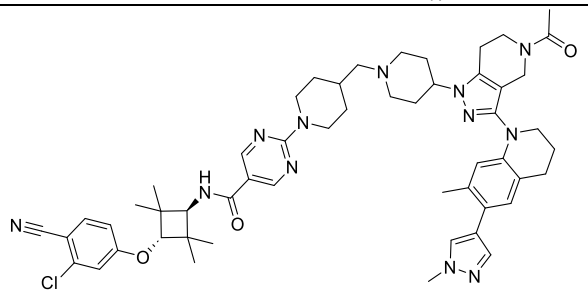
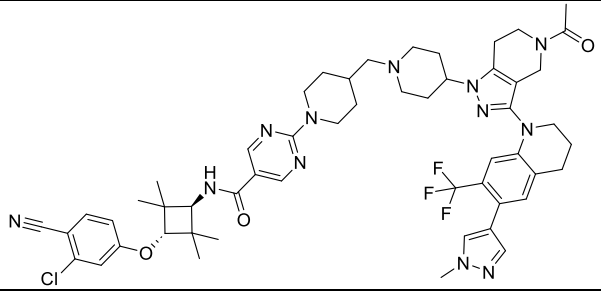
Tabla 1

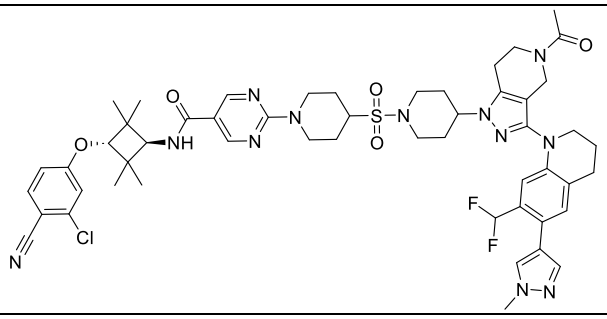
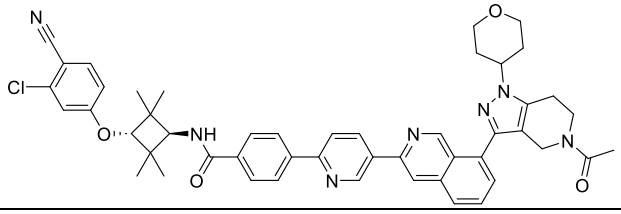
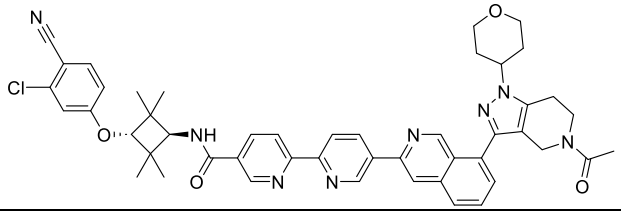
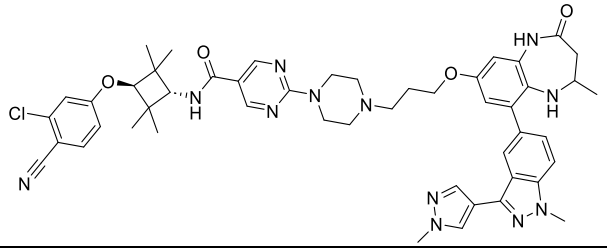
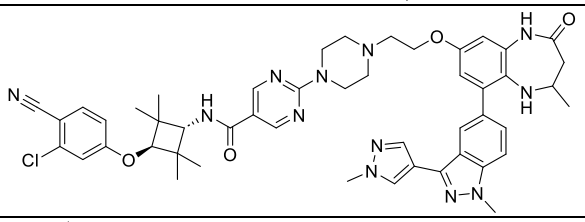
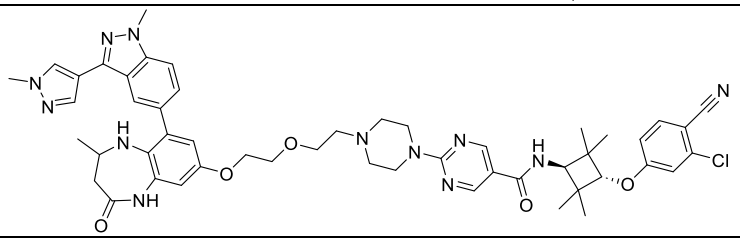
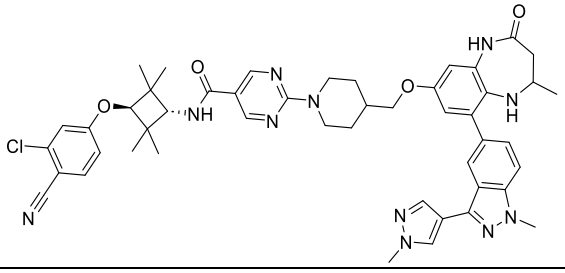
Compuesto	Estructura
1	
2	
3	

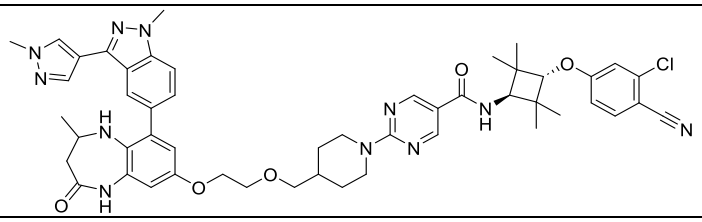
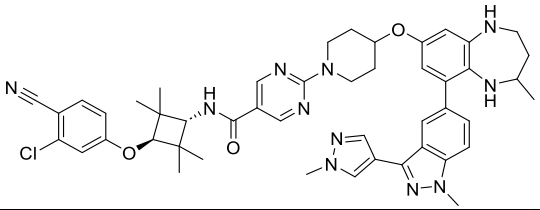
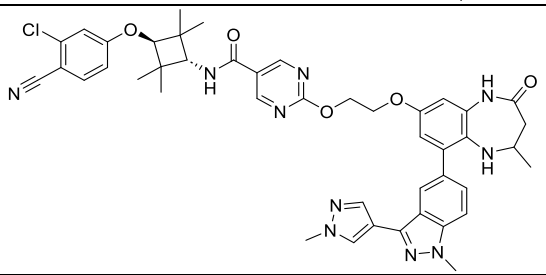
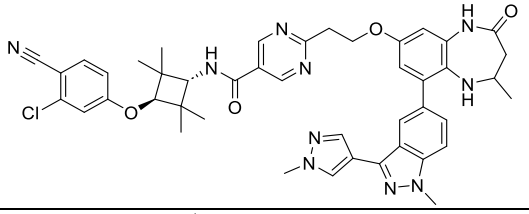
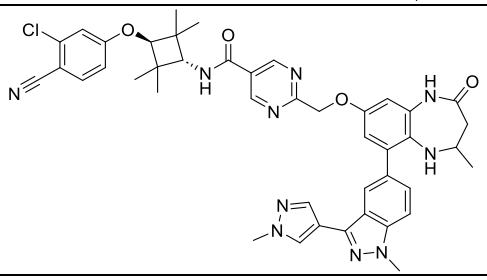
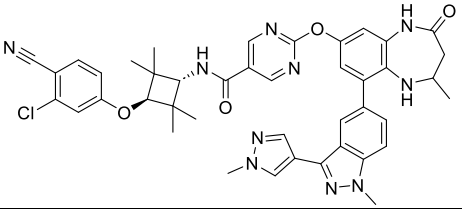
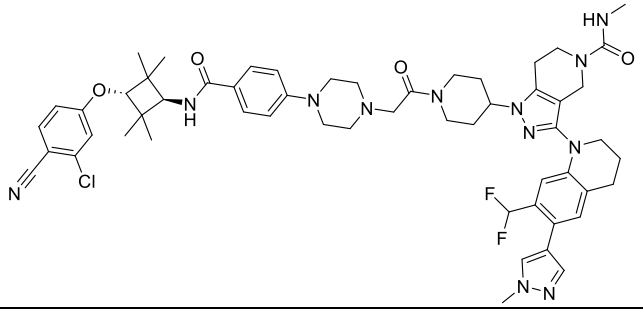
Compuesto	Estructura
4	
5	
6	
7	
8	
9	

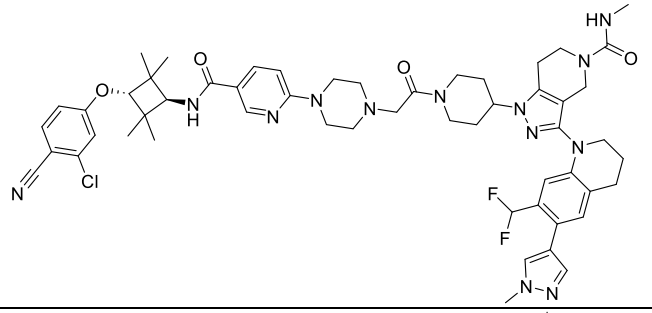
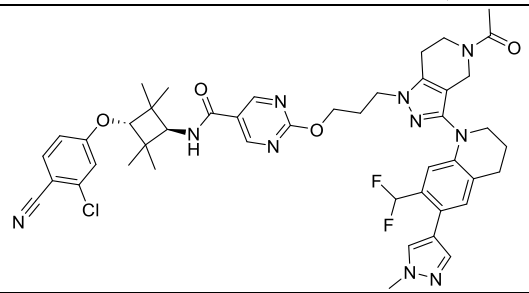
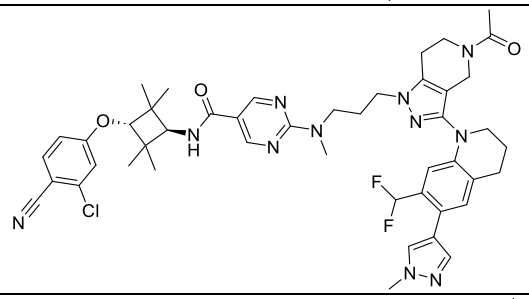
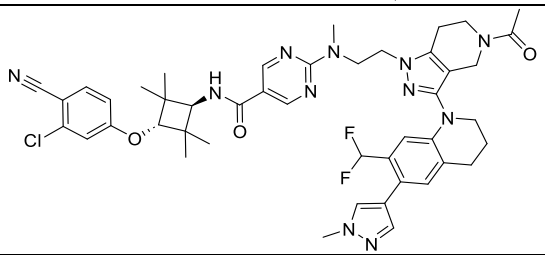
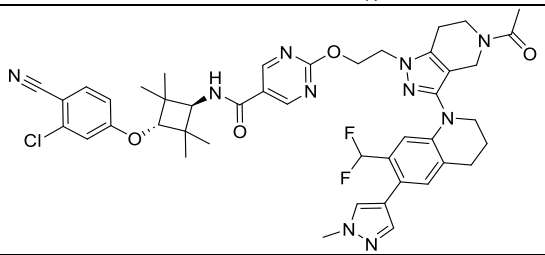
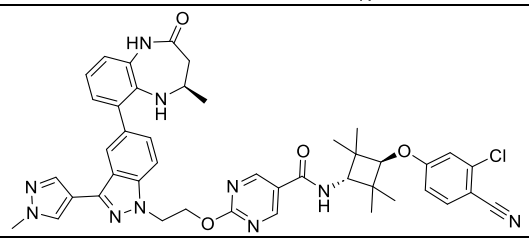
Compuesto	Estructura
10	
11	
12	
13	
14	
15	

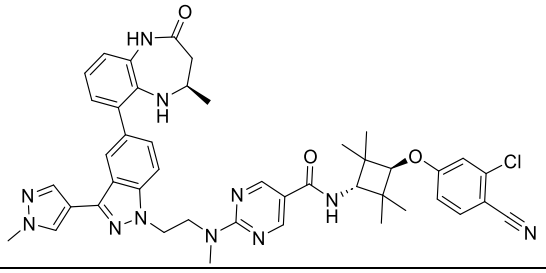
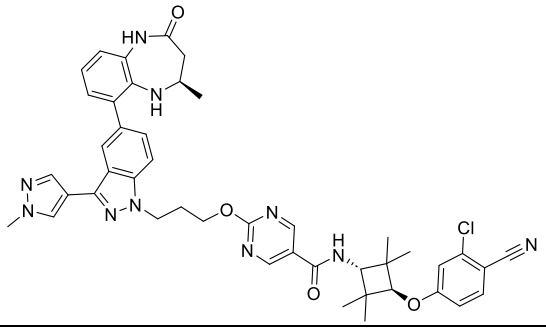
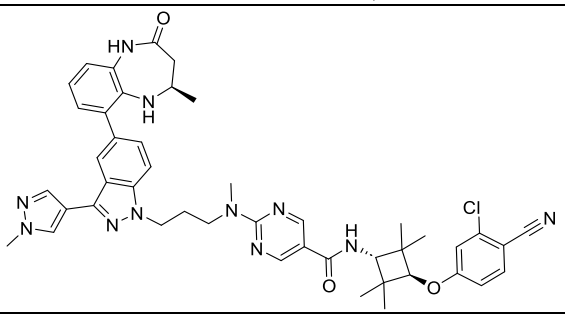
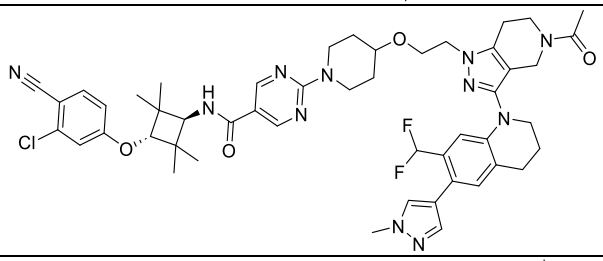
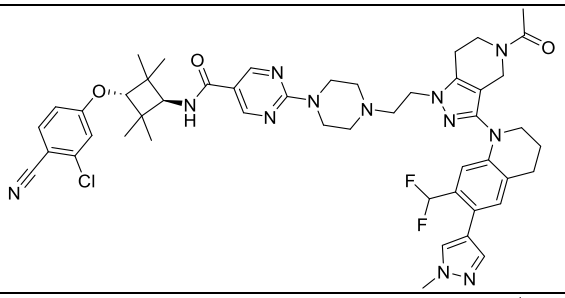
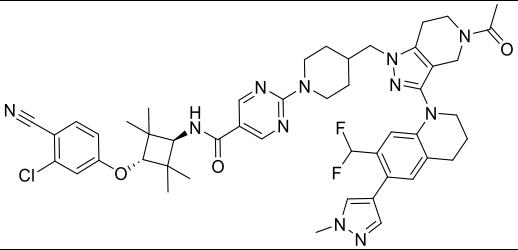
Compuesto	Estructura
16	
17	
18	
19	
20	
21	

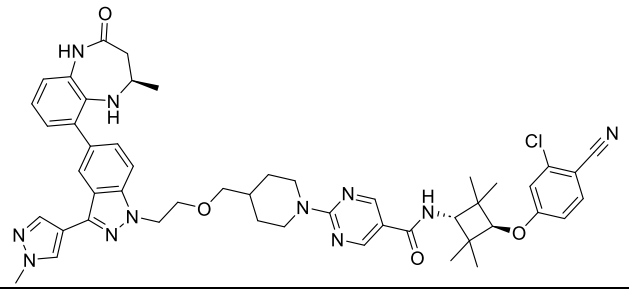
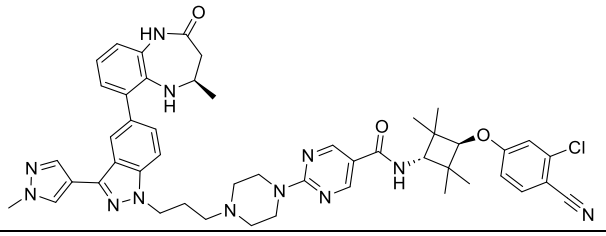
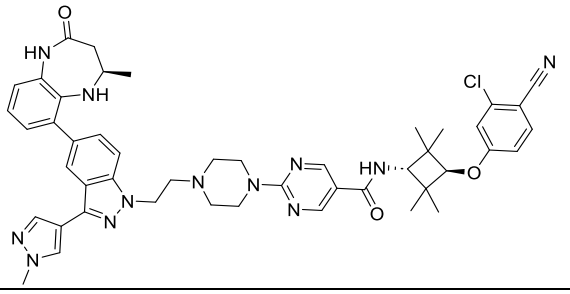
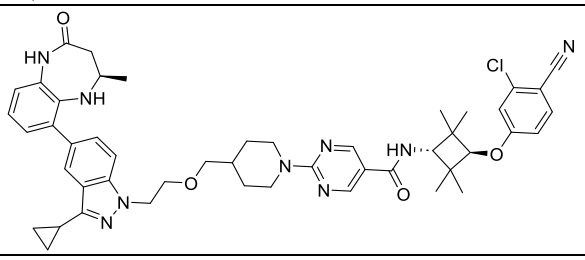
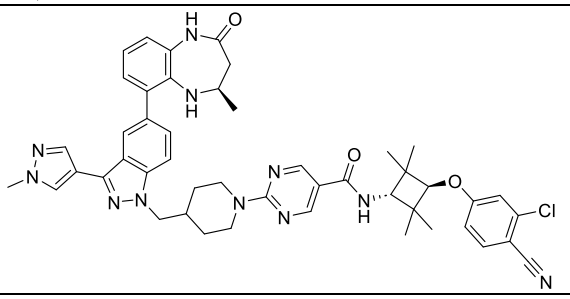
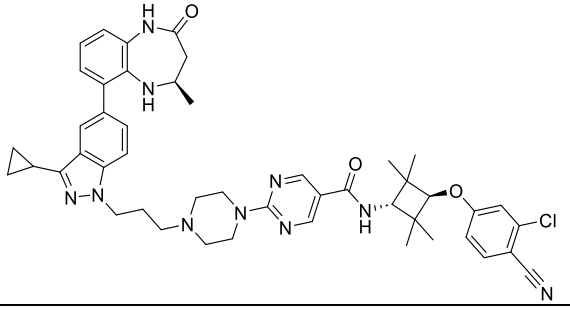
Compuesto	Estructura
22	
23	
24	
25	
26	
27	

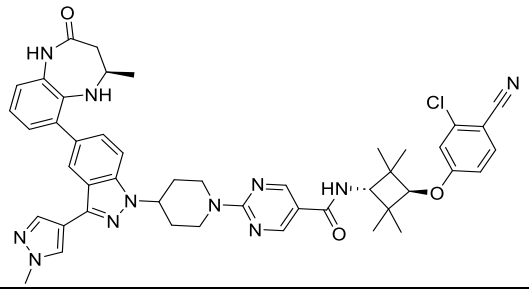
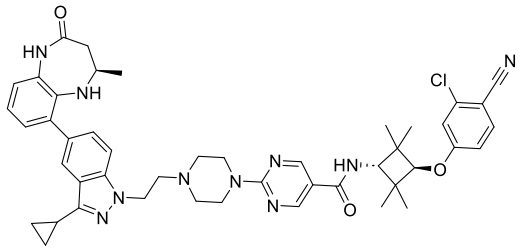
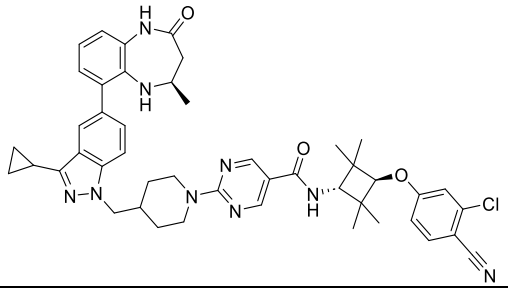
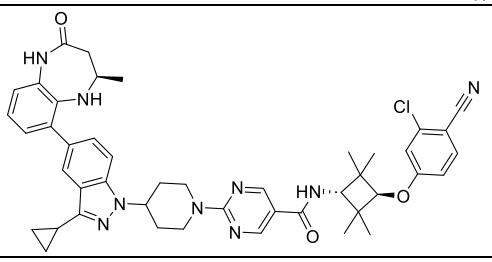
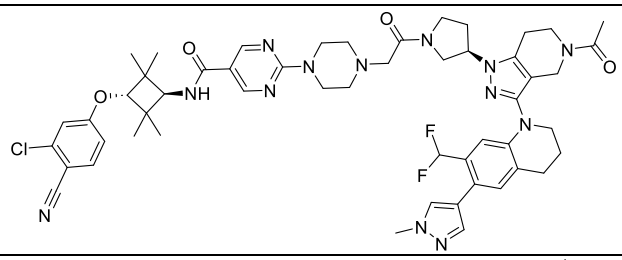
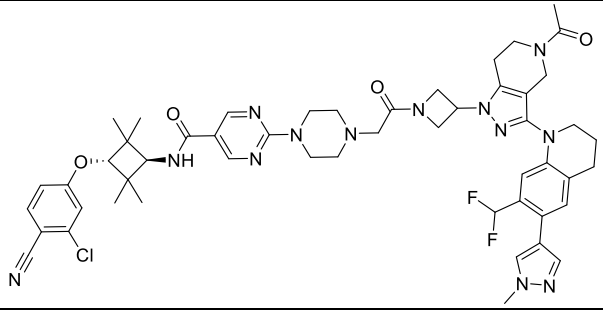
Compuesto	Estructura
28	
29	
30	
31	
32	
33	
34	

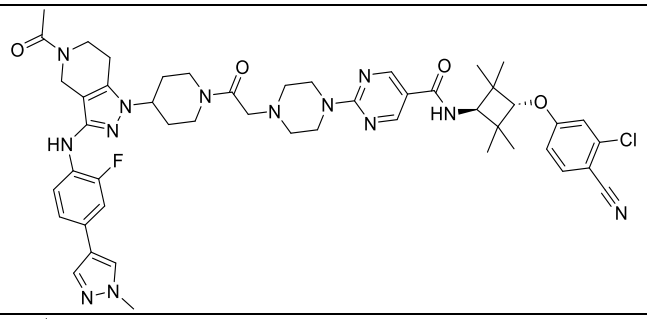
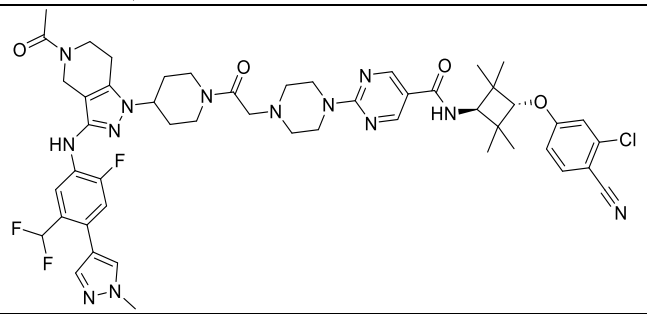
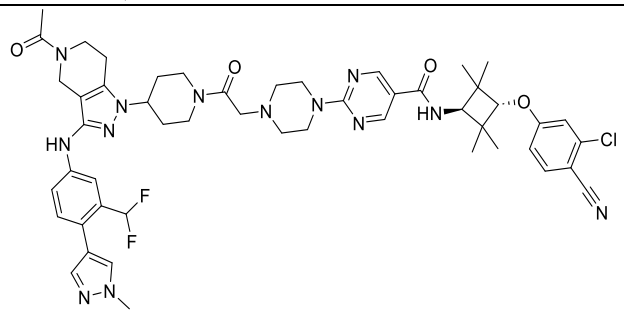
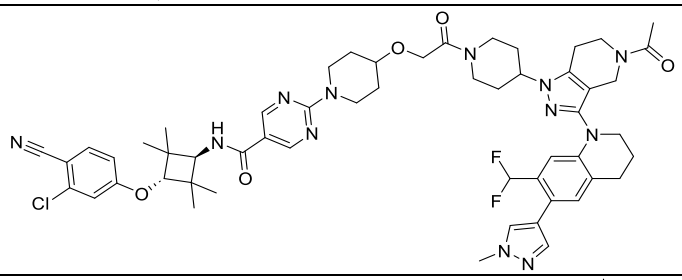
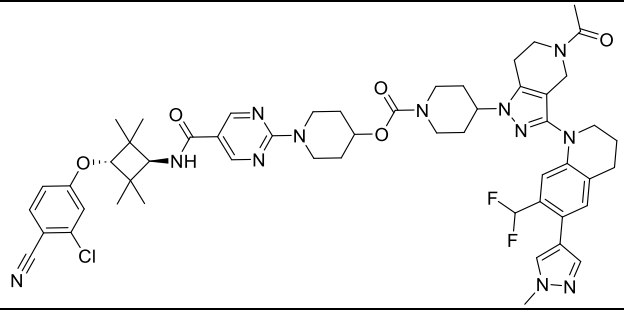
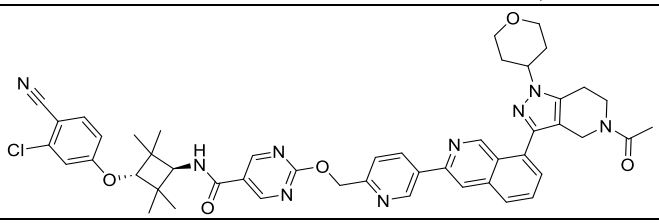
Compuesto	Estructura
35	
36	
37	
38	
39	
40	
41	

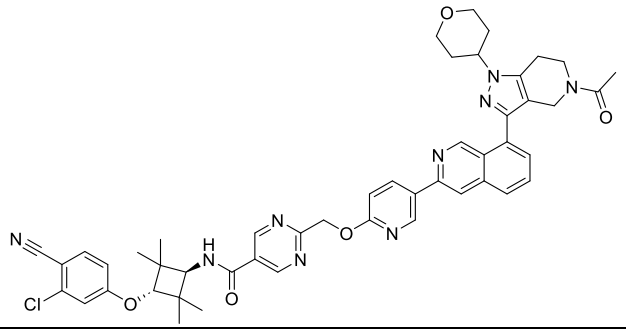
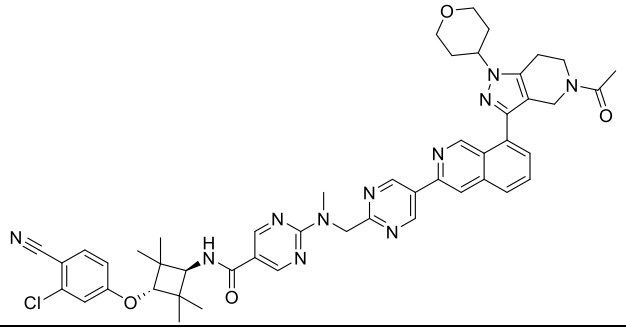
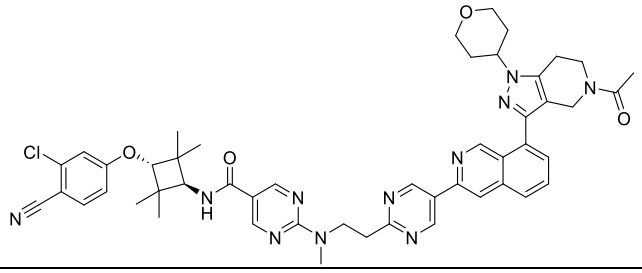
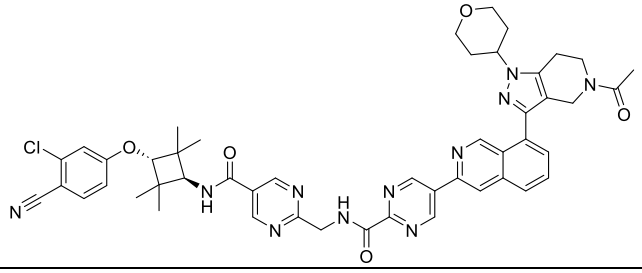
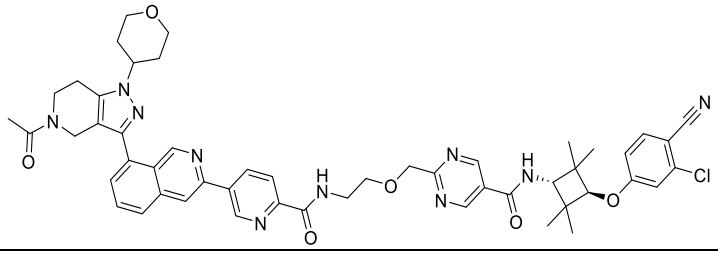
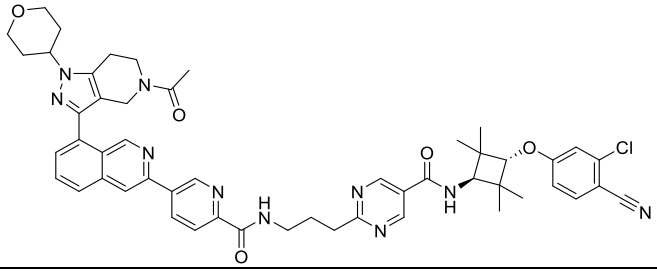
Compuesto	Estructura
42	
43	
44	
45	
46	
47	

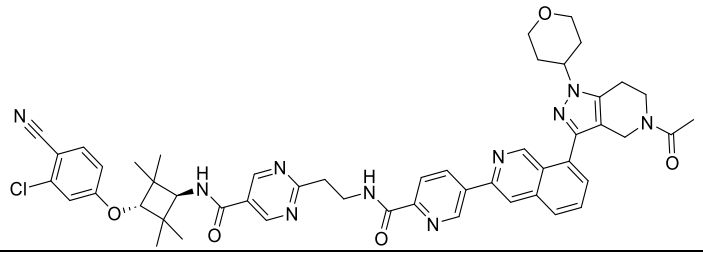
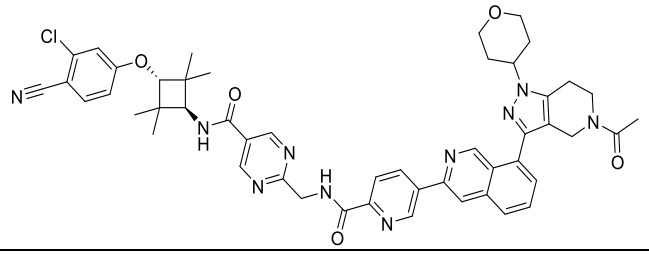
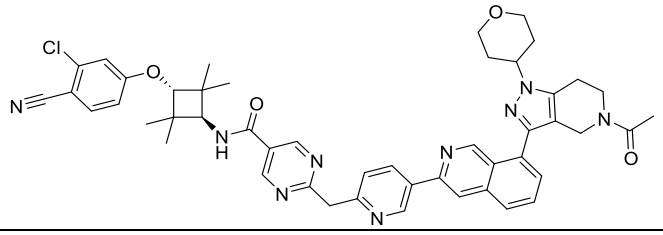
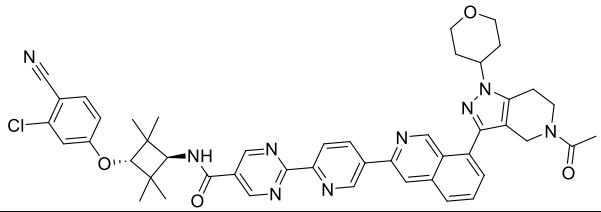
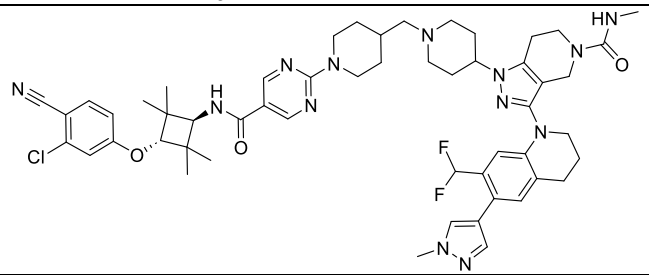
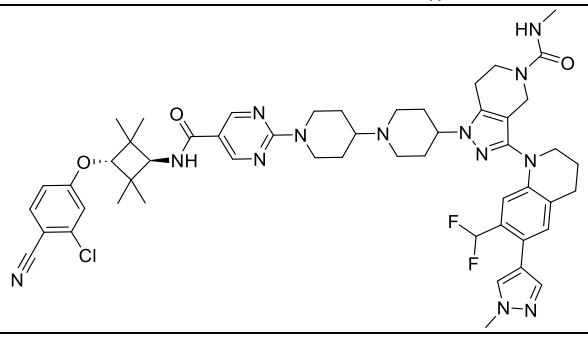
Compuesto	Estructura
48	
49	
50	
51	
52	
53	

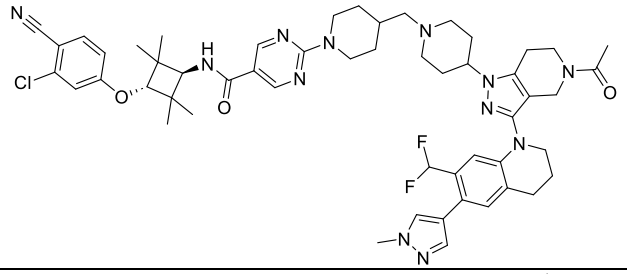
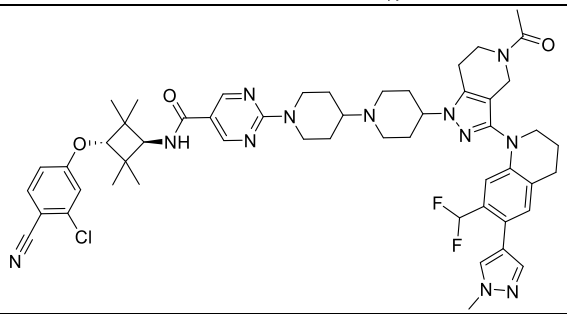
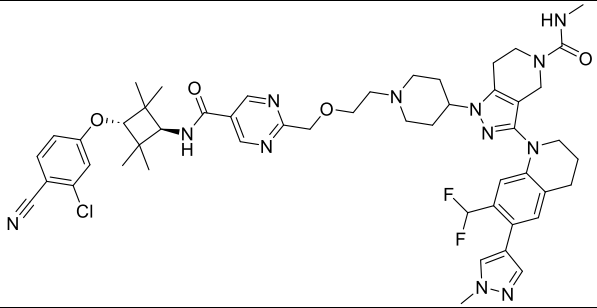
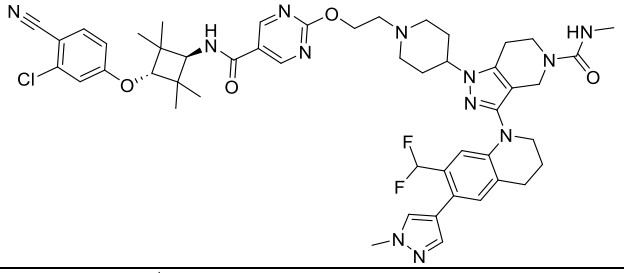
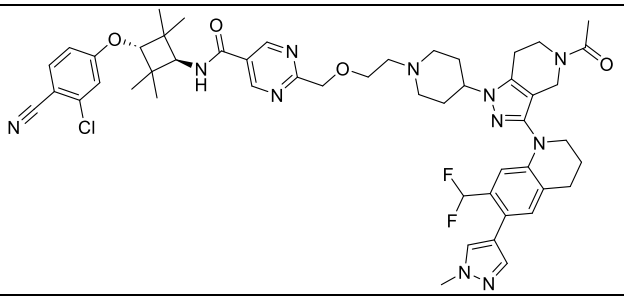
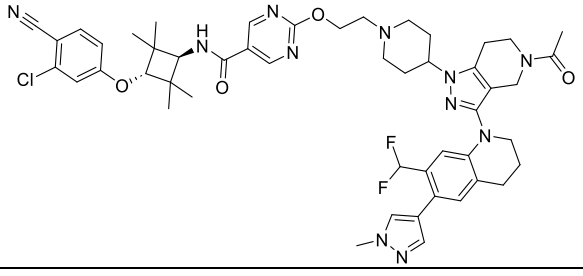
Compuesto	Estructura
54	
55	
56	
57	
58	
59	

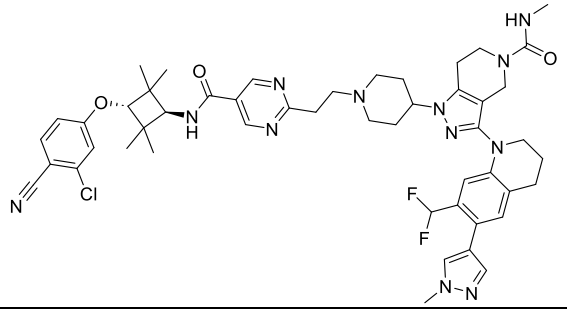
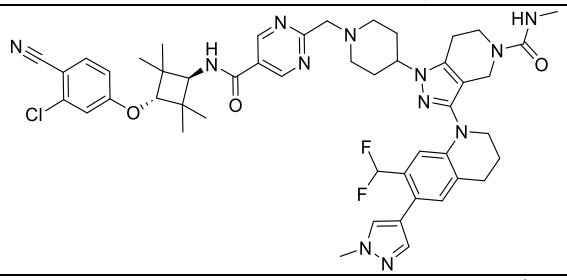
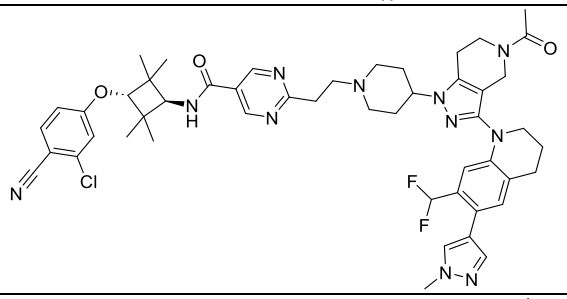
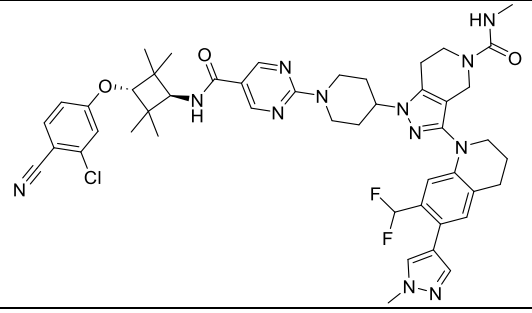
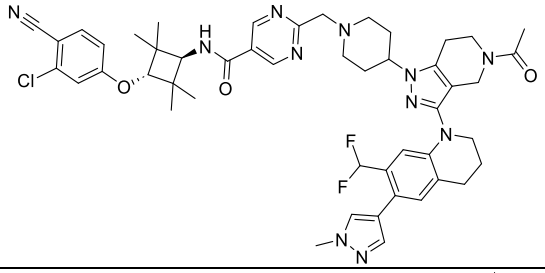
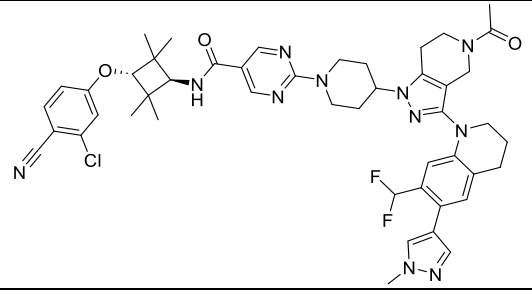
Compuesto	Estructura
60	
61	
62	
63	
64	
65	

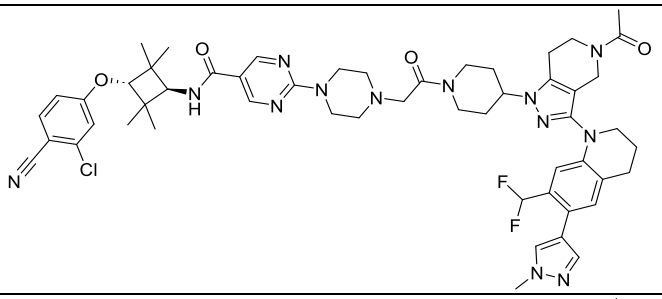
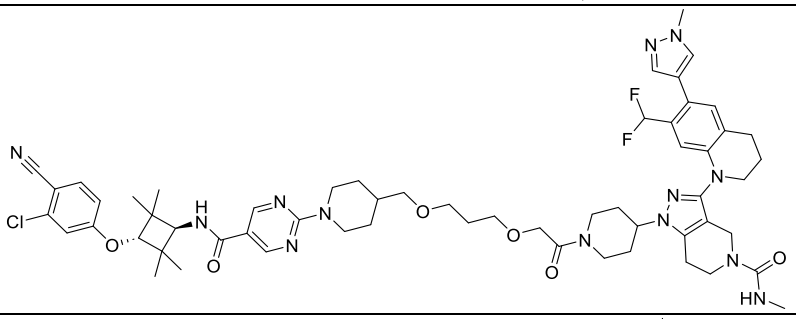
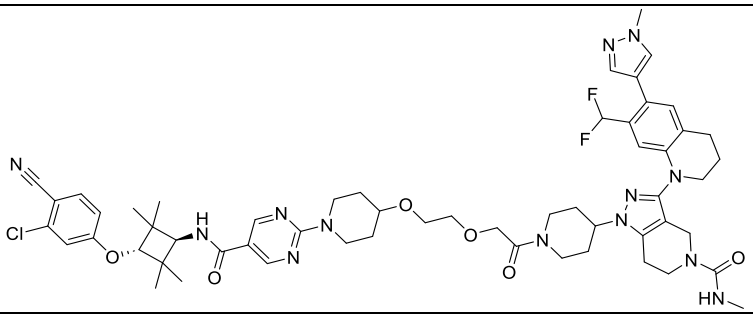
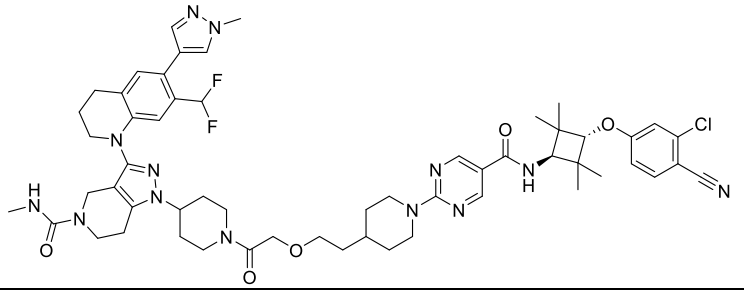
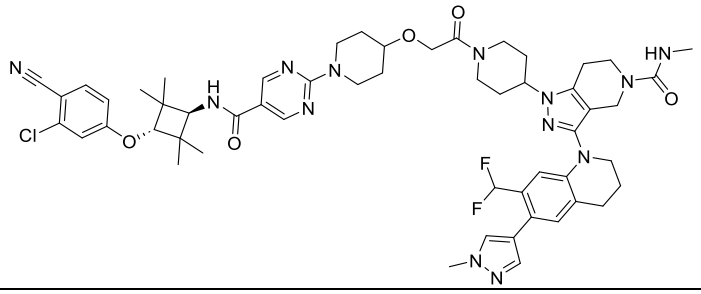
Compuesto	Estructura
66	
67	
68	
69	
70	
71	

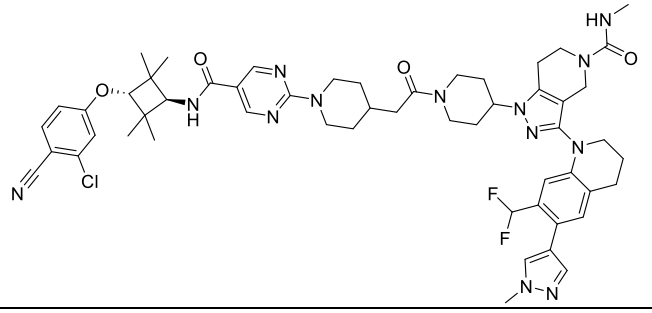
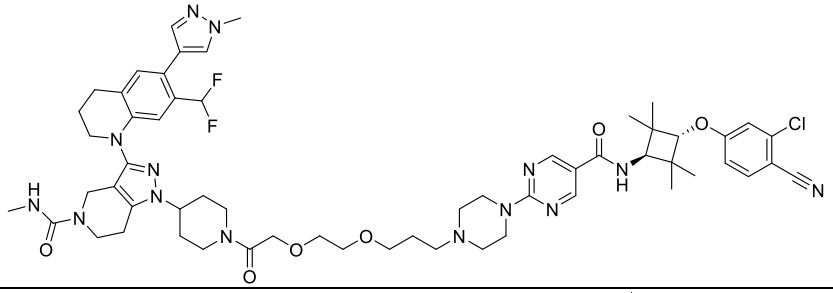
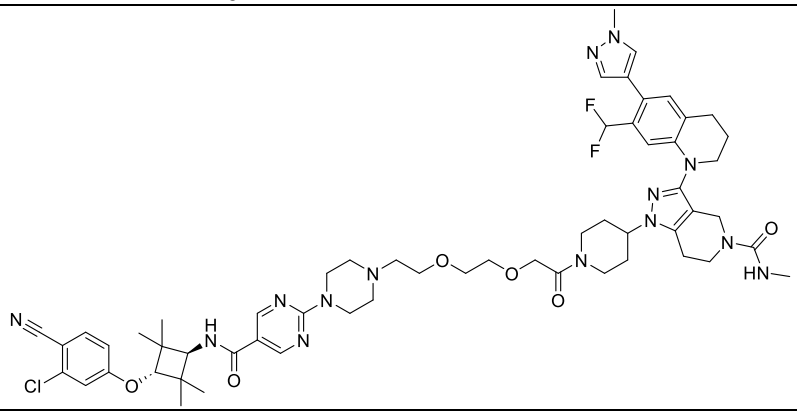
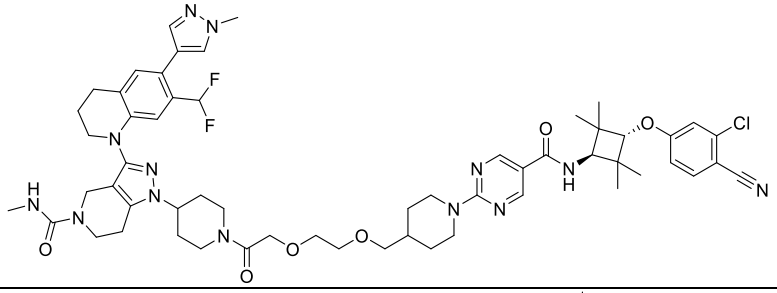
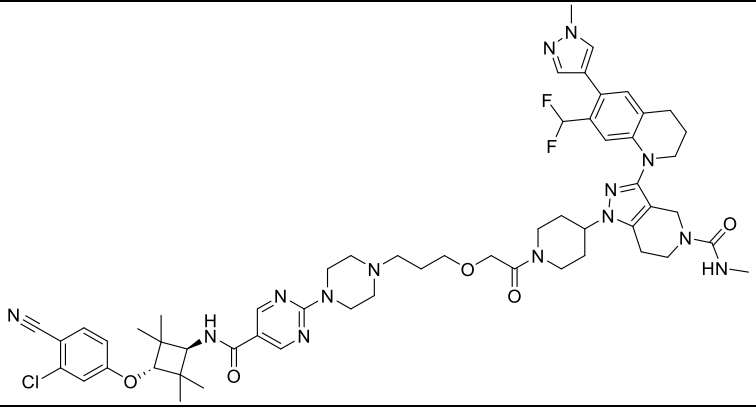
Compuesto	Estructura
72	
73	
74	
75	
76	
77	

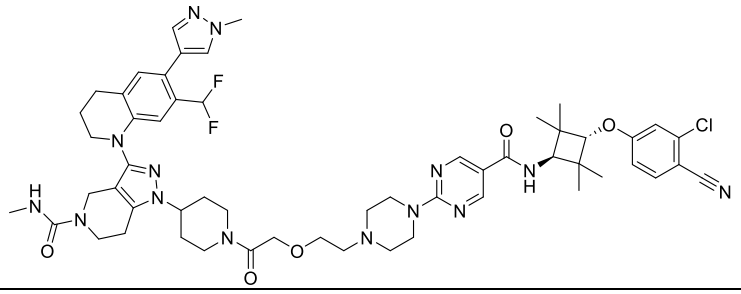
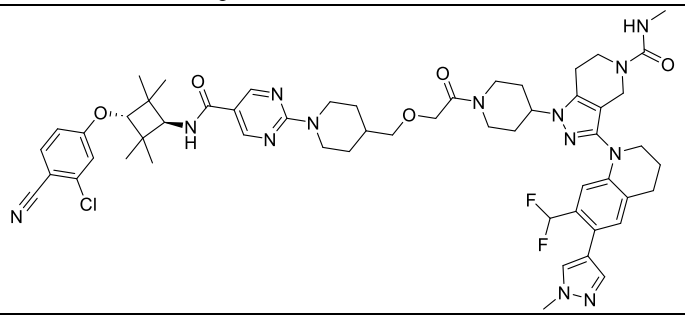
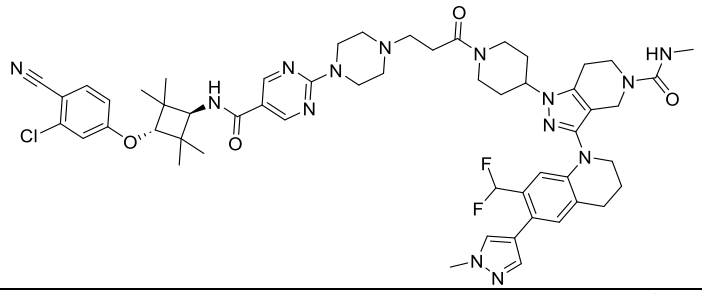
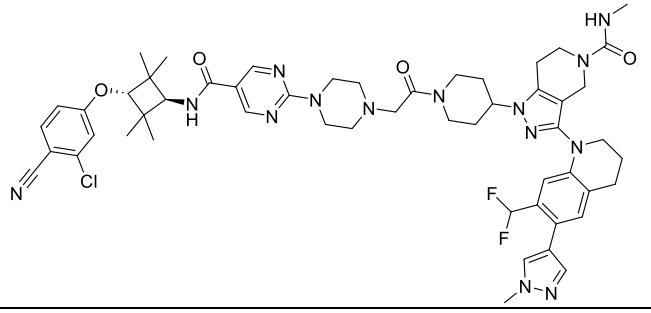
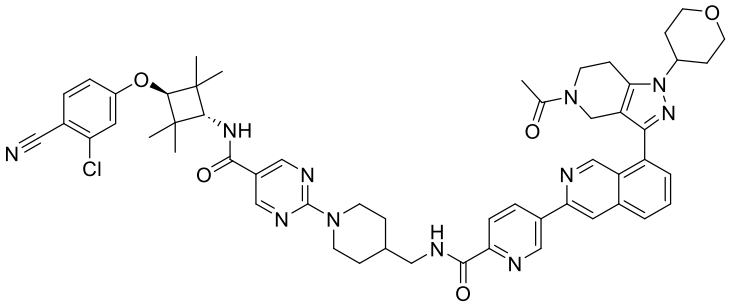
Compuesto	Estructura
78	
79	
80	
81	
82	
83	

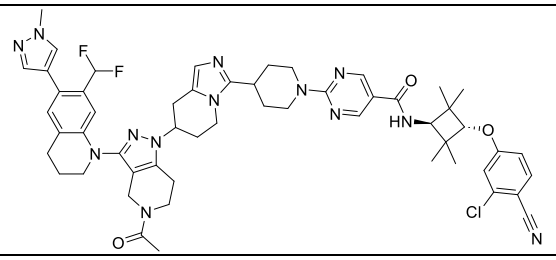
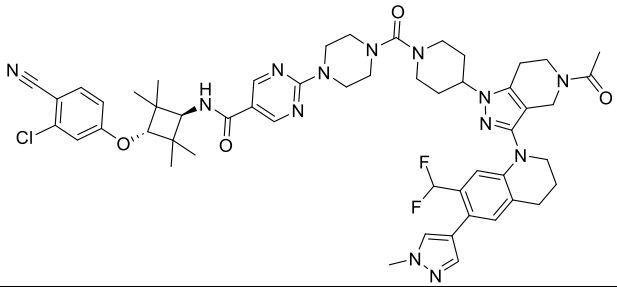
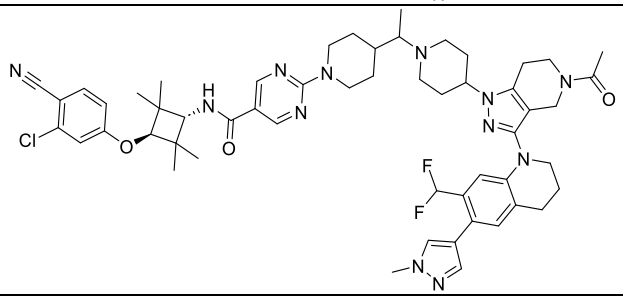
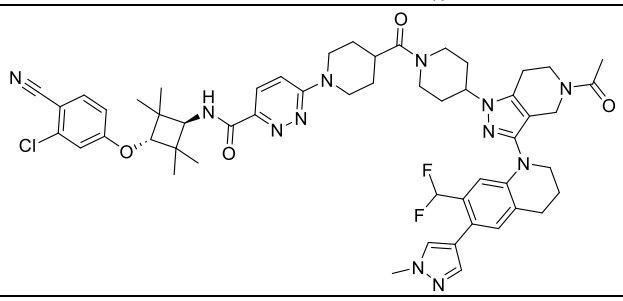
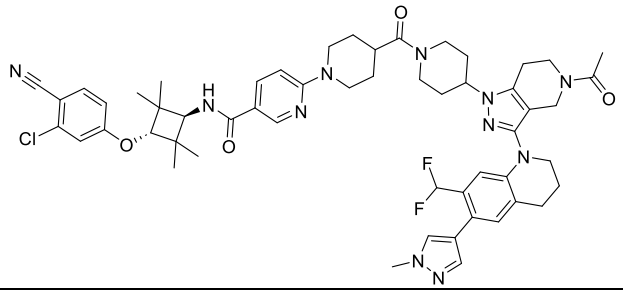
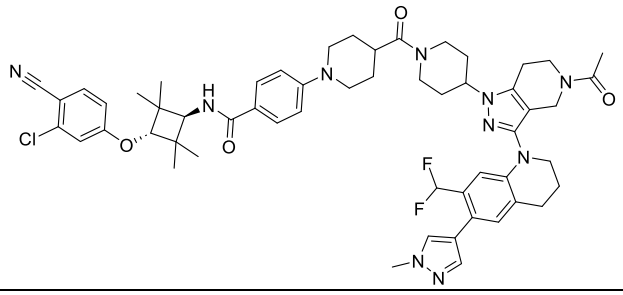
Compuesto	Estructura
84	
85	
86	
87	
88	
89	

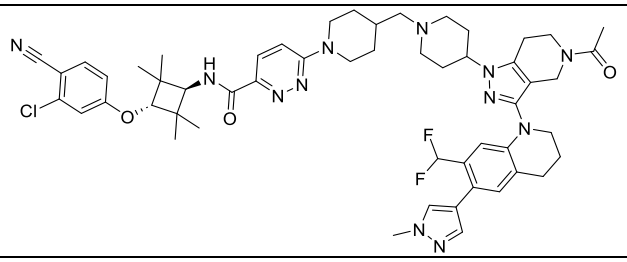
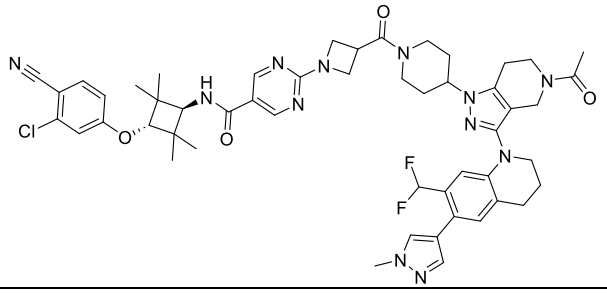
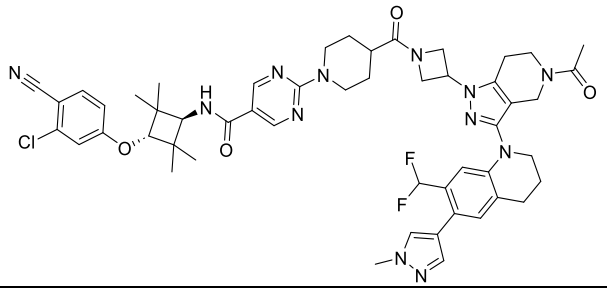
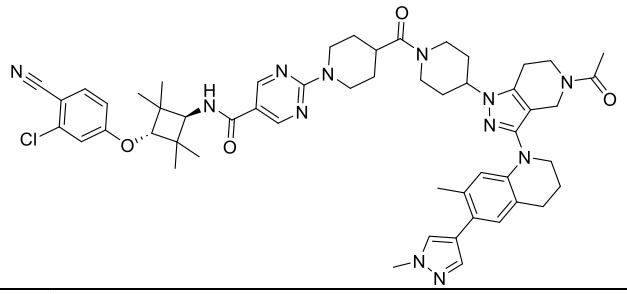
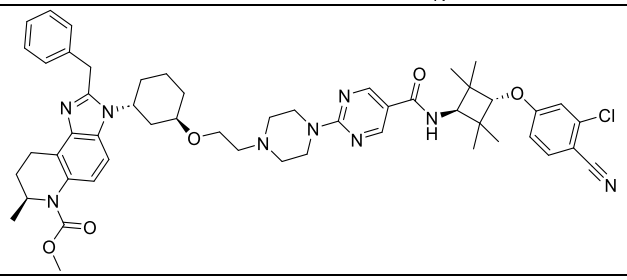
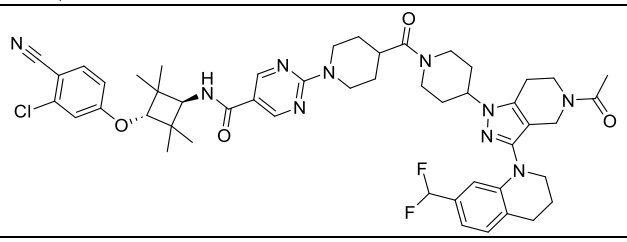
Compuesto	Estructura
90	
91	
92	
93	
94	
95	

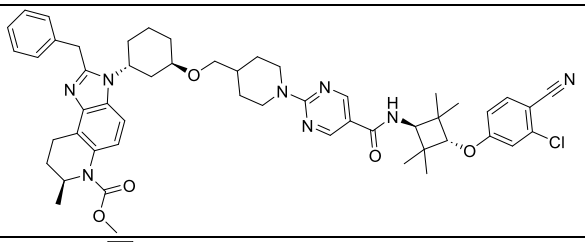
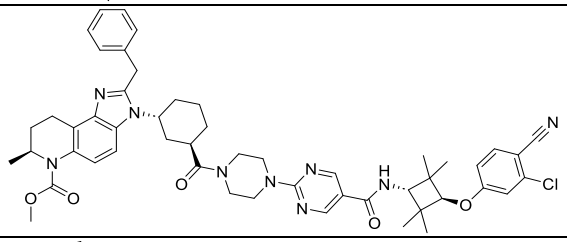
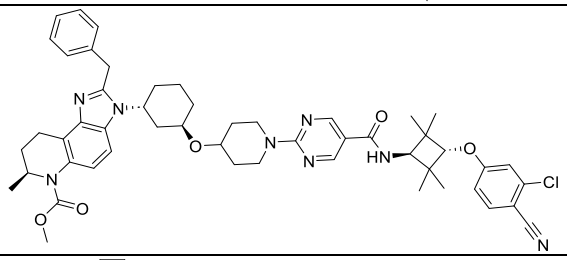
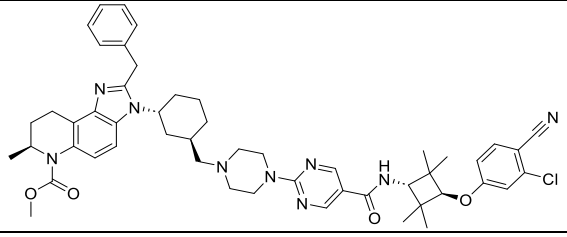
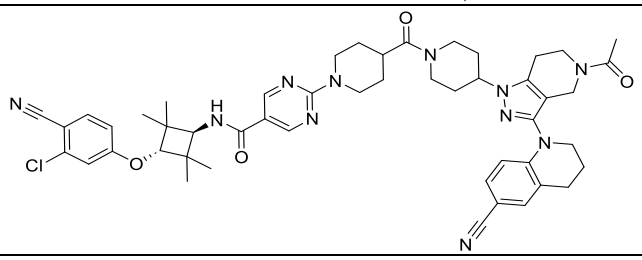
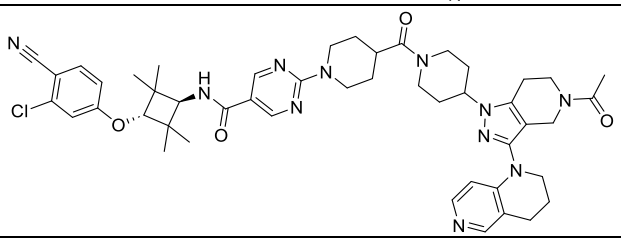
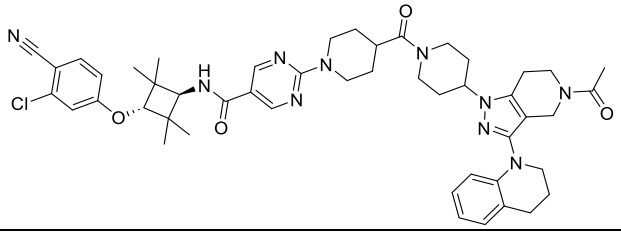
Compuesto	Estructura
96	
97	
98	
99	
100	

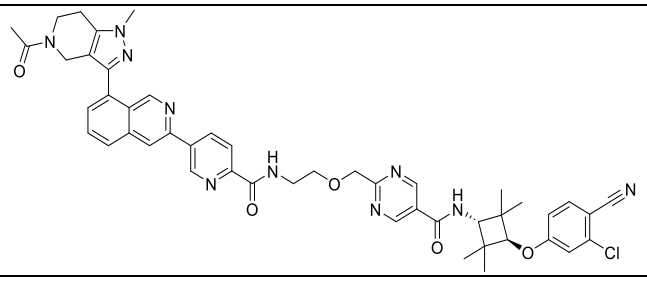
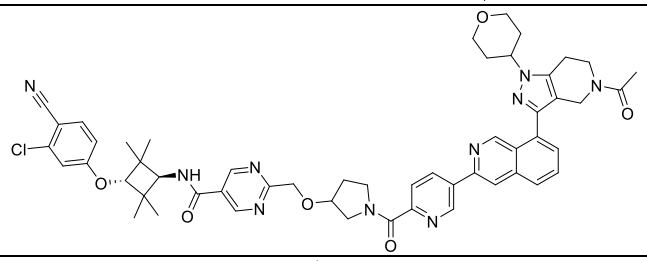
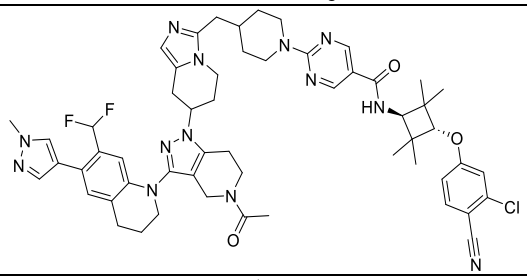
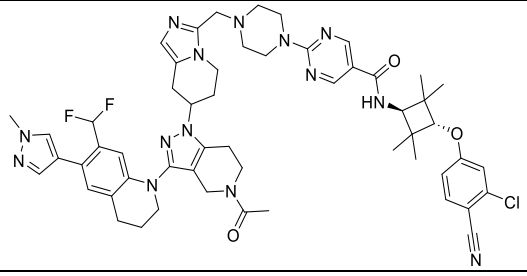
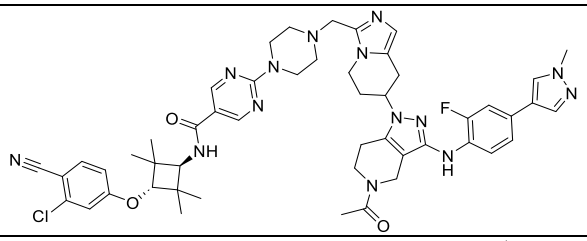
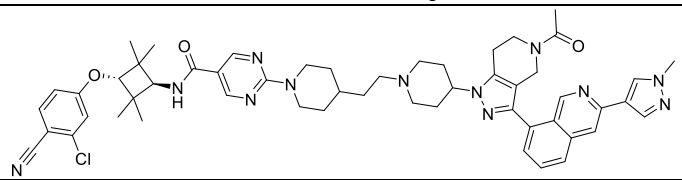
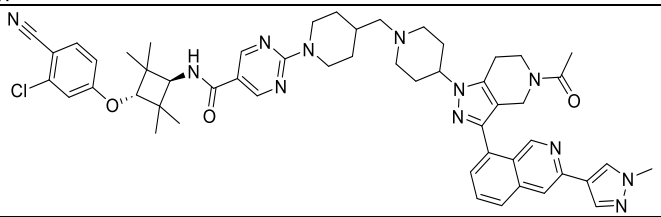
Compuesto	Estructura
101	
102	
103	
104	
105	

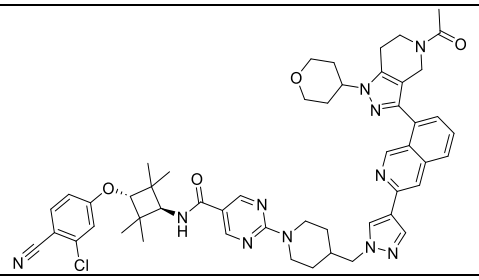
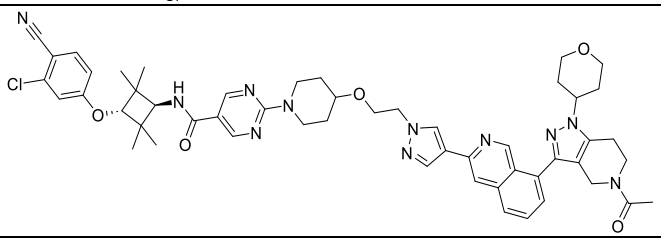
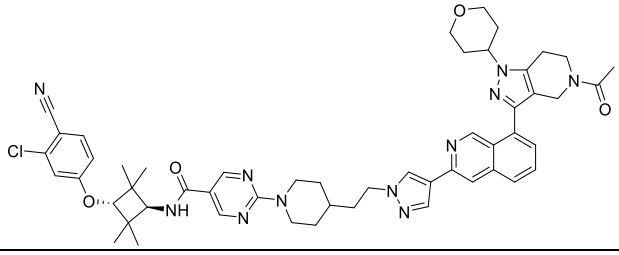
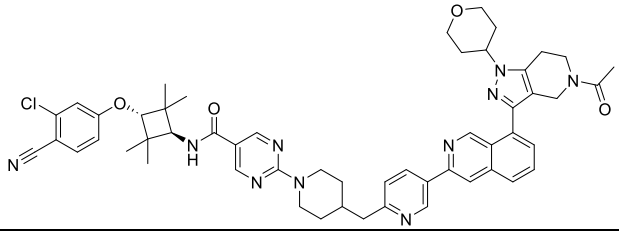
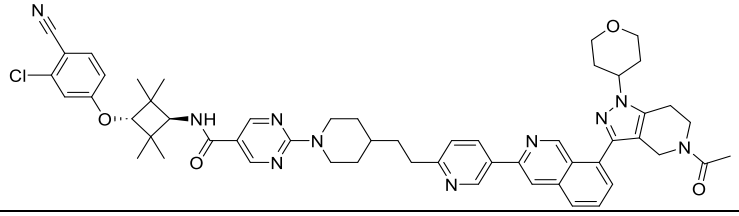
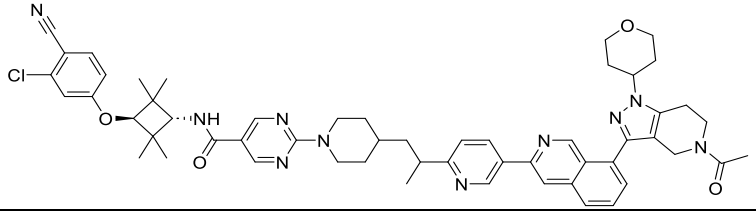
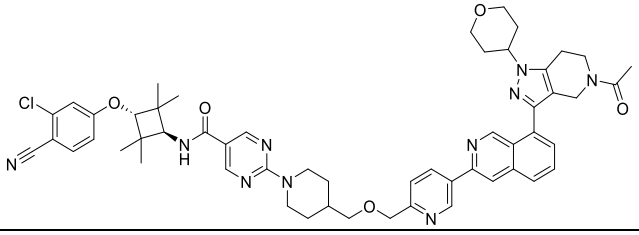
Compuesto	Estructura
106	
107	
108	
109	
110	

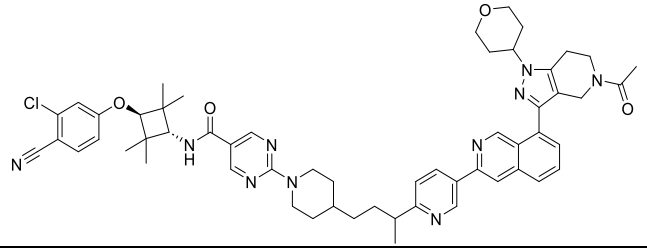
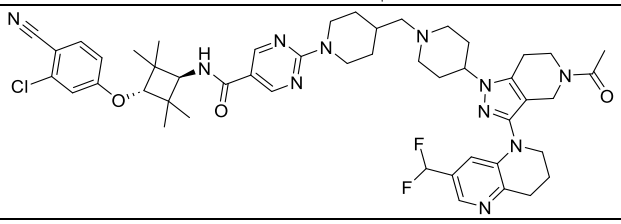
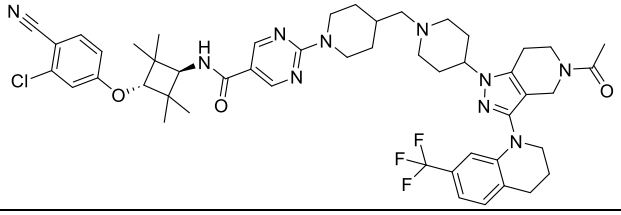
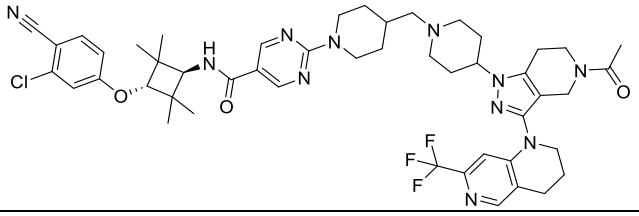
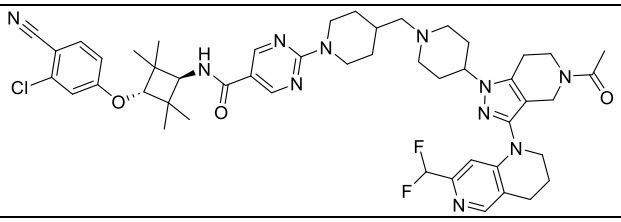
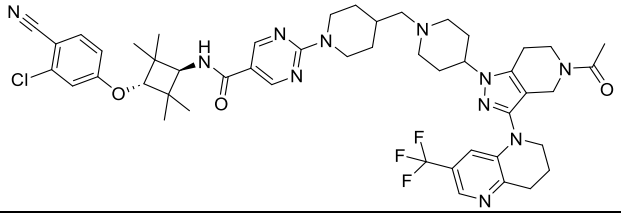
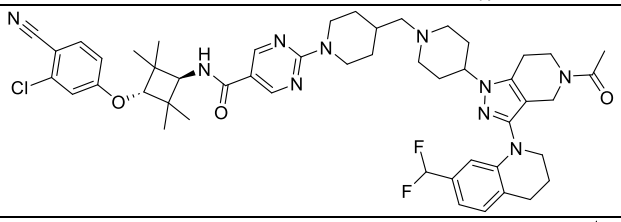
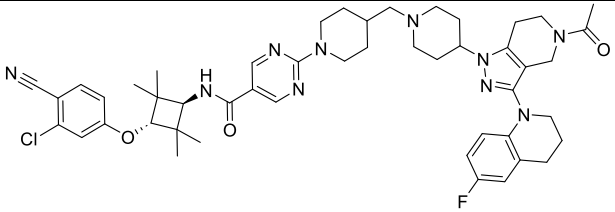
Compuesto	Estructura
111	
112	
113	
114	
115	
116	

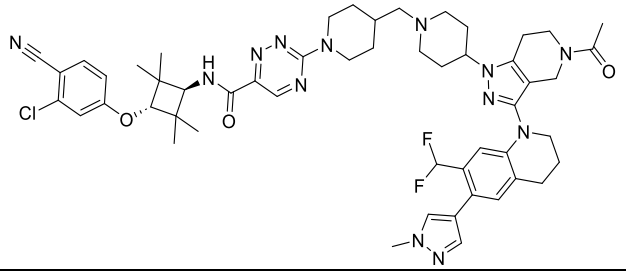
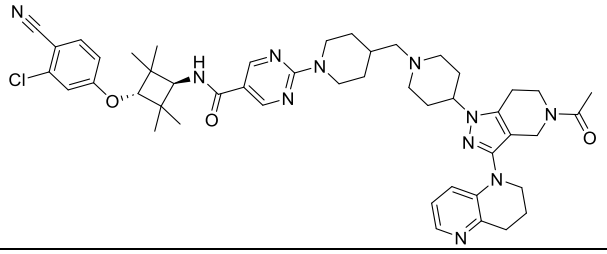
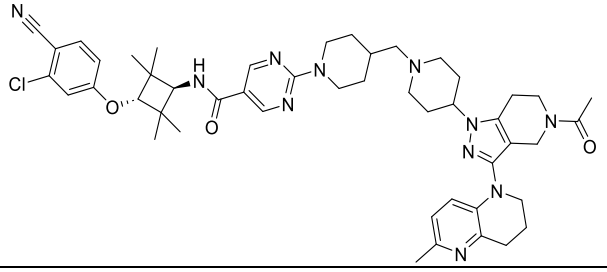
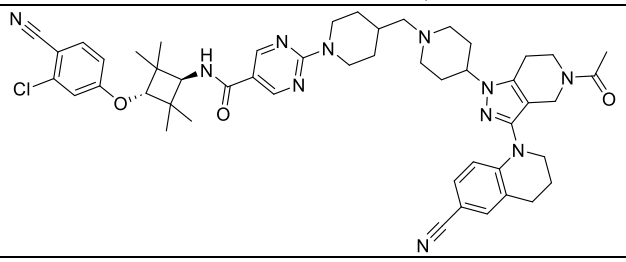
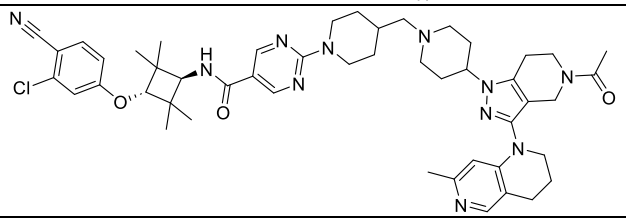
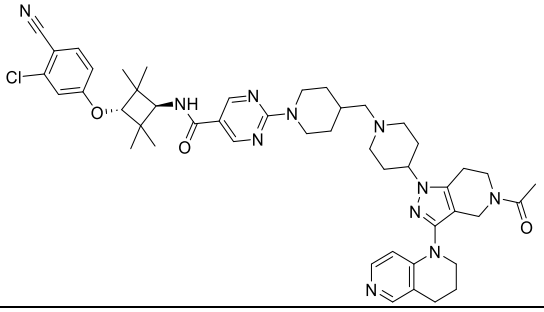
Compuesto	Estructura
117	
118	
119	
120	
121	
122	

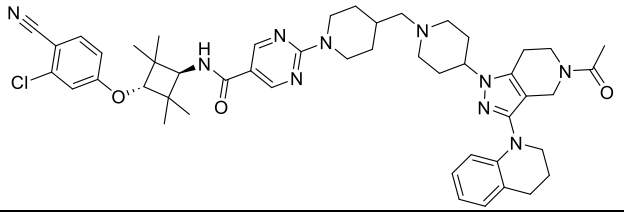
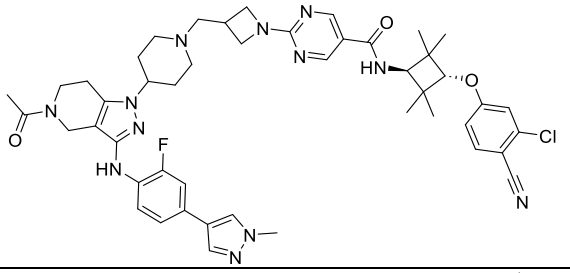
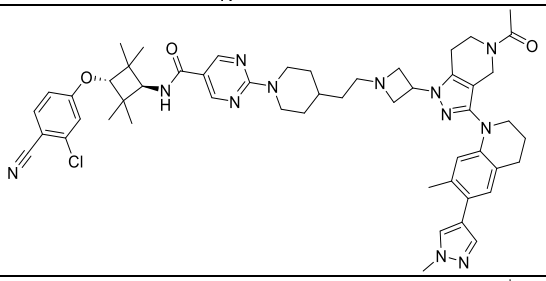
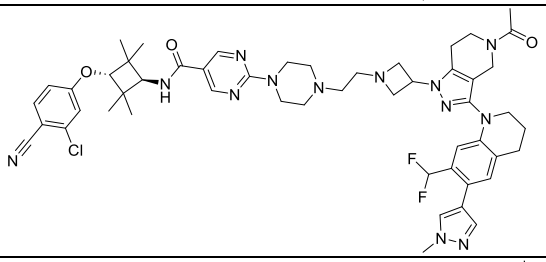
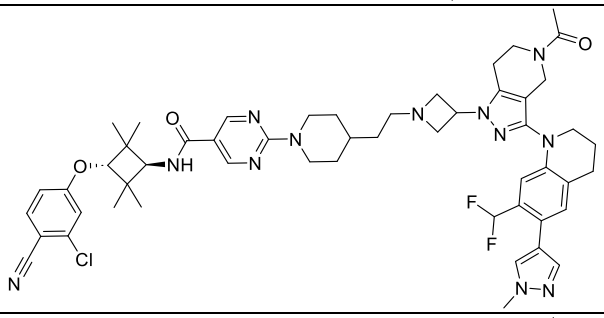
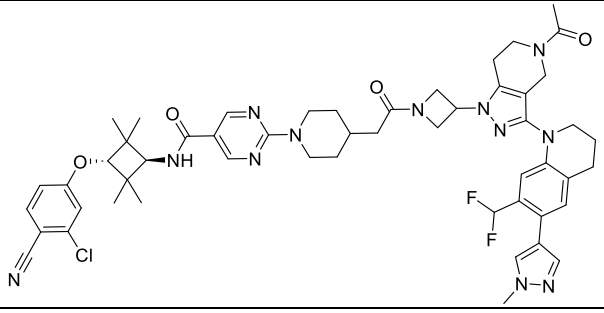
Compuesto	Estructura
123	
124	
125	
126	
127	
128	
129	

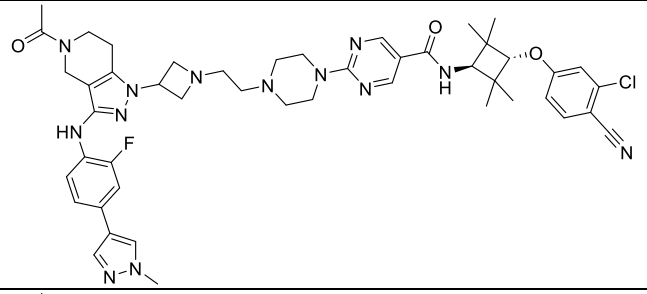
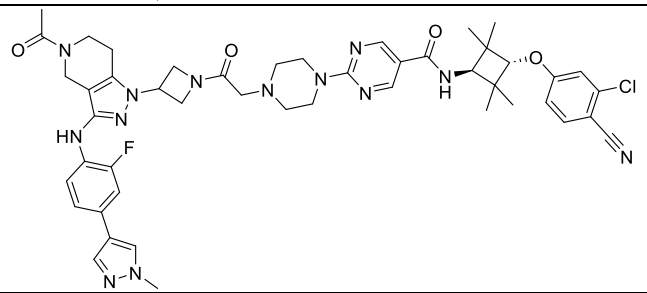
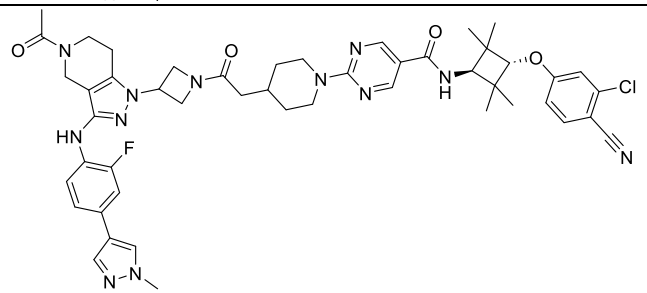
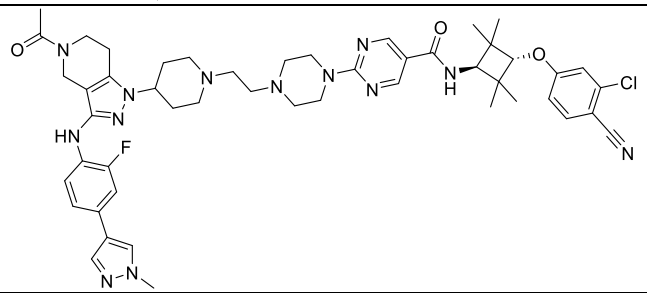
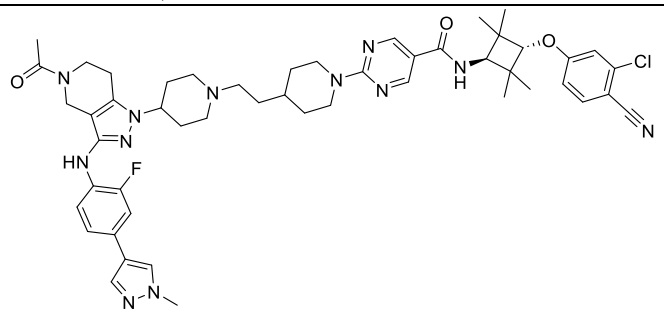
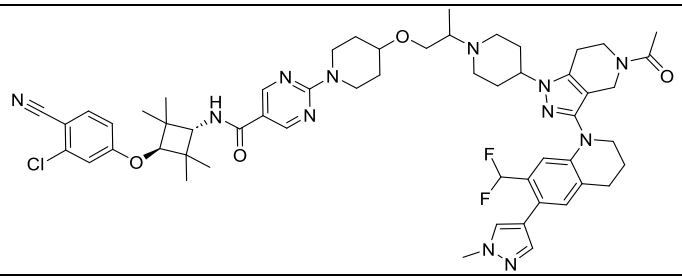
Compuesto	Estructura
130	
131	
132	
133	
134	
135	
136	

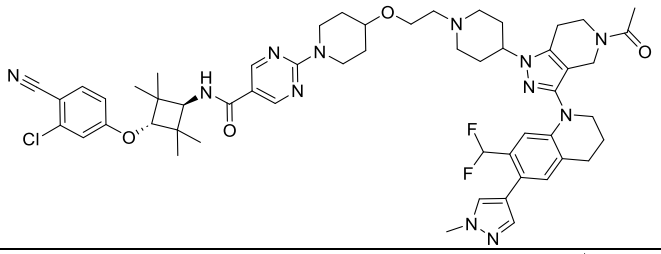
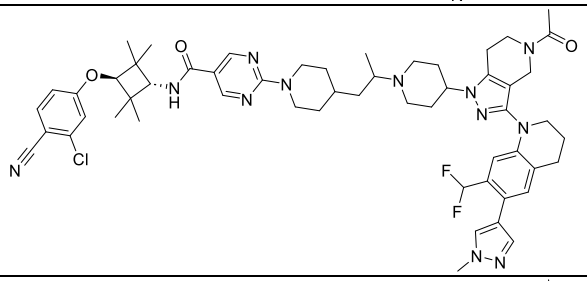
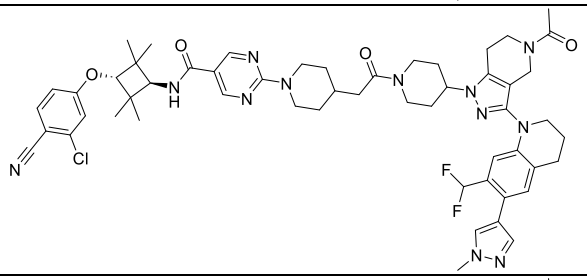
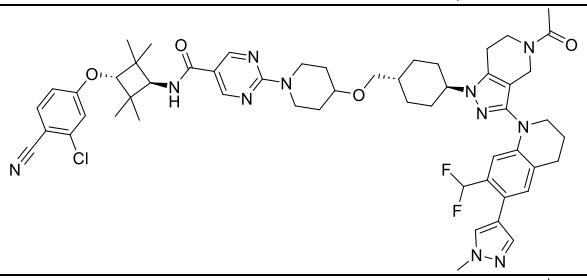
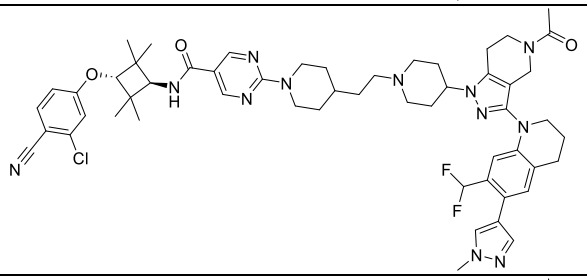
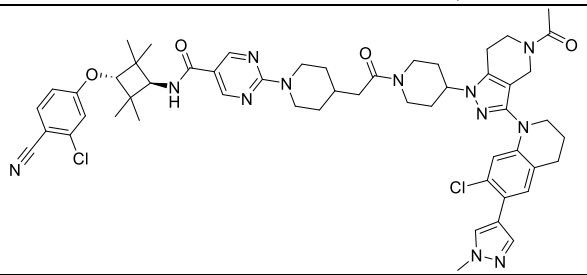
Compuesto	Estructura
137	
138	
139	
140	
141	
142	
143	

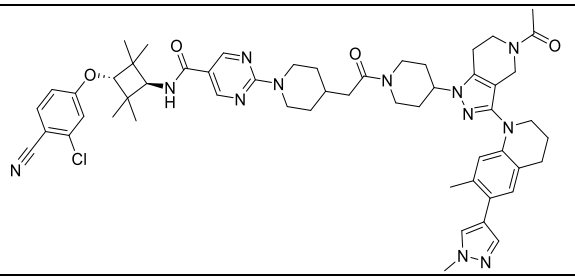
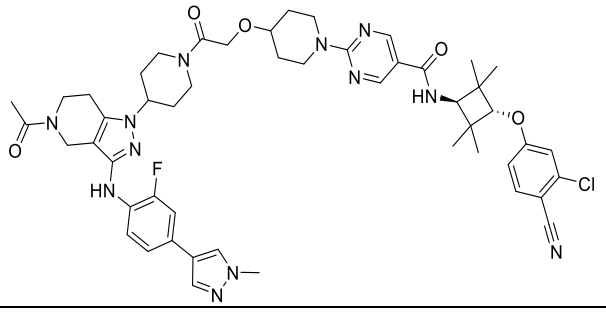
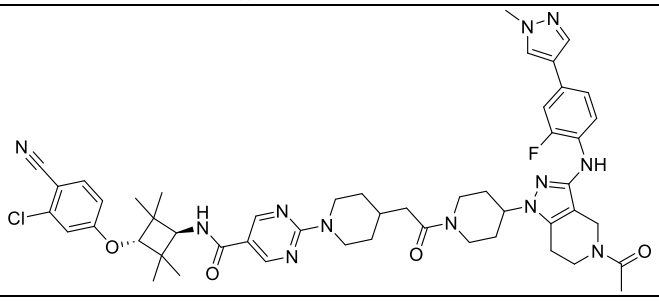
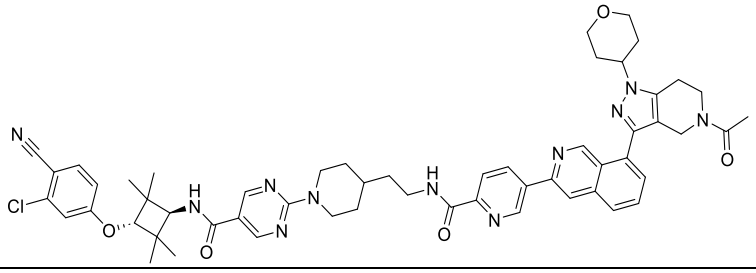
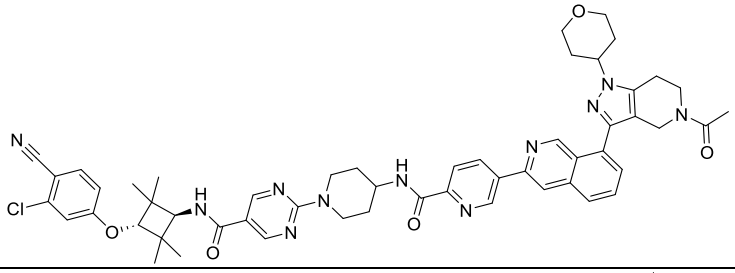
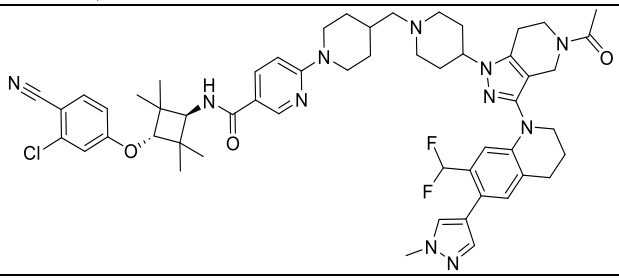
Compuesto	Estructura
144	
145	
146	
147	
148	
149	
150	
151	

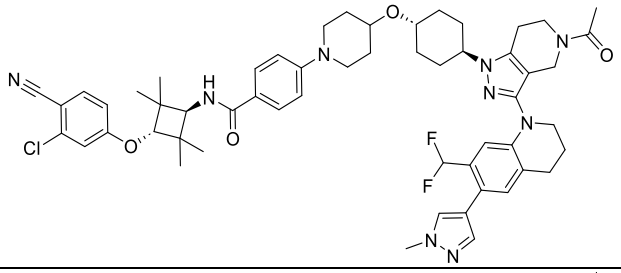
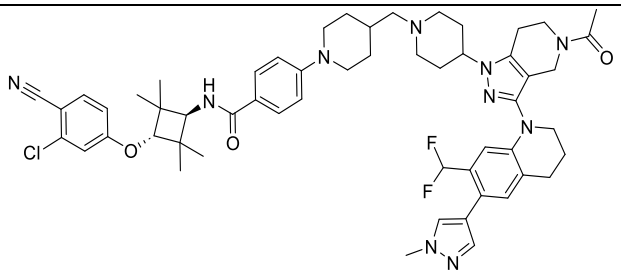
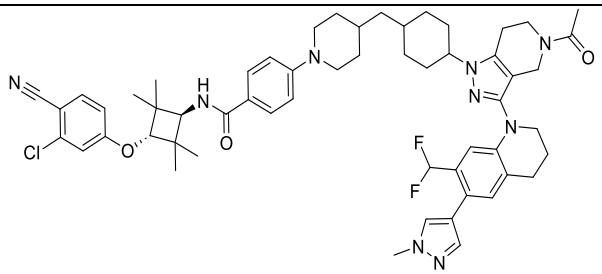
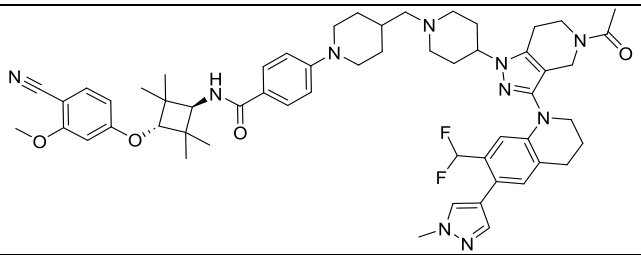
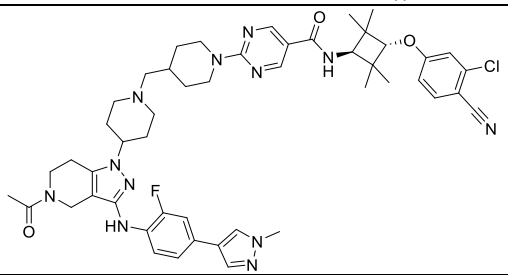
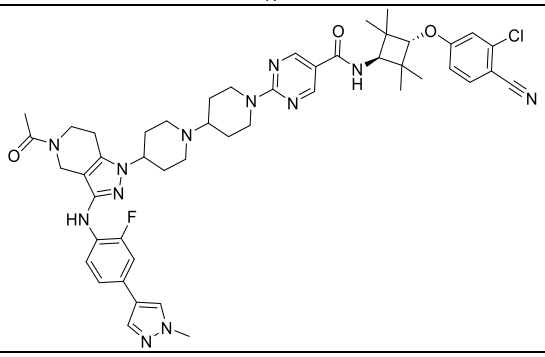
Compuesto	Estructura
152	
153	
154	
155	
156	
157	

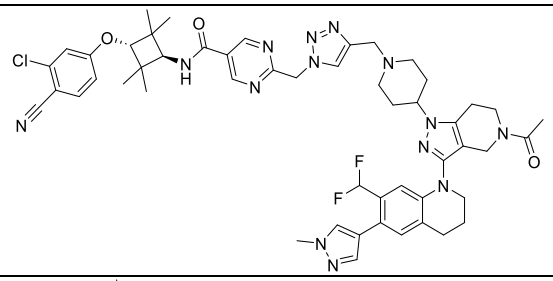
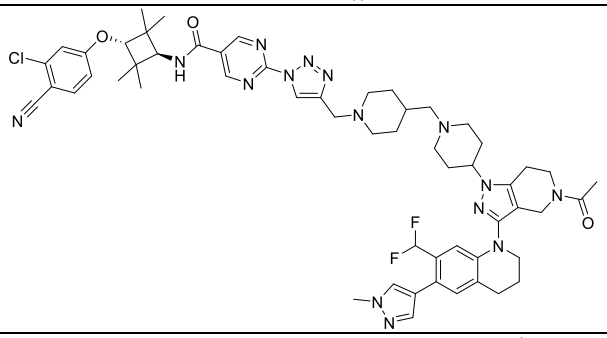
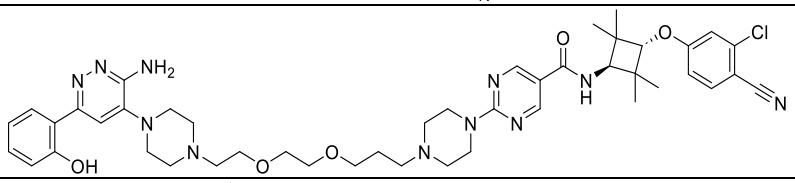
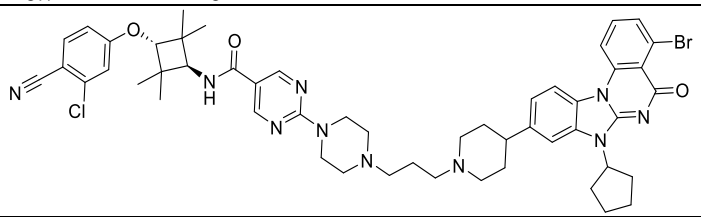
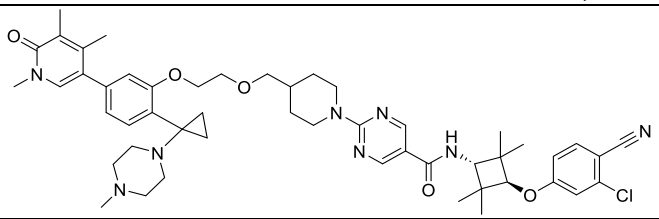
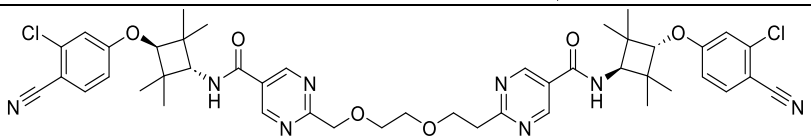
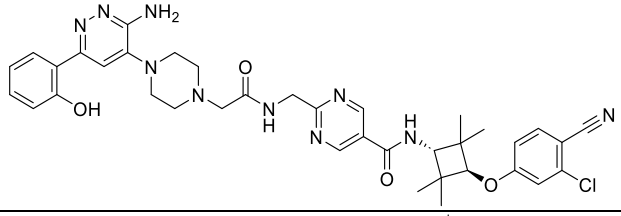
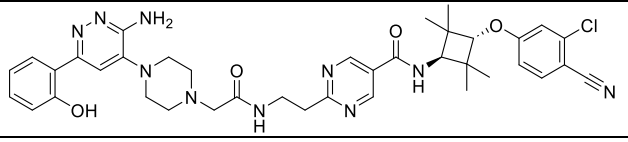
Compuesto	Estructura
158	
159	
160	
161	
162	
163	

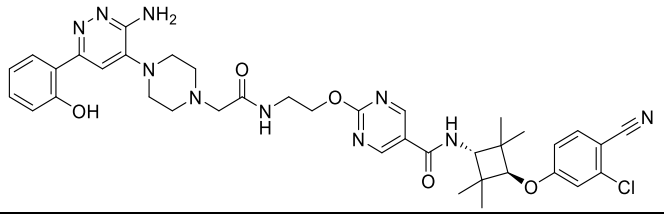
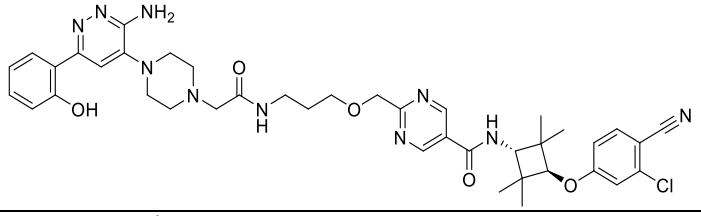
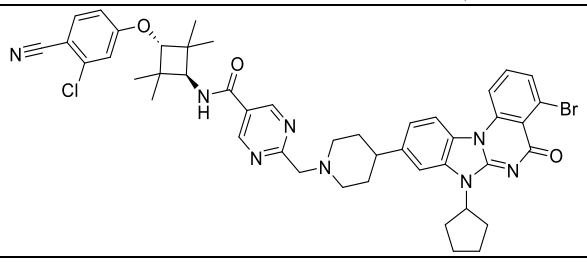
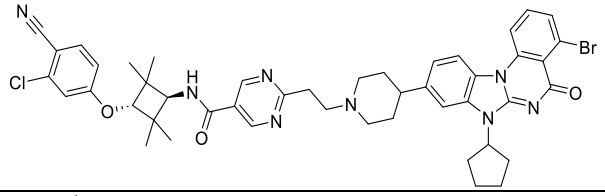
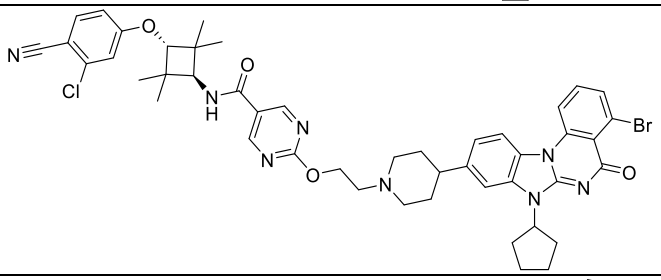
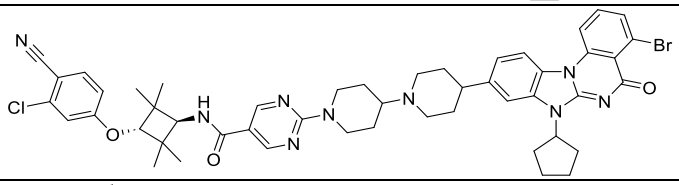
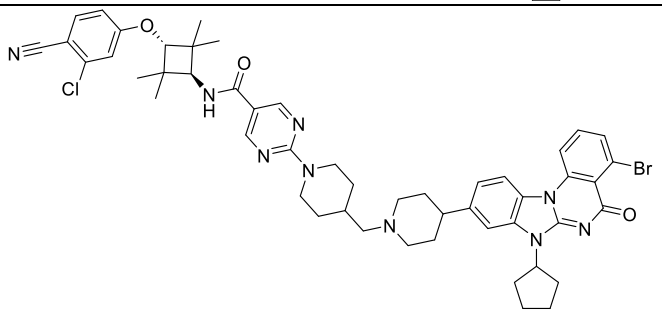
Compuesto	Estructura
164	
165	
166	
167	
168	
169	

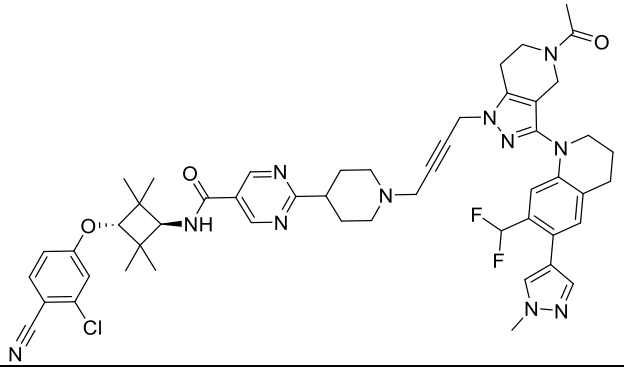
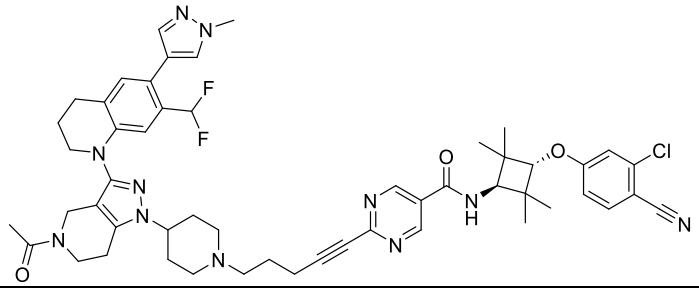
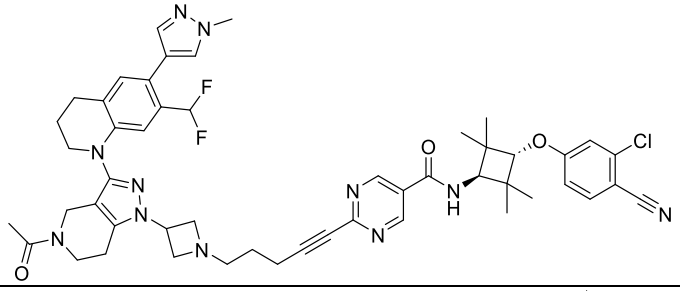
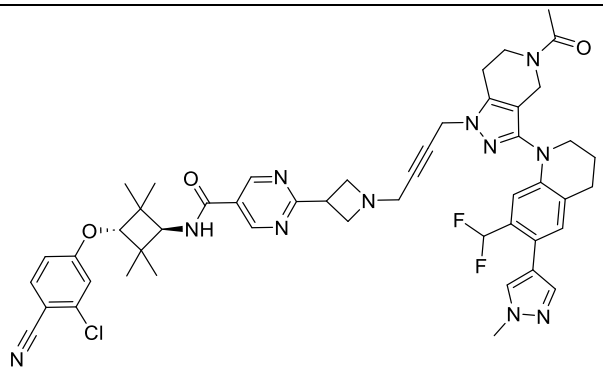
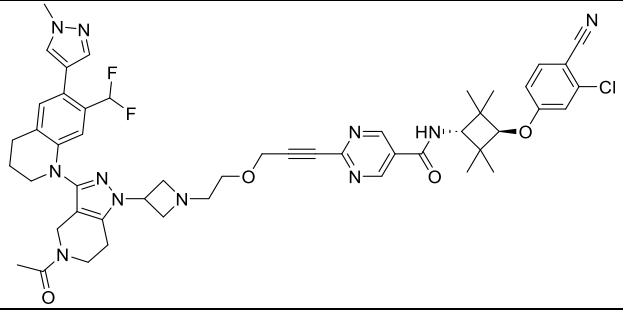
Compuesto	Estructura
170	
171	
172	
173	
174	
175	

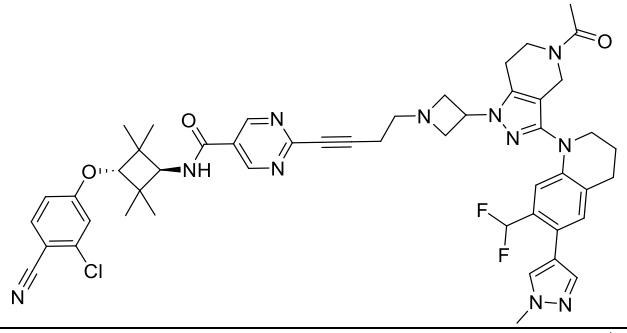
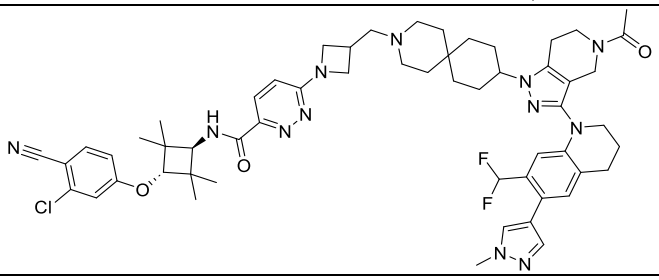
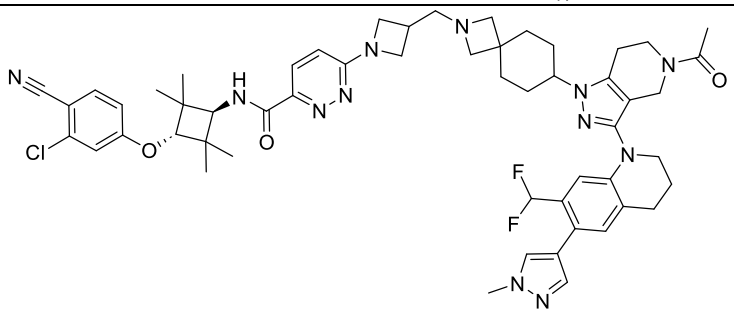
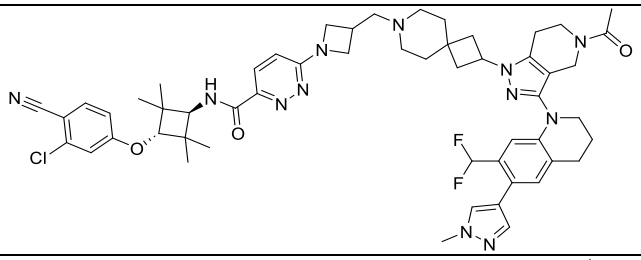
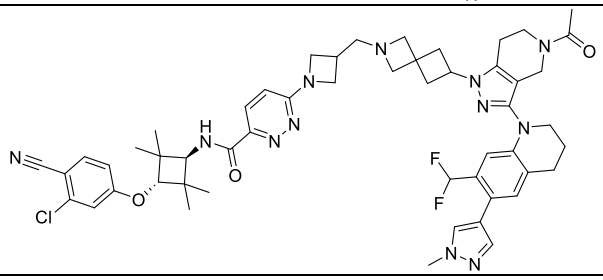
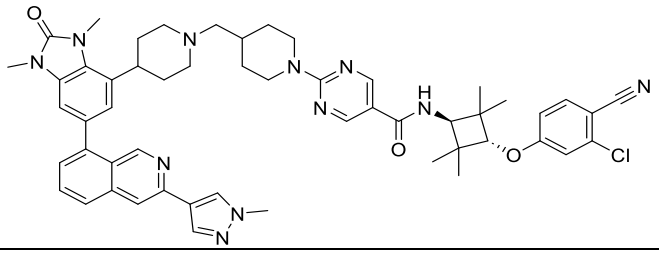
Compuesto	Estructura
176	
177	
178	
179	
180	
181	

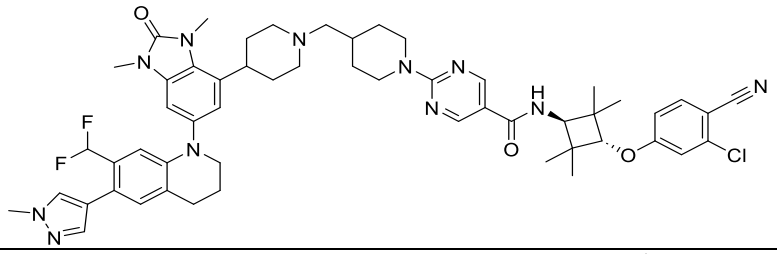
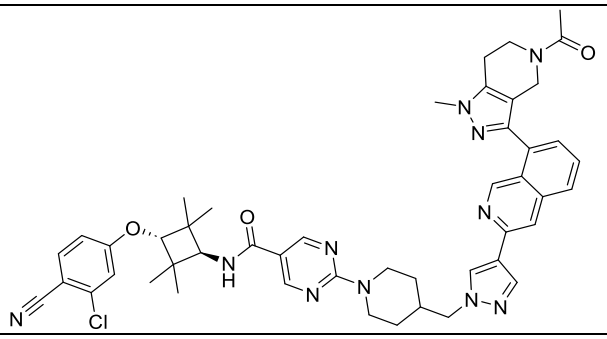
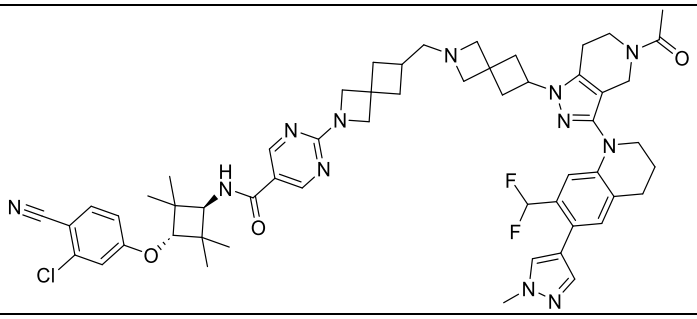
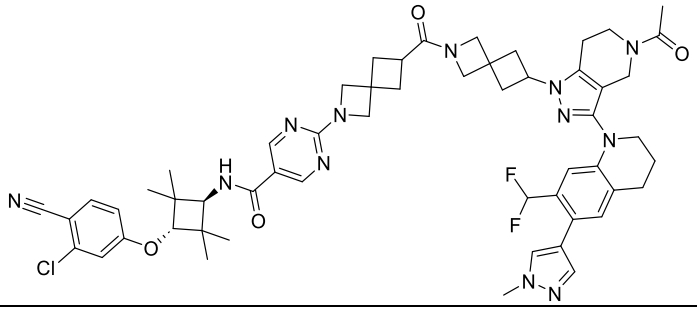
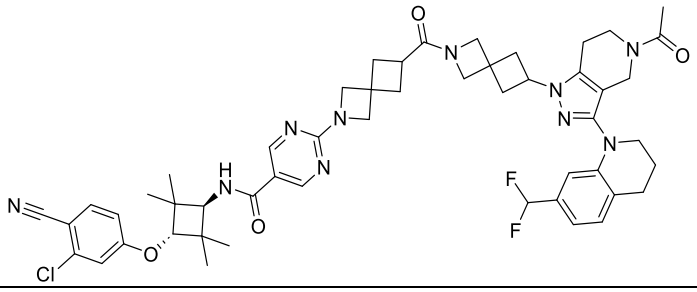
Compuesto	Estructura
182	
183	
184	
185	
186	
187	

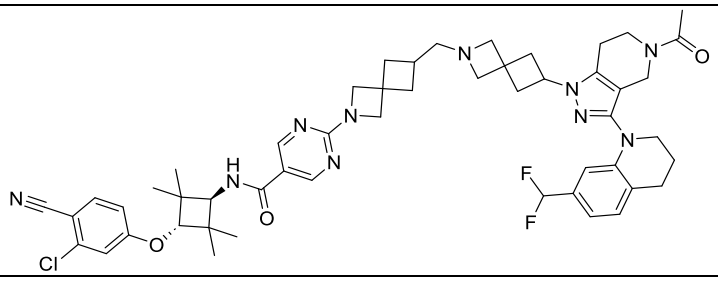
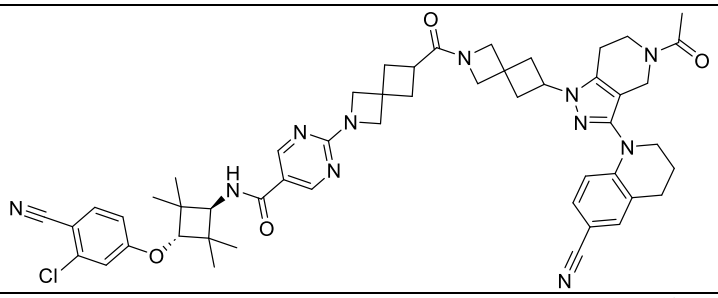
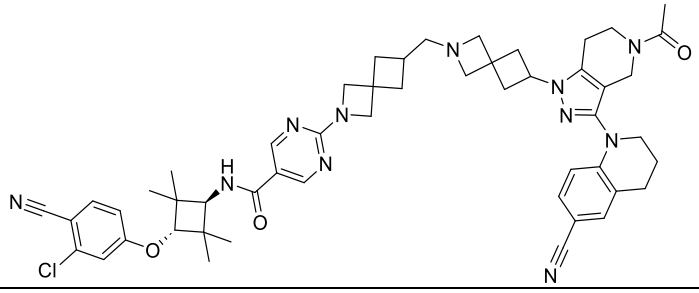
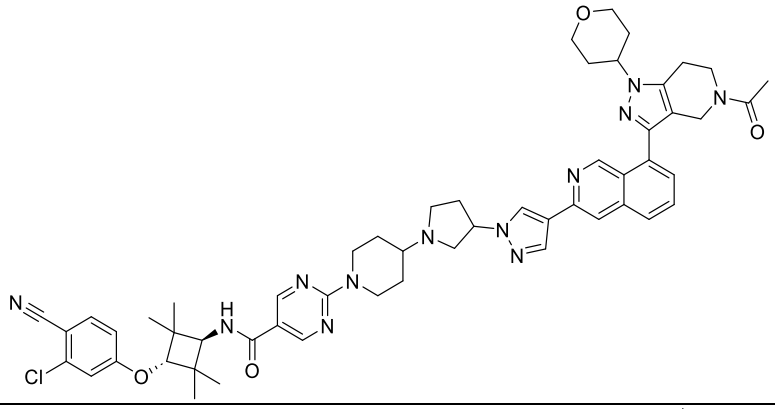
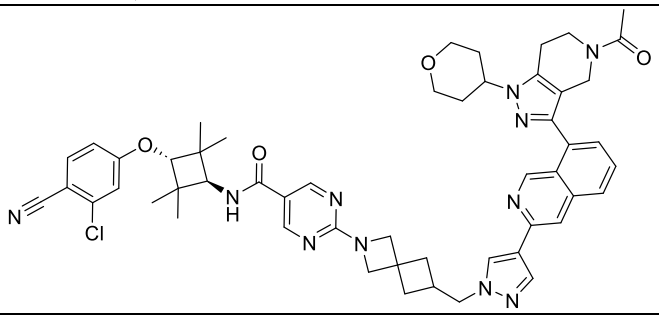
Compuesto	Estructura
188	
189	
190	
191	
192	
193	
194	
195	

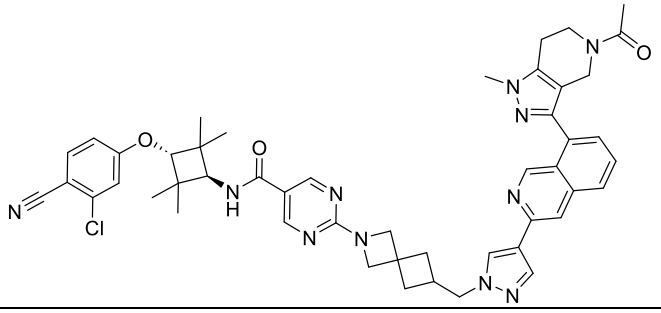
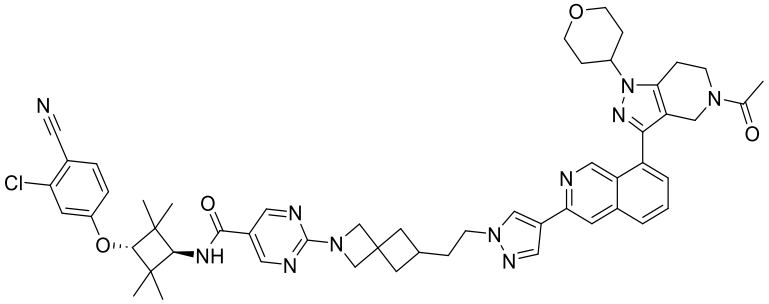
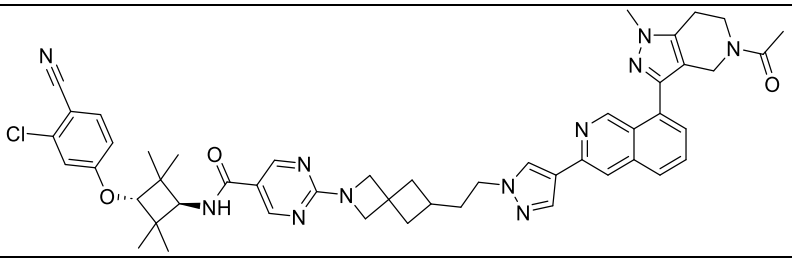
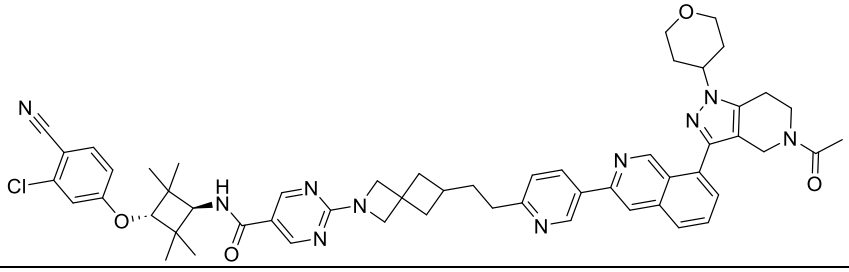
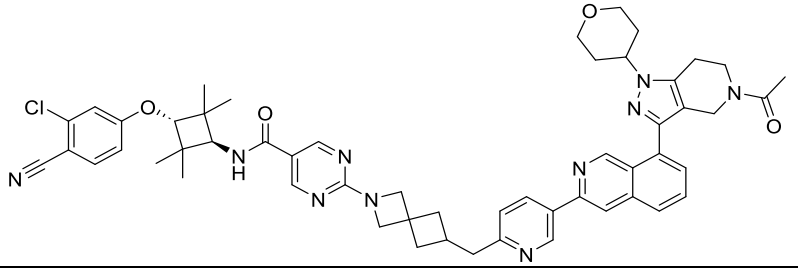
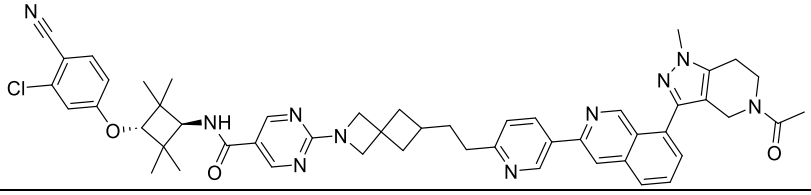
Compuesto	Estructura
196	
197	
198	
199	
200	
201	
202	

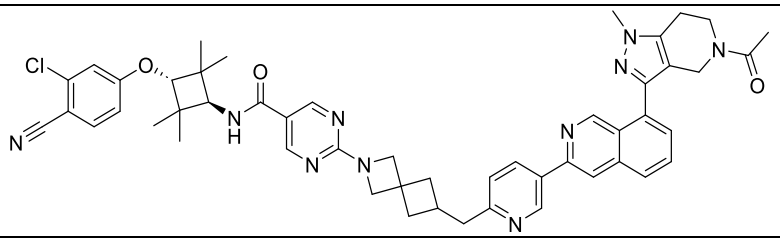
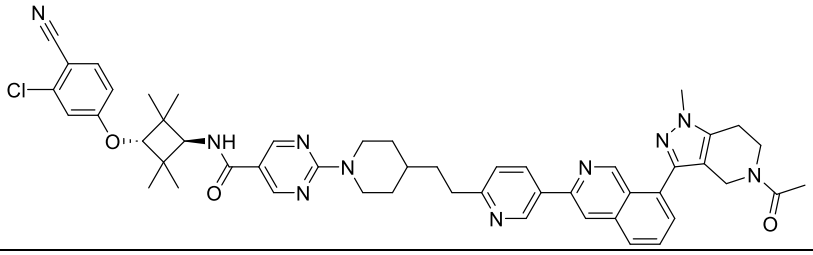
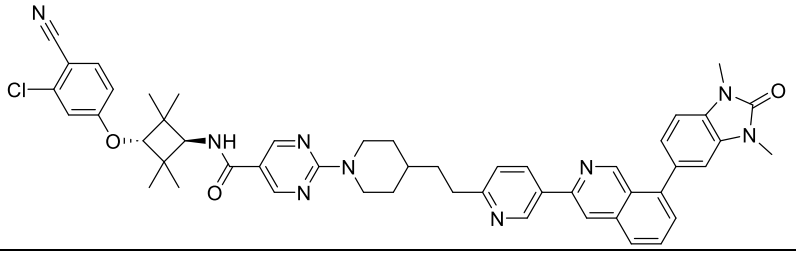
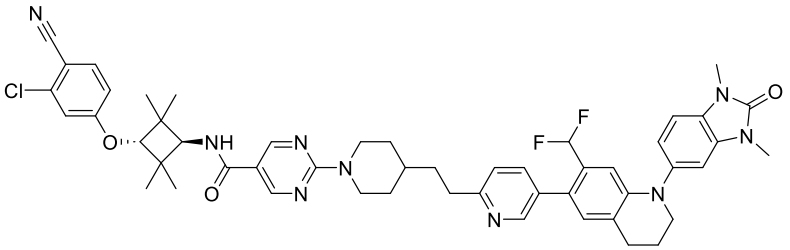
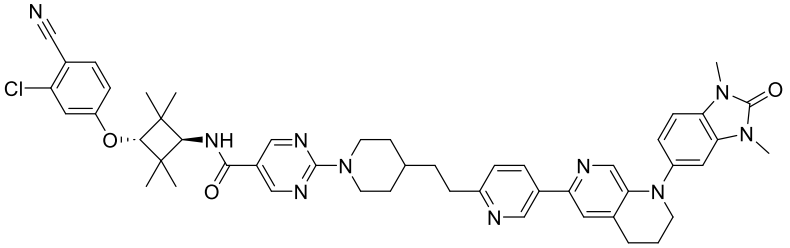
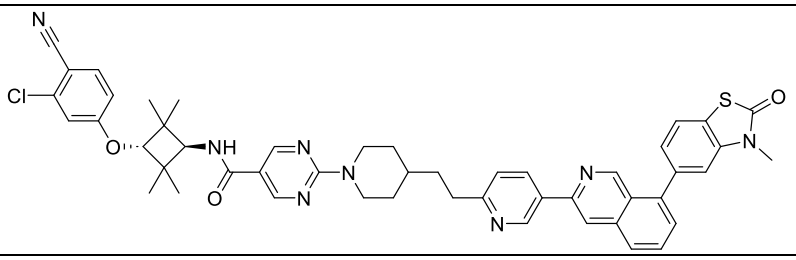
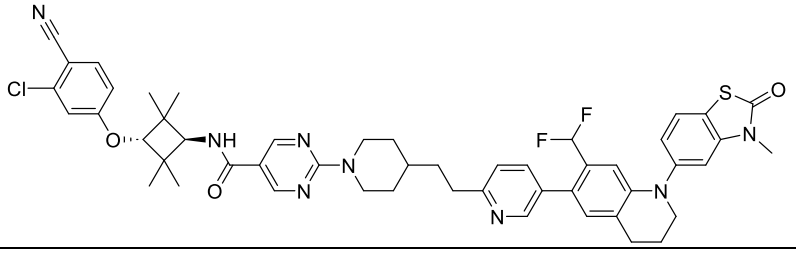
Compuesto	Estructura
203	
204	
205	
206	
207	

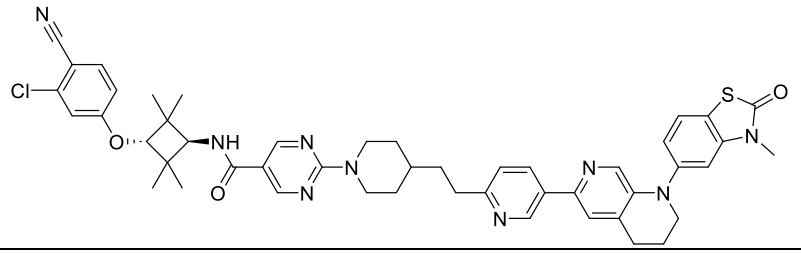
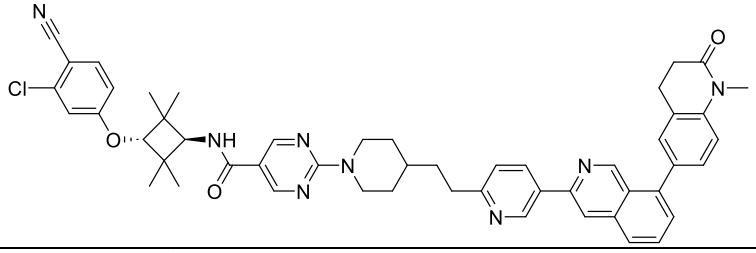
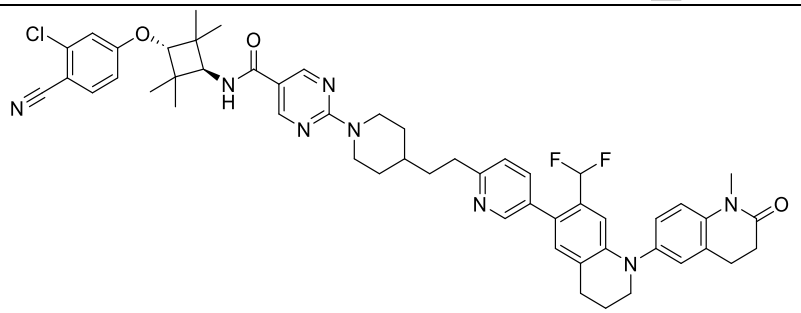
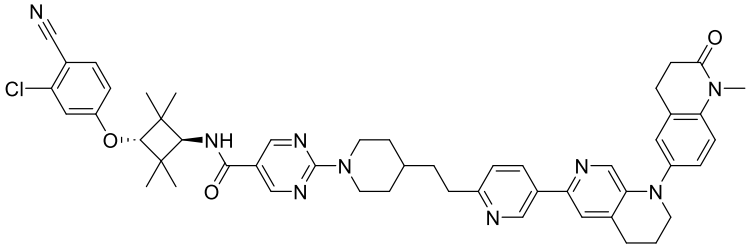
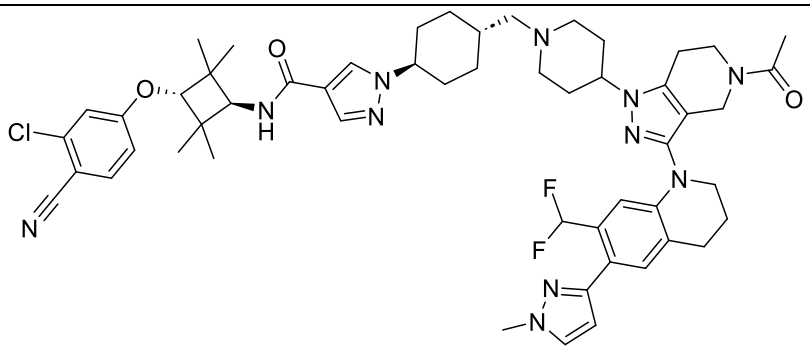
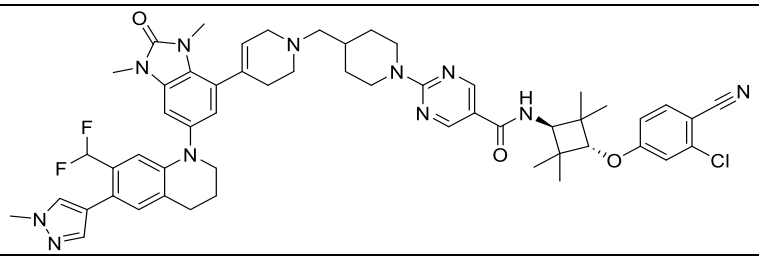
Compuesto	Estructura
208	
209	
210	
211	
212	
213	

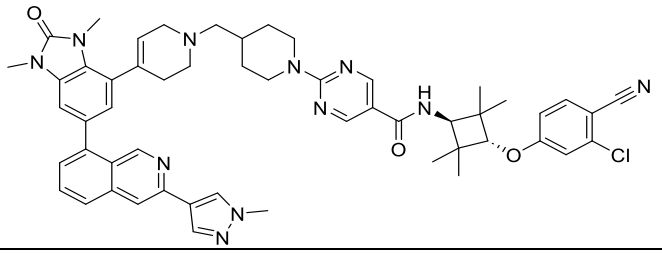
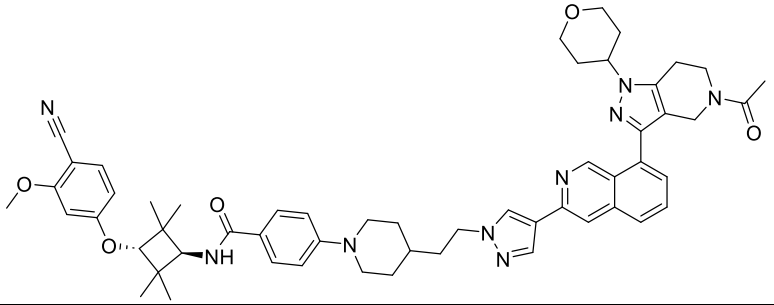
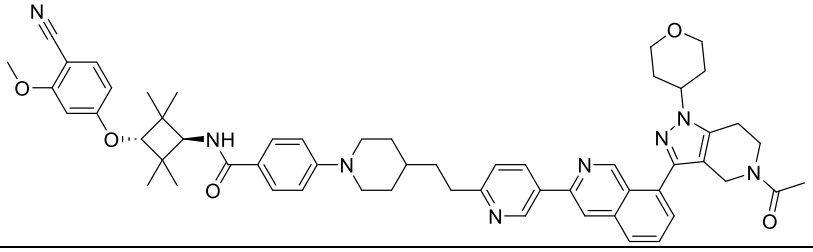
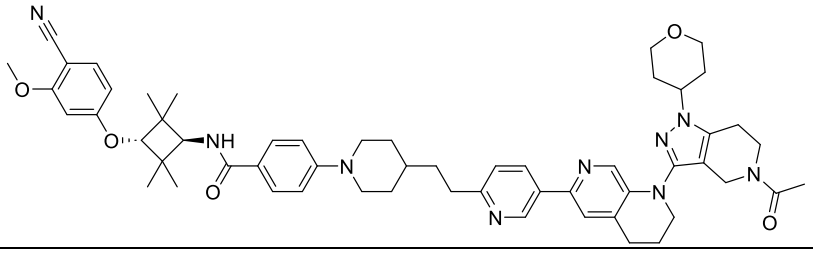
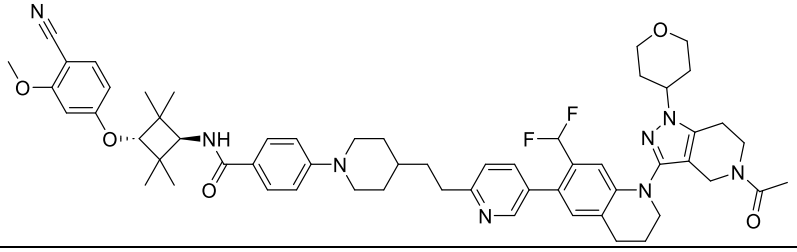
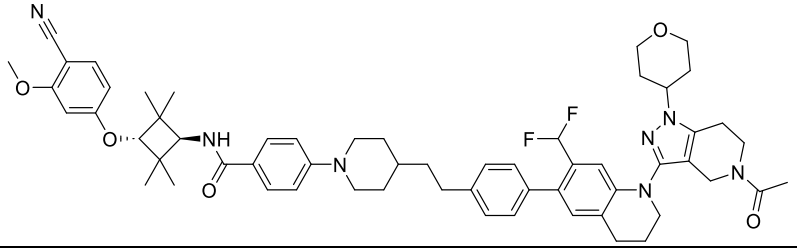
Compuesto	Estructura
214	
215	
216	
217	
218	

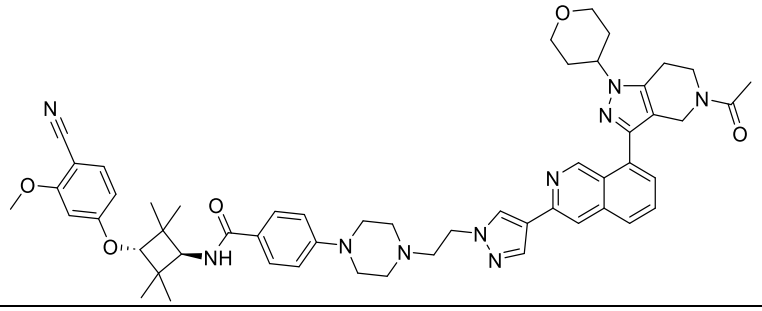
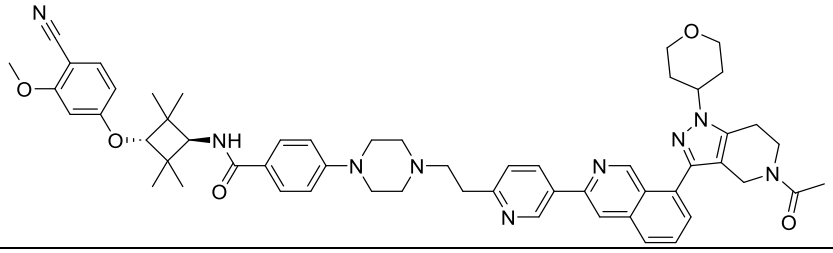
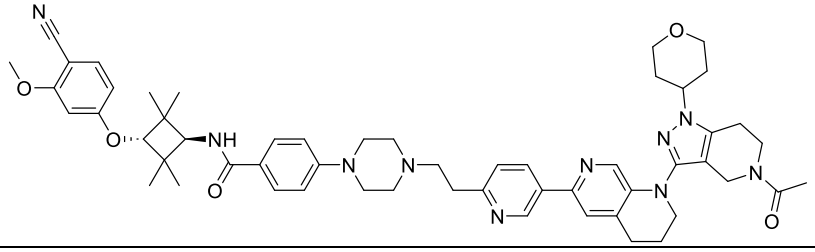
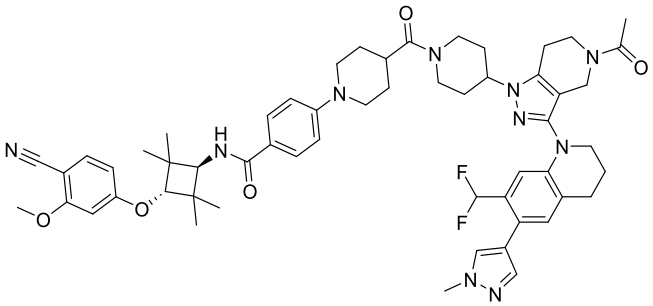
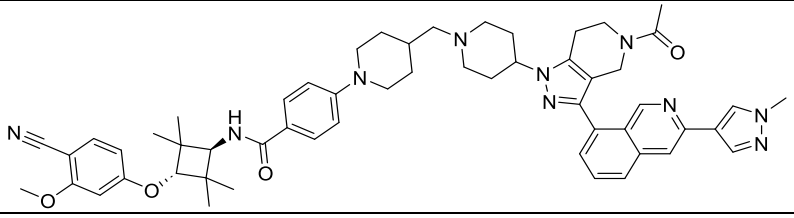
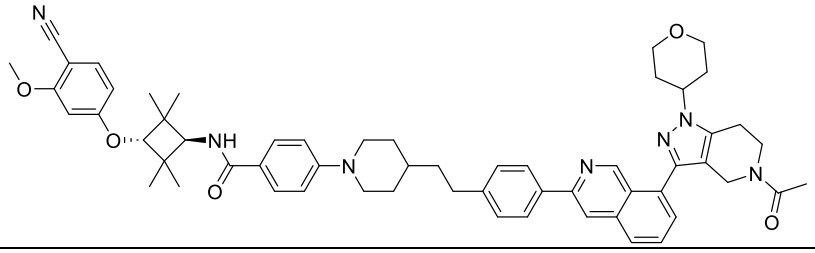
Compuesto	Estructura
219	
220	
221	
222	
223	

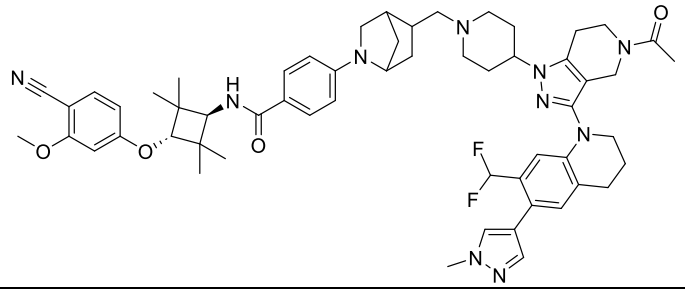
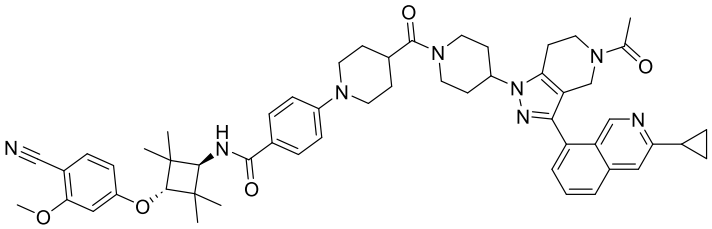
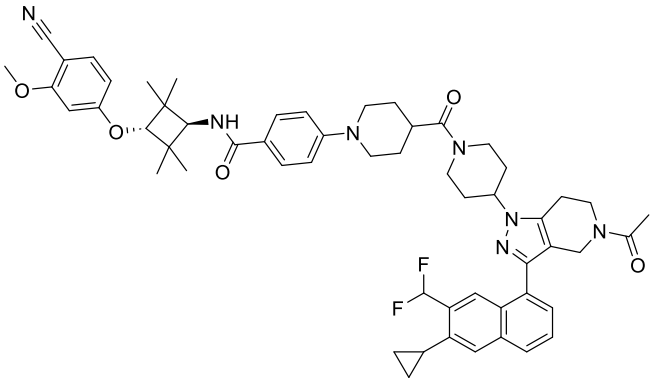
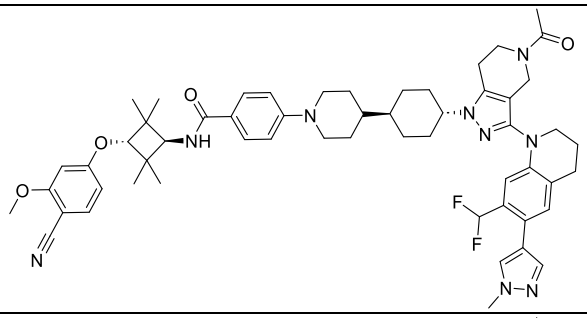
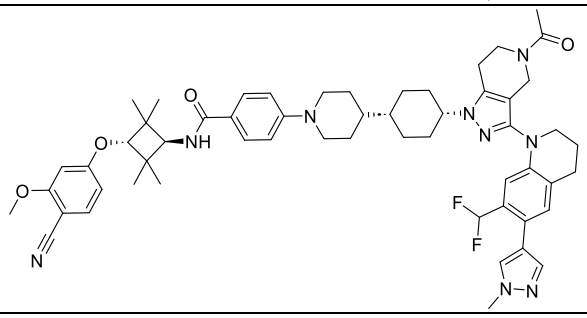
Compuesto	Estructura
224	
225	
226	
227	
228	
229	

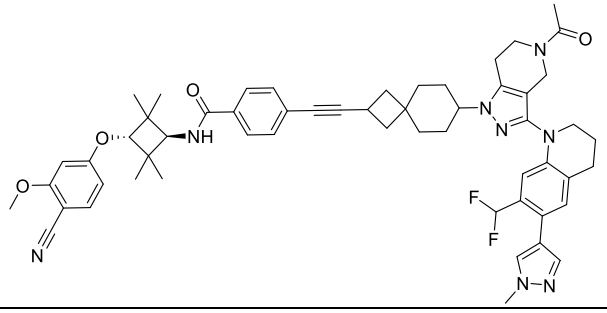
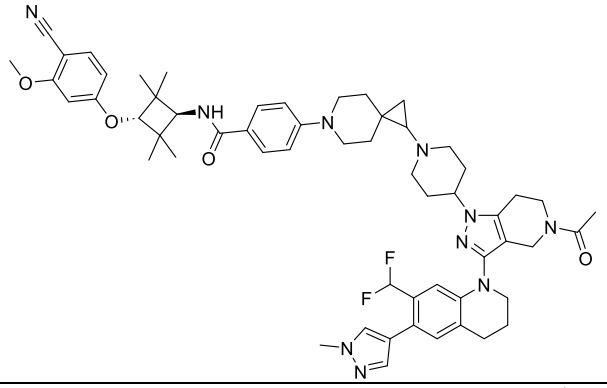
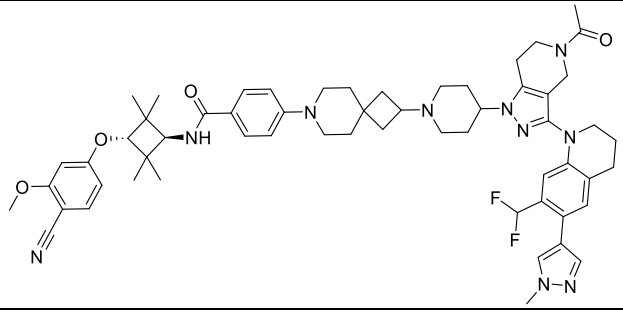
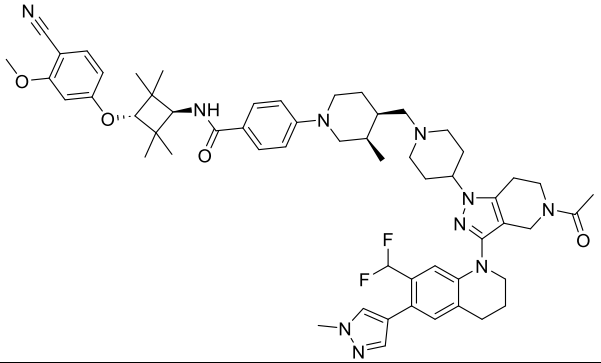
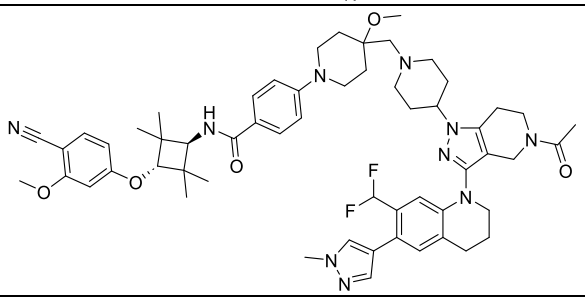
Compuesto	Estructura
230	
231	
232	
233	
234	
235	
236	

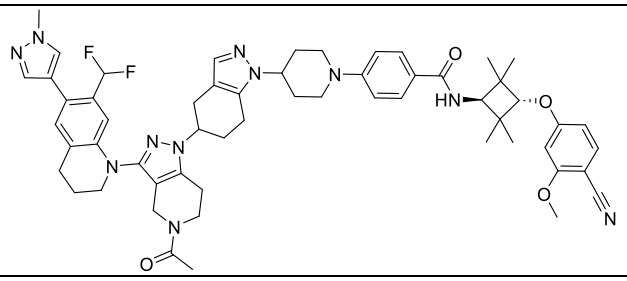
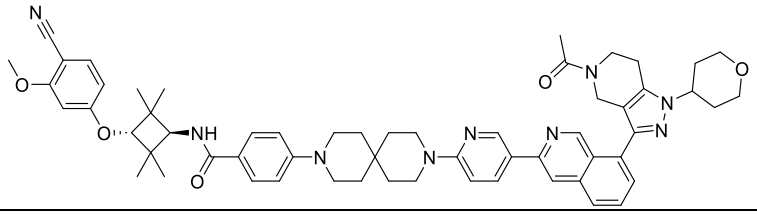
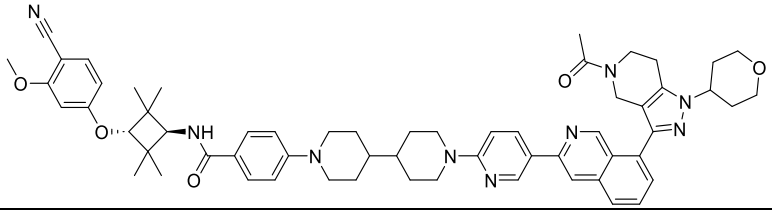
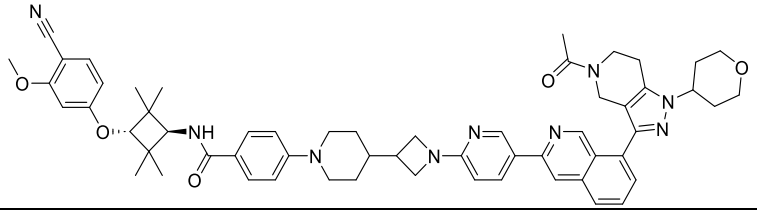
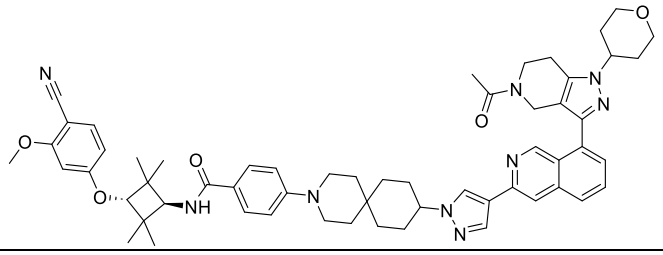
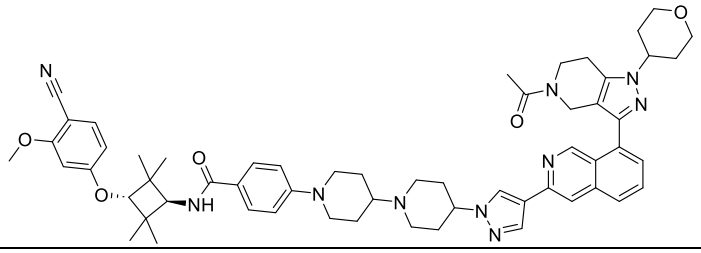
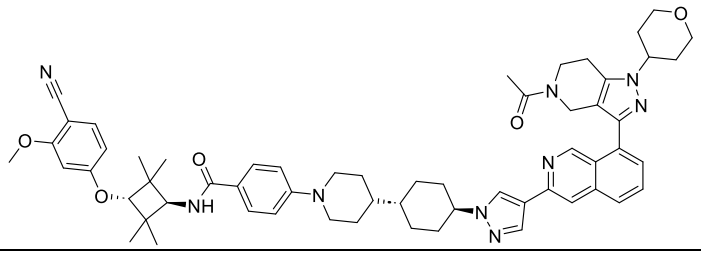
Compuesto	Estructura
237	
238	
239	
240	
241	
242	

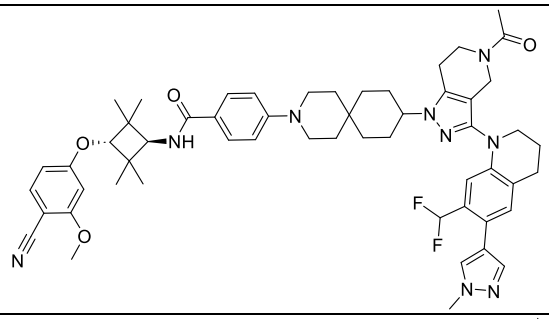
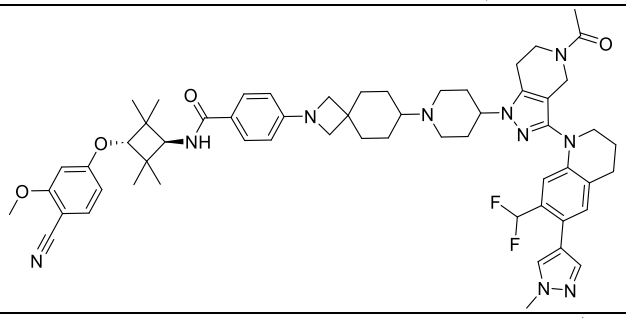
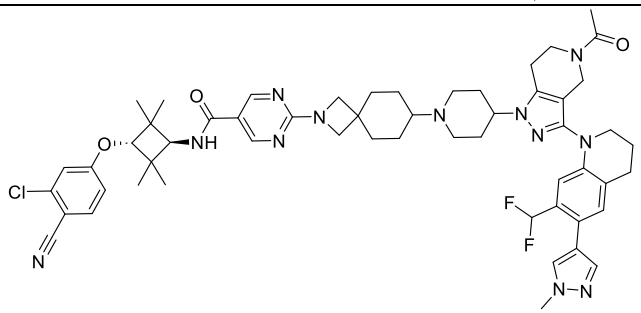
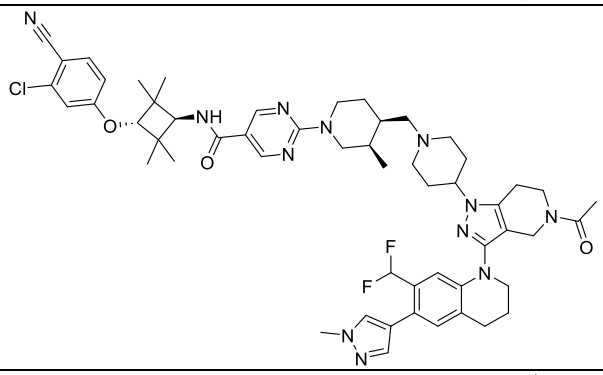
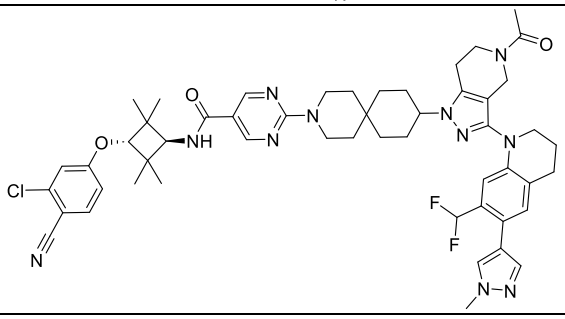
Compuesto	Estructura
243	
244	
245	
246	
247	
248	

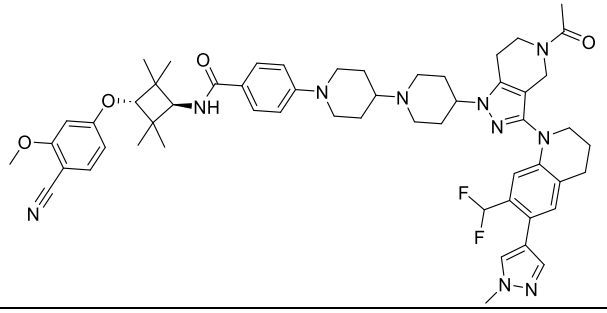
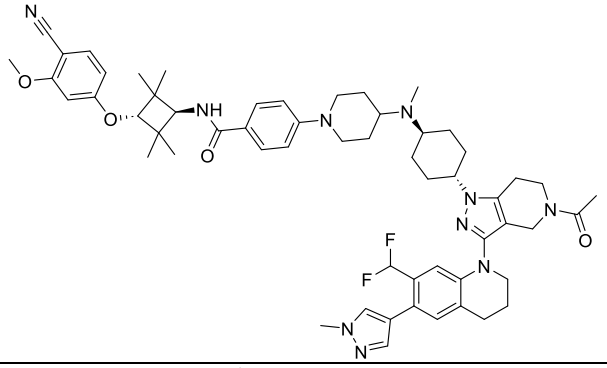
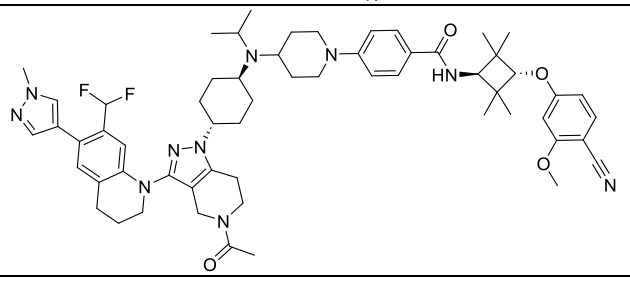
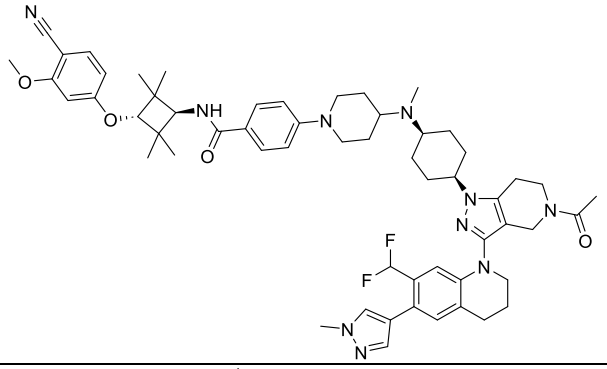
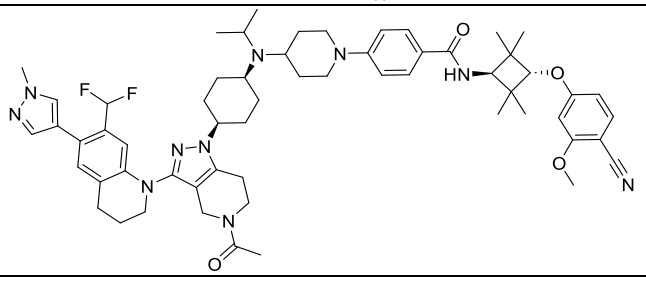
Compuesto	Estructura
249	
250	
251	
252	
253	
254	

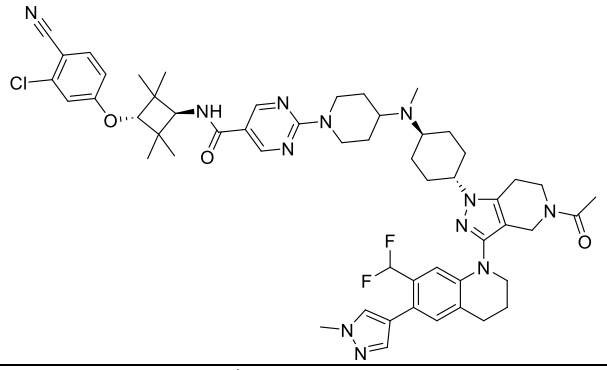
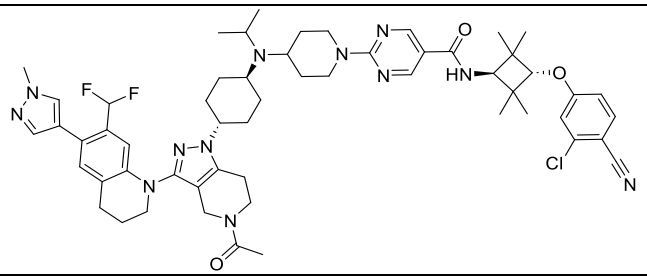
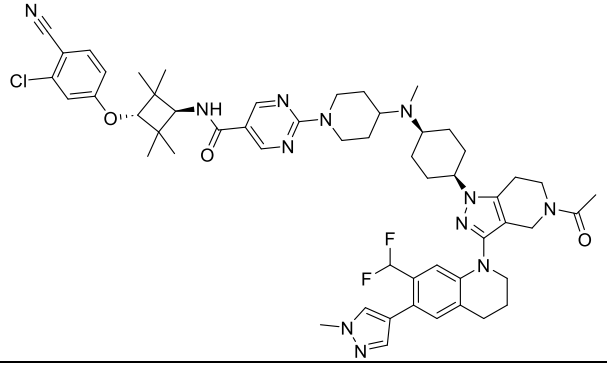
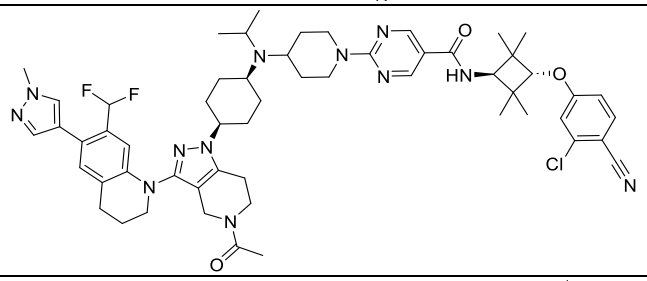
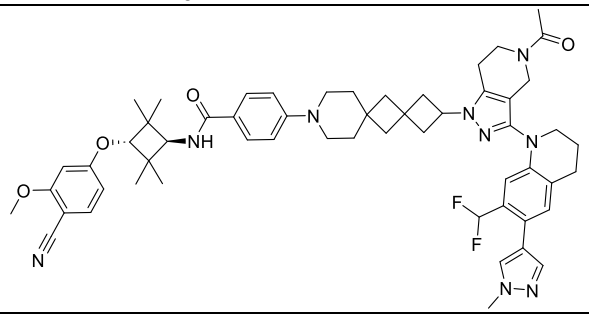
Compuesto	Estructura
255	
256	
257	
258	
259	

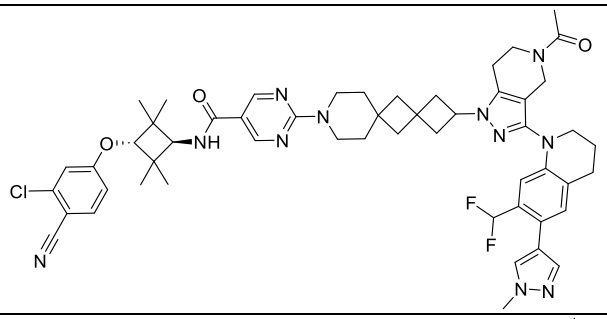
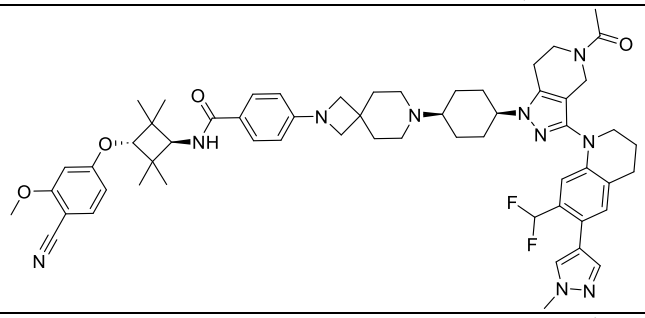
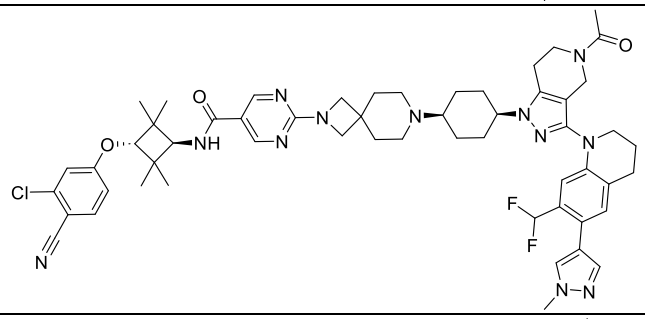
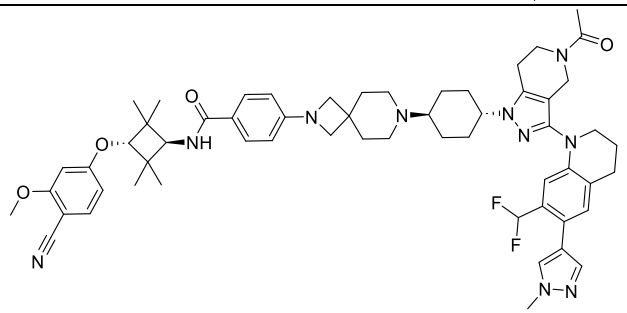
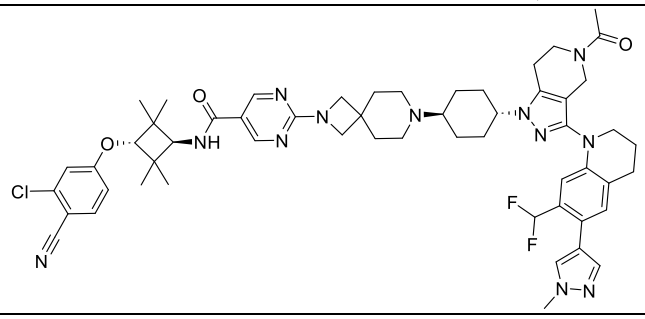
Compuesto	Estructura
260	
261	
262	
263	
264	

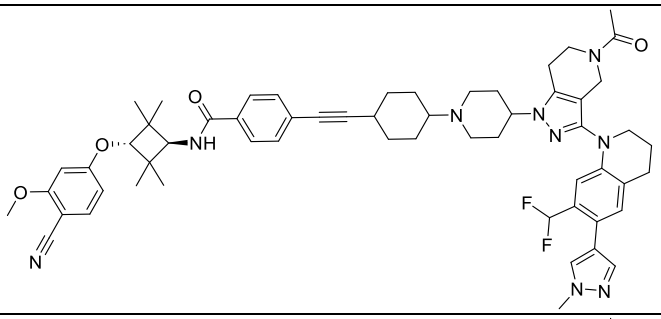
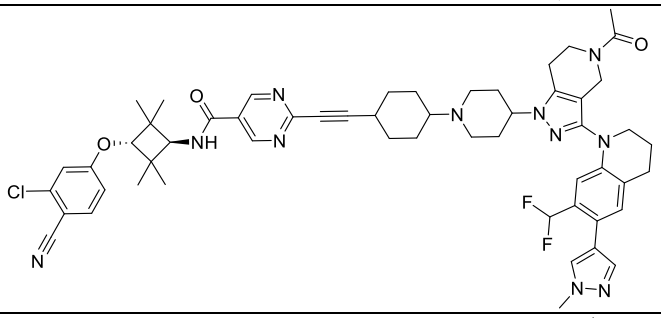
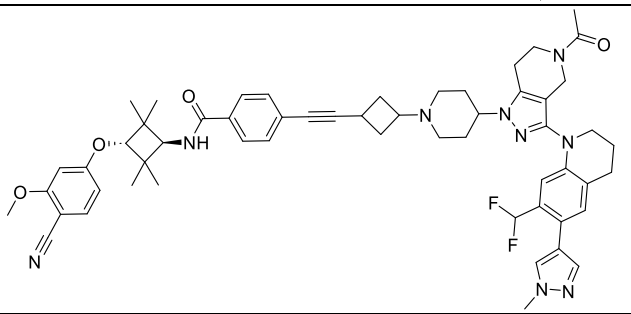
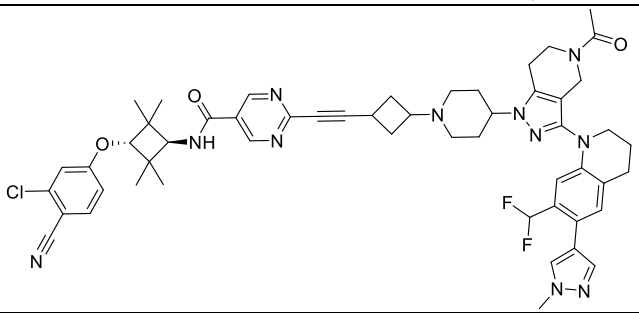
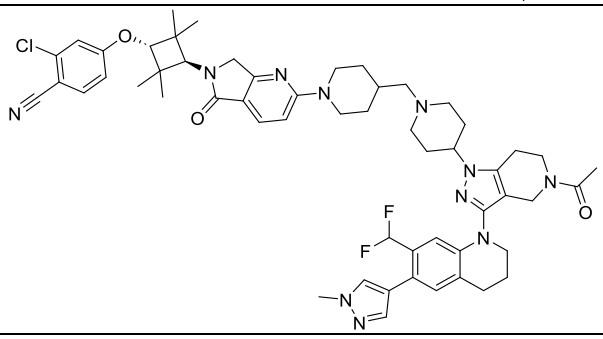
Compuesto	Estructura
265	
266	
267	
268	
269	
270	
271	

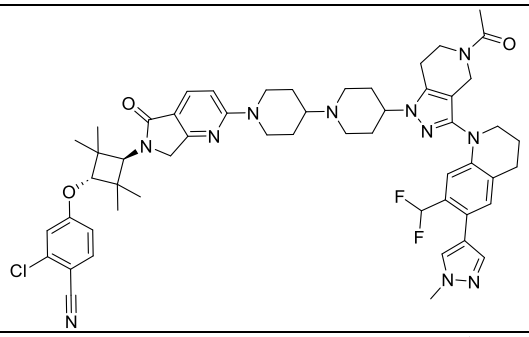
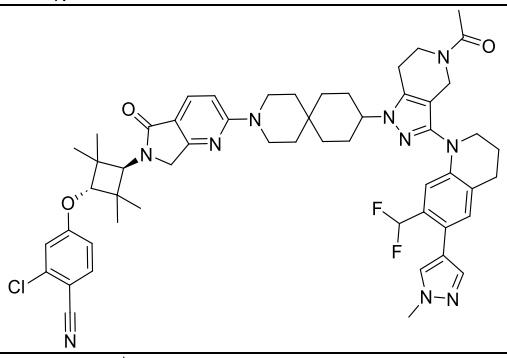
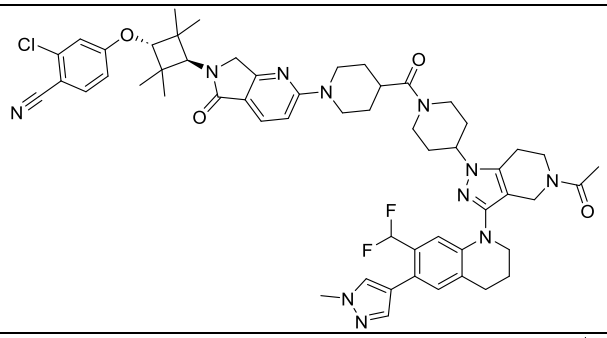
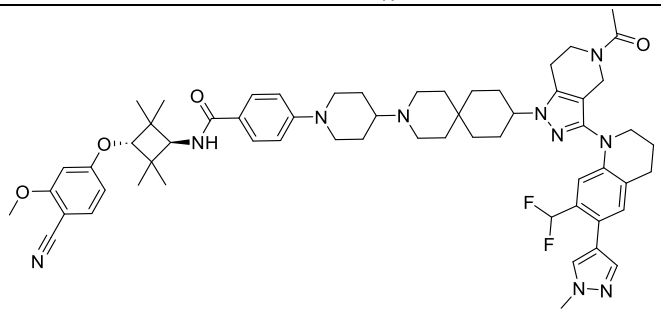
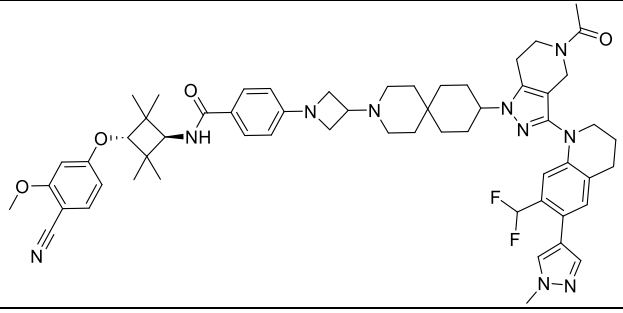
Compuesto	Estructura
272	
273	
274	
275	
276	

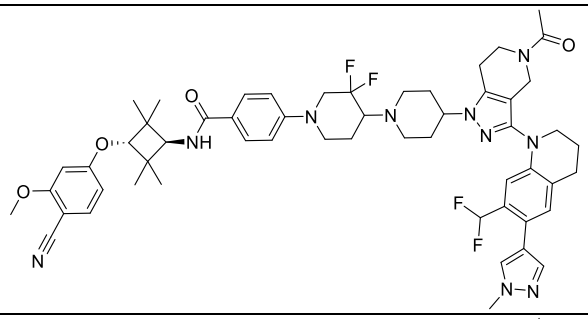
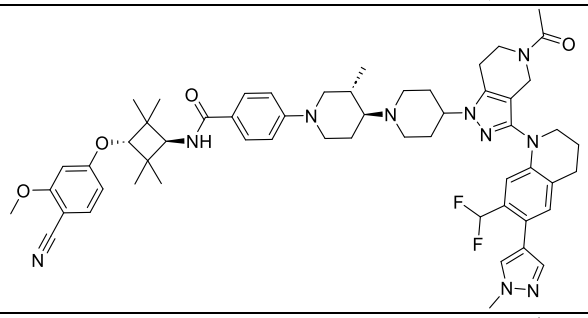
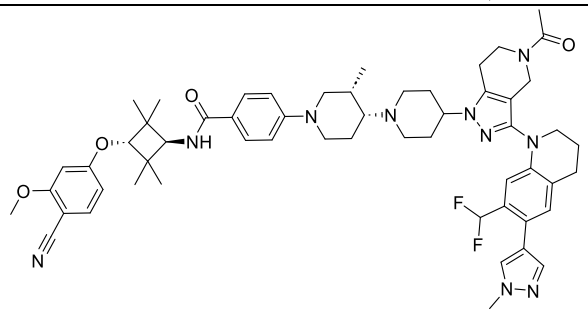
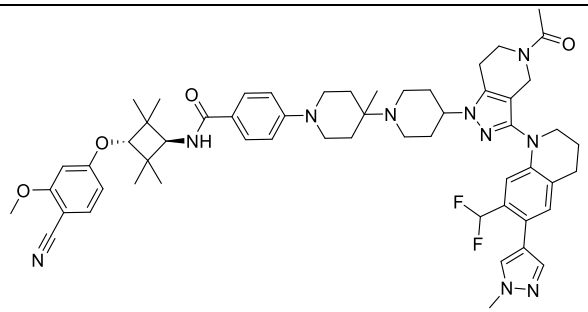
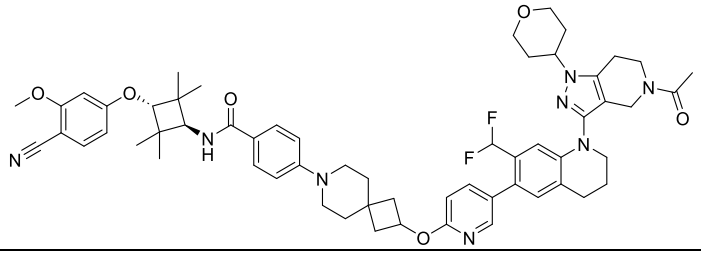
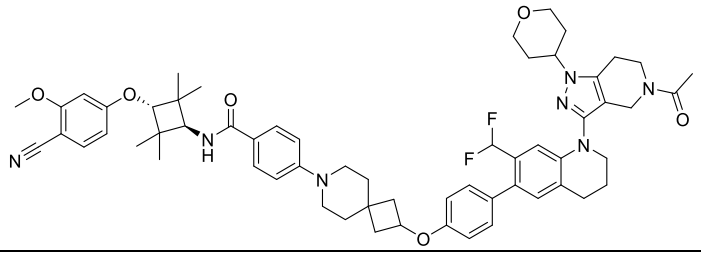
Compuesto	Estructura
277	
278	
279	
280	
281	

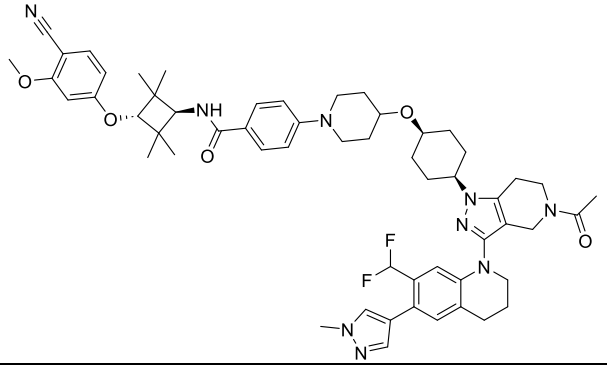
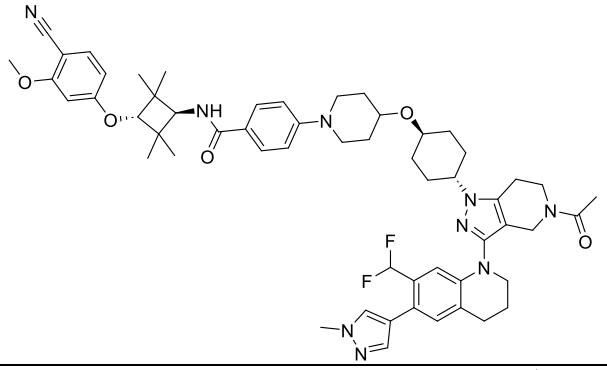
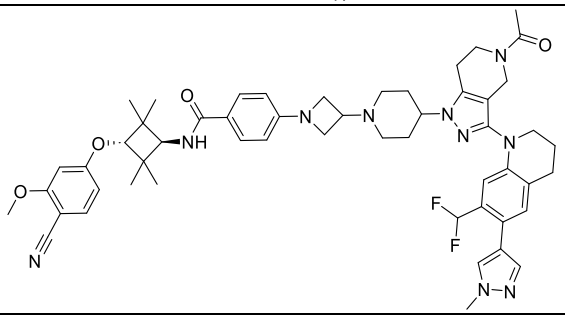
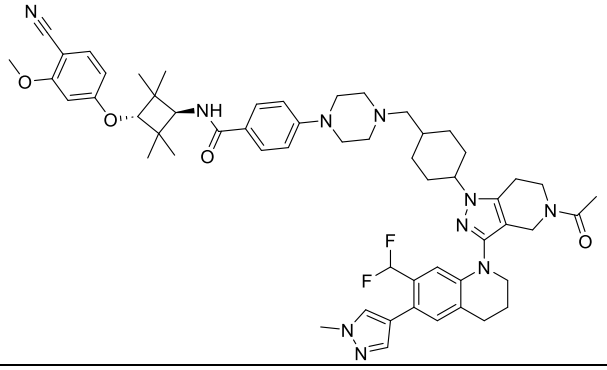
Compuesto	Estructura
282	
283	
284	
285	
286	

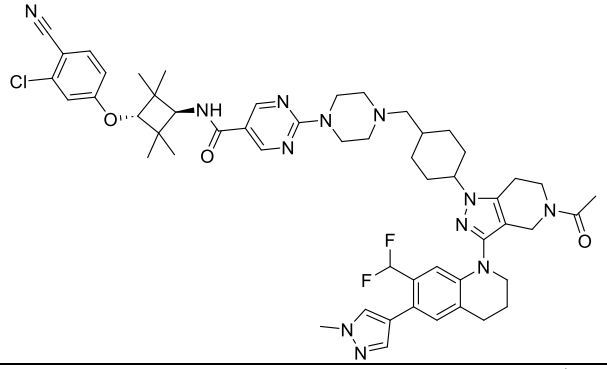
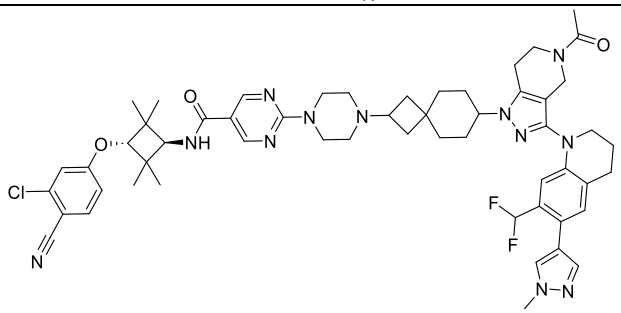
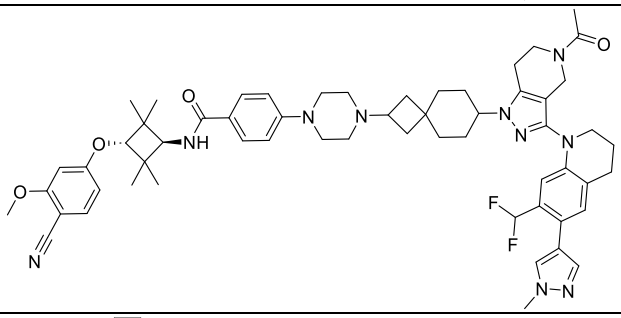
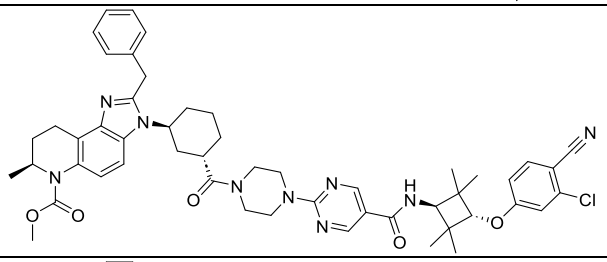
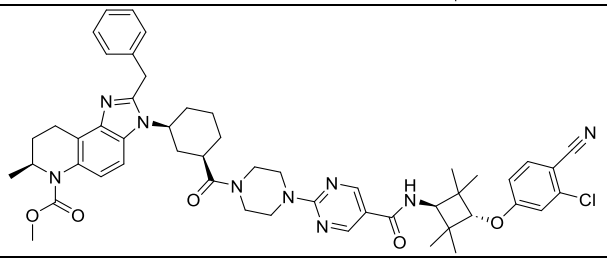
Compuesto	Estructura
287	
288	
289	
290	
291	

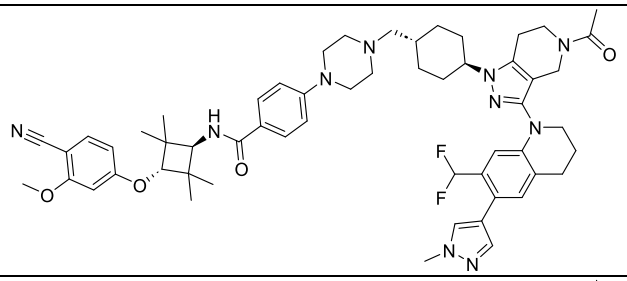
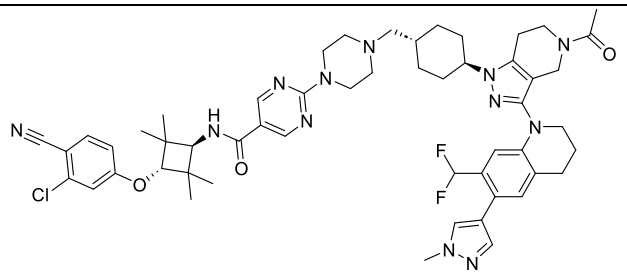
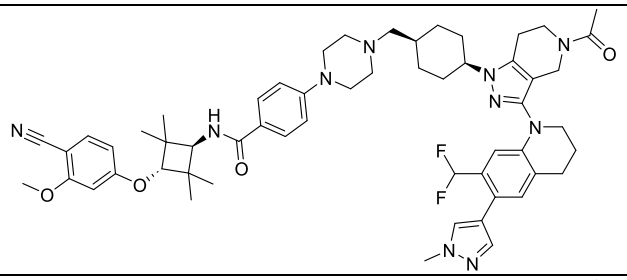
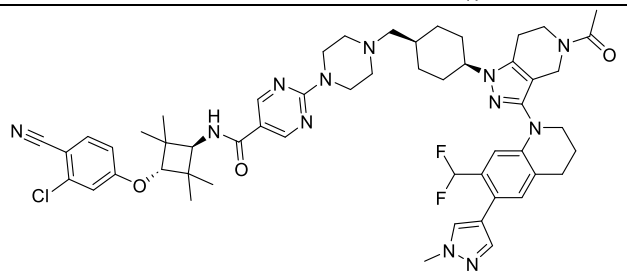
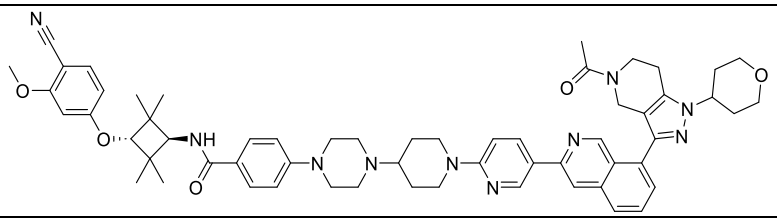
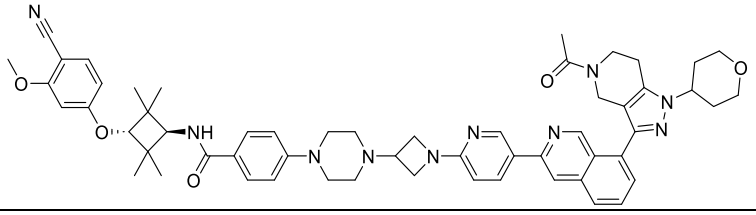
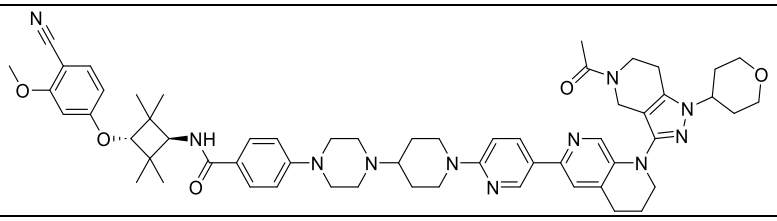
Compuesto	Estructura
292	
293	
294	
295	
296	

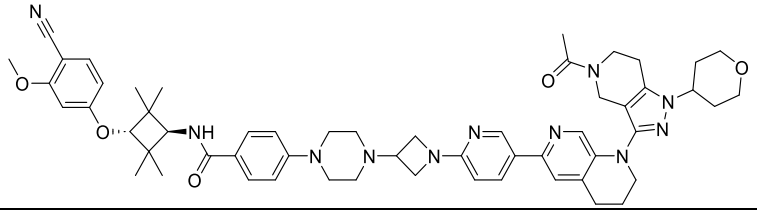
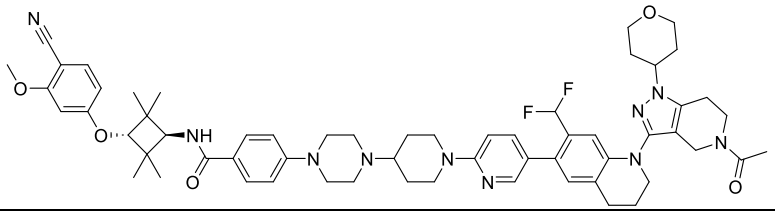
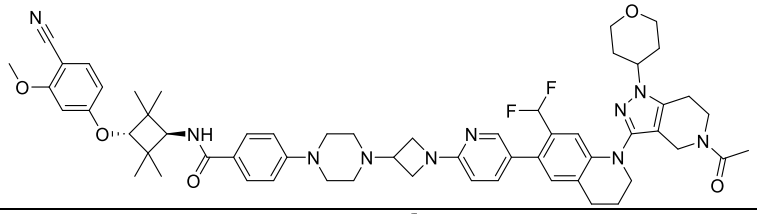
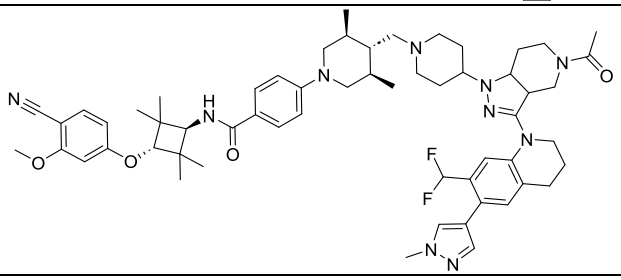
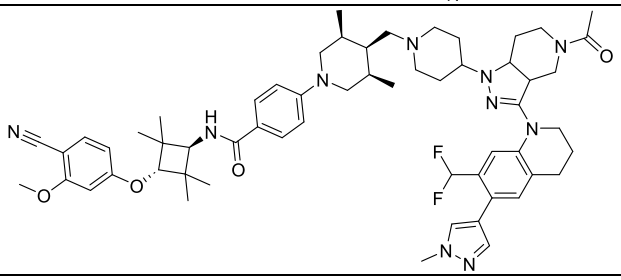
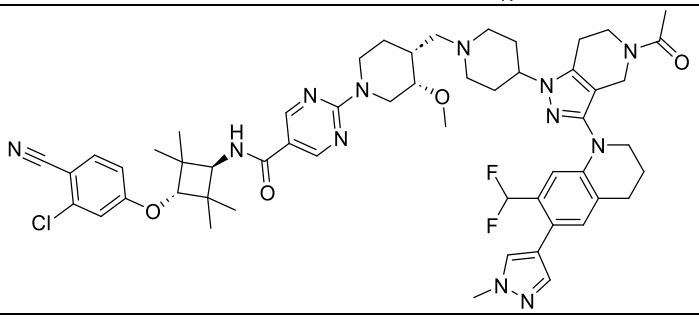
Compuesto	Estructura
297	
298	
299	
300	
301	

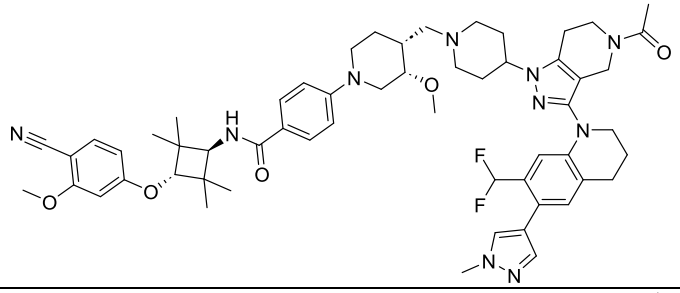
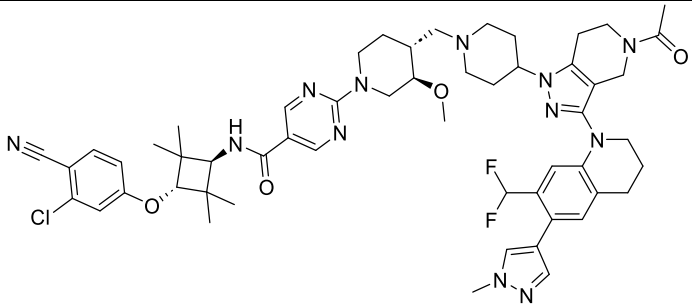
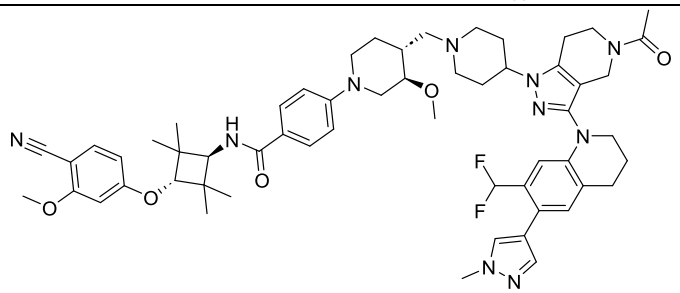
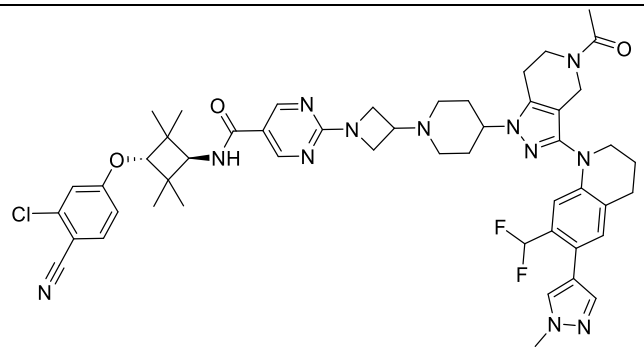
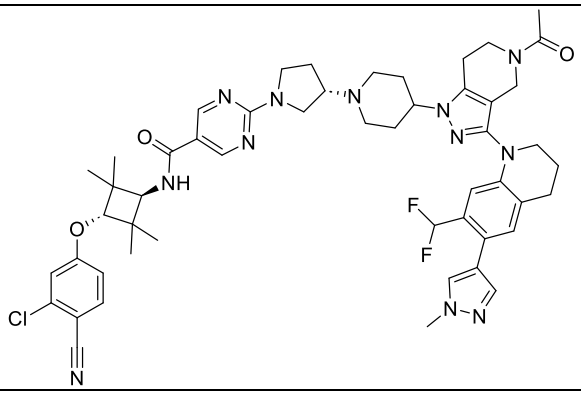
Compuesto	Estructura
302	
303	
304	
305	
306	
307	

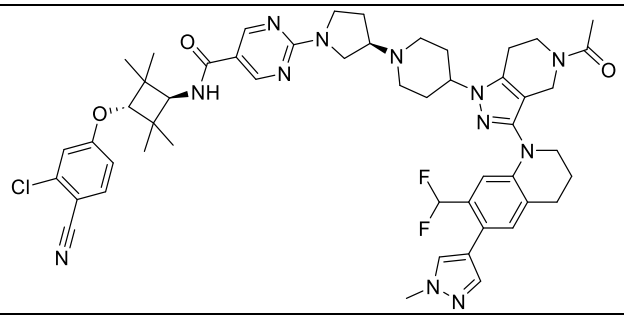
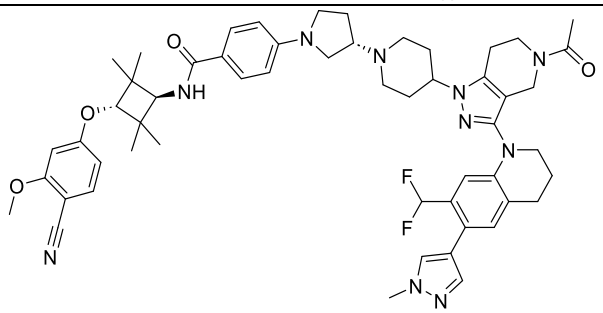
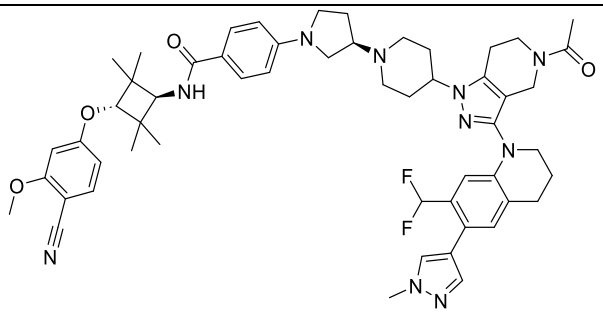
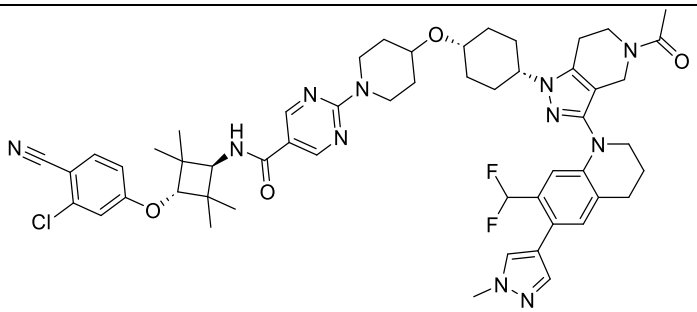
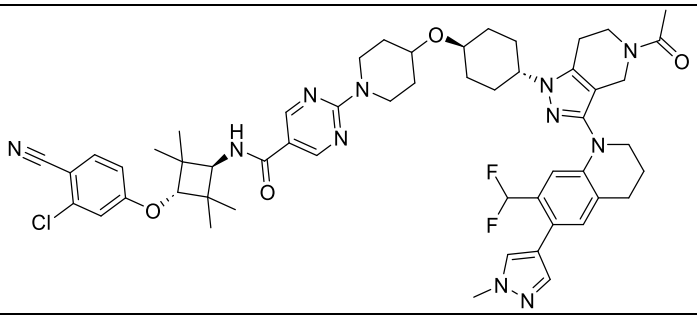
Compuesto	Estructura
308	
309	
310	
311	

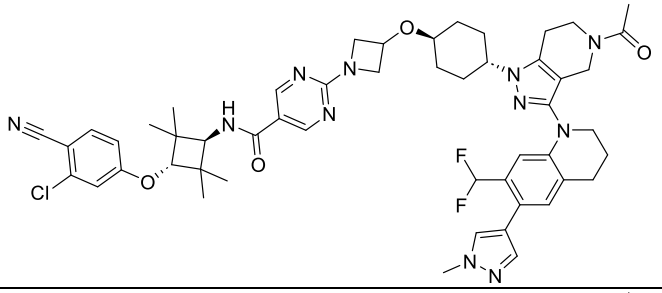
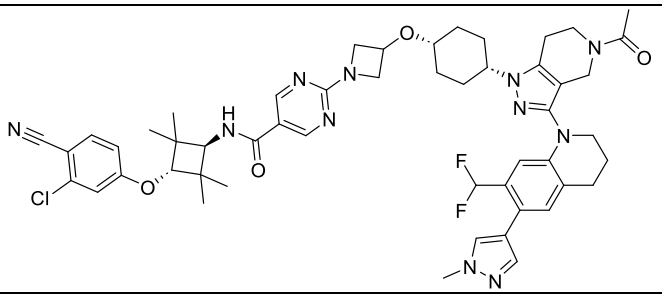
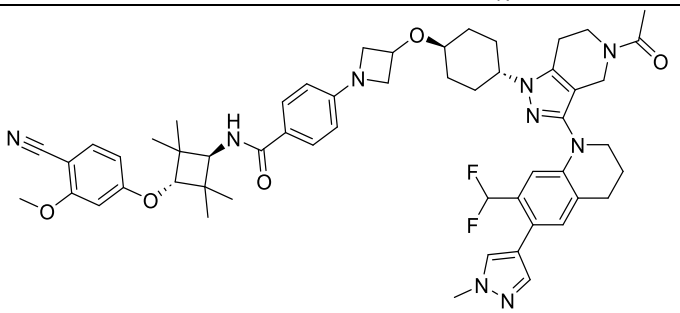
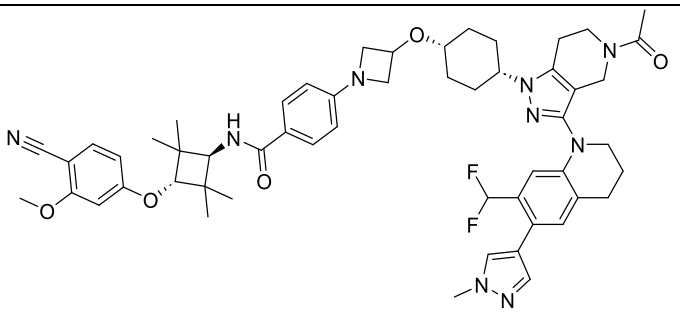
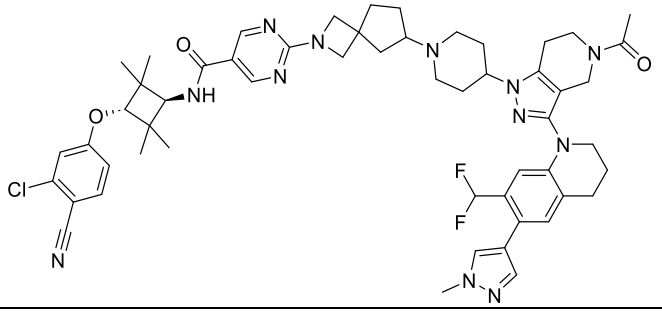
Compuesto	Estructura
312	
313	
314	
315	
316	

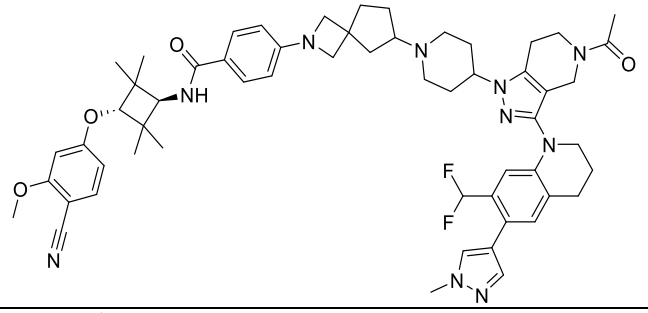
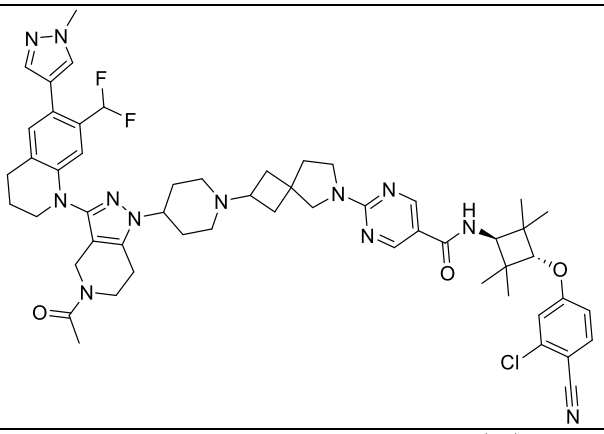
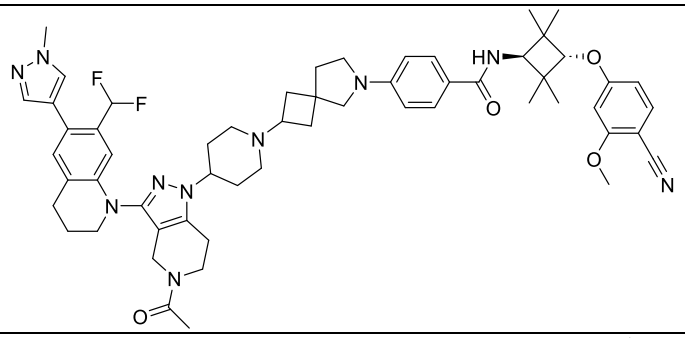
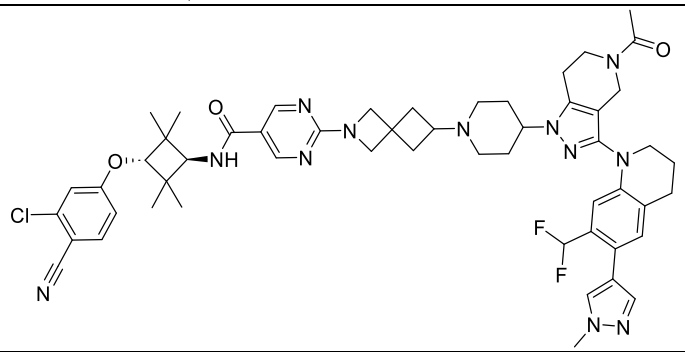
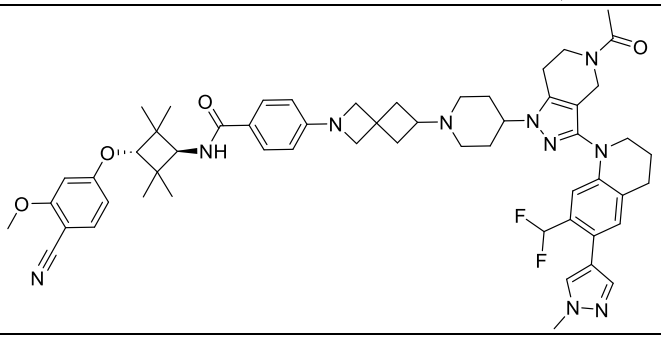
Compuesto	Estructura
317	
318	
319	
320	
321	
322	
323	

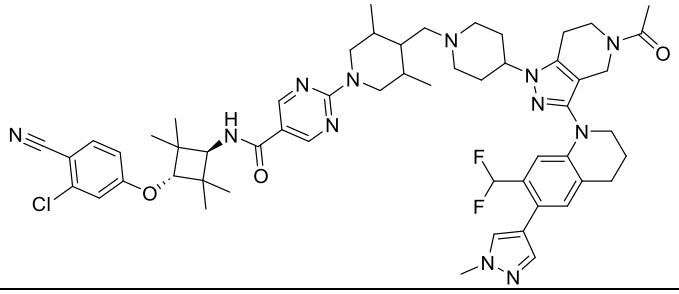
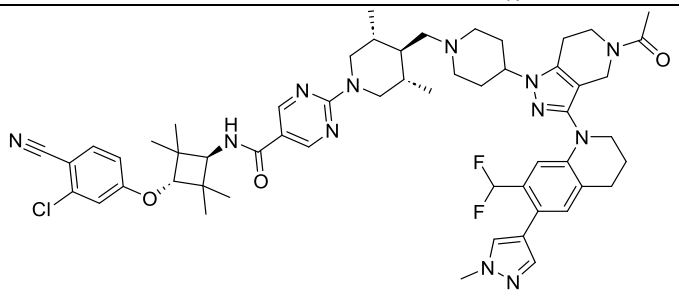
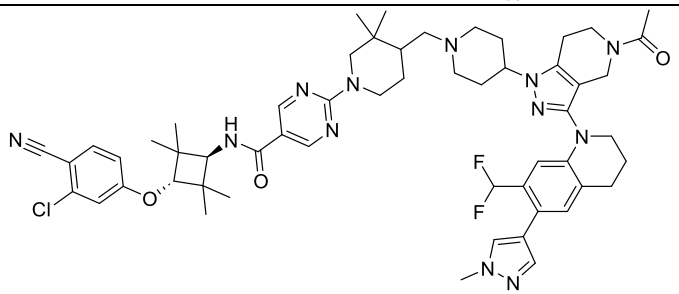
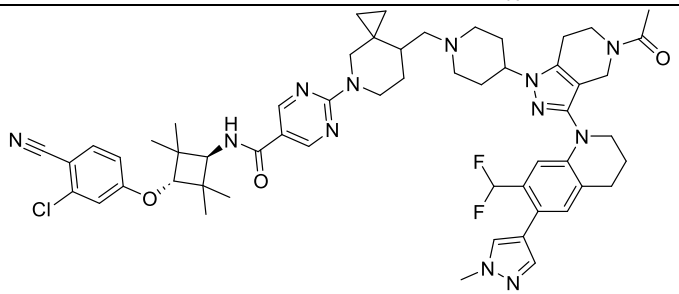
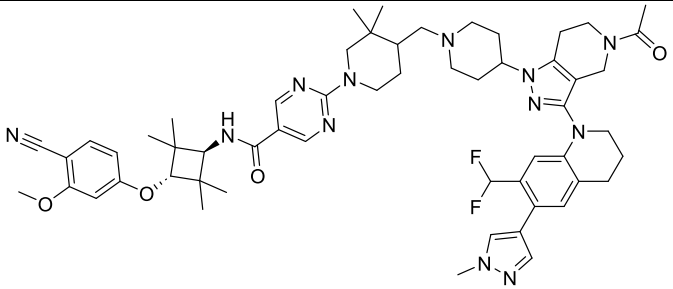
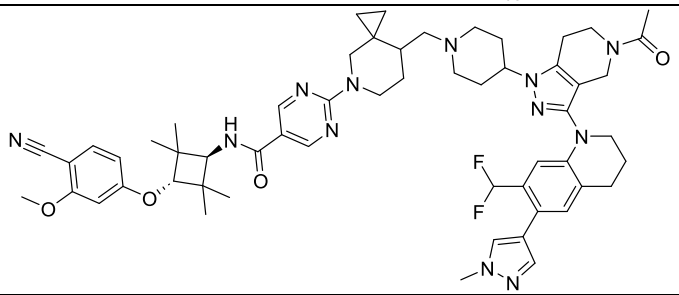
Compuesto	Estructura
324	
325	
326	
327	
328	
329	

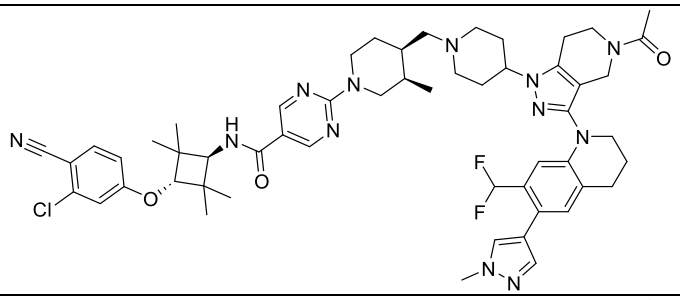
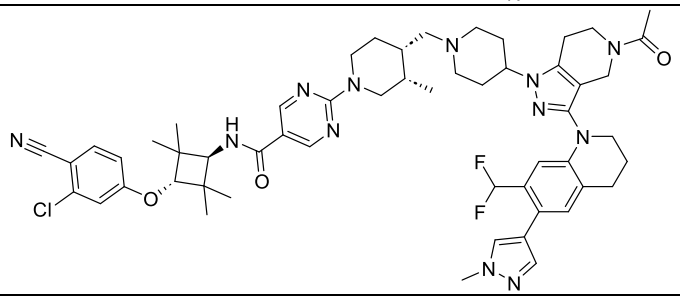
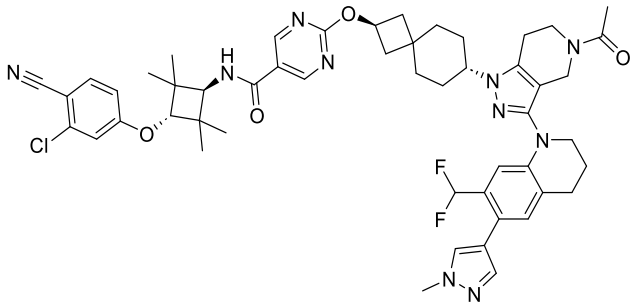
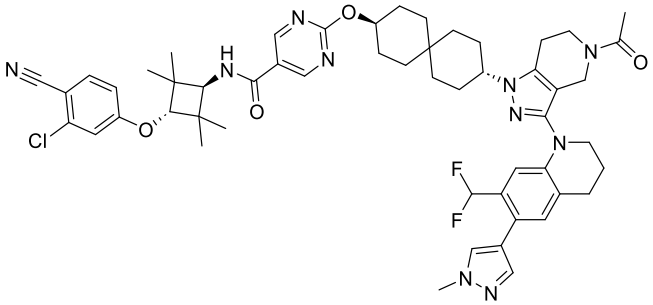
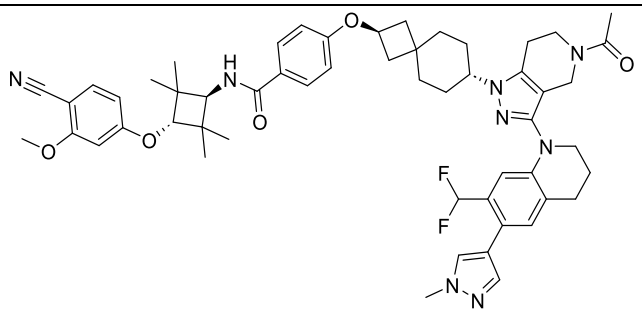
Compuesto	Estructura
330	
331	
332	
333	
334	

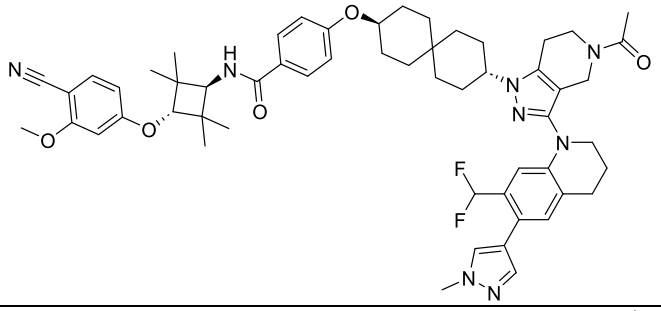
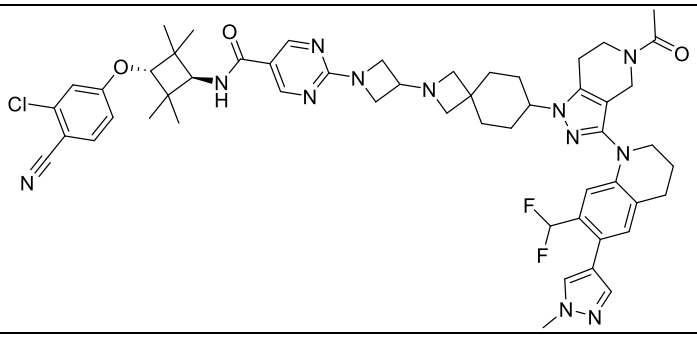
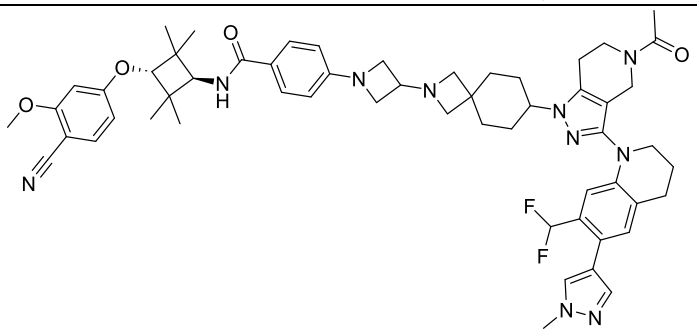
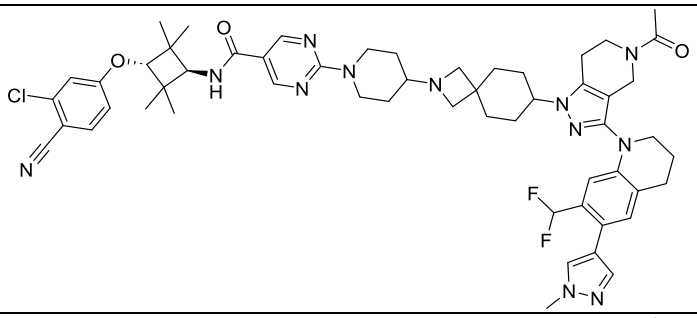
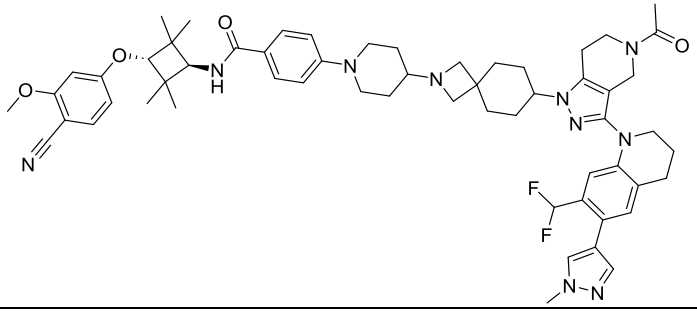
Compuesto	Estructura
335	
336	
337	
338	
339	

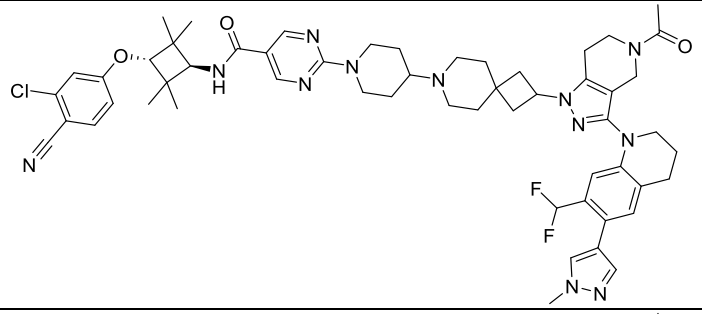
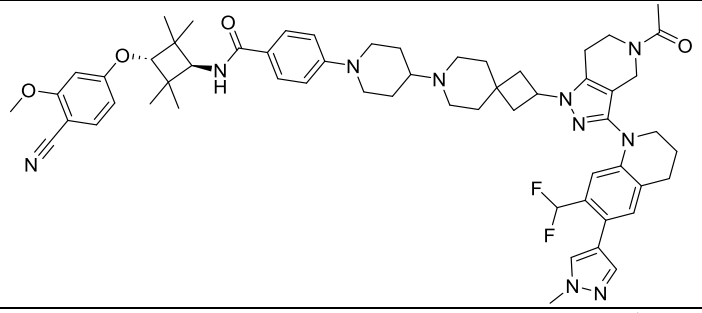
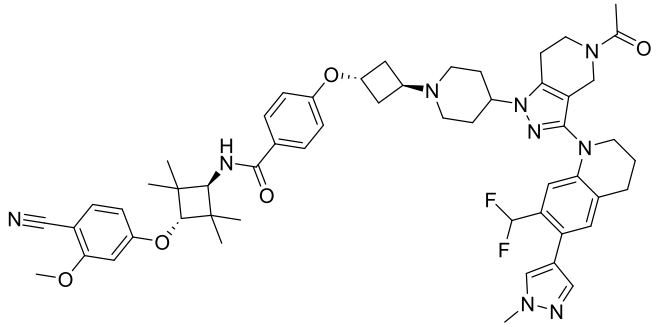
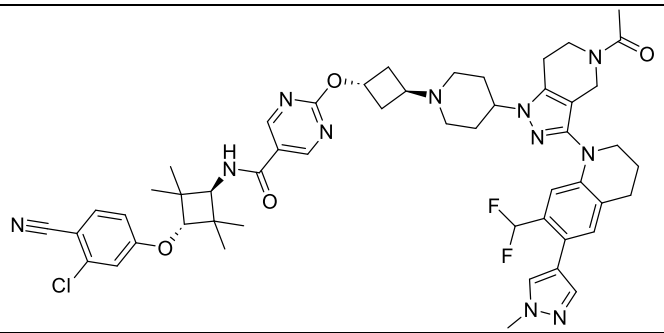
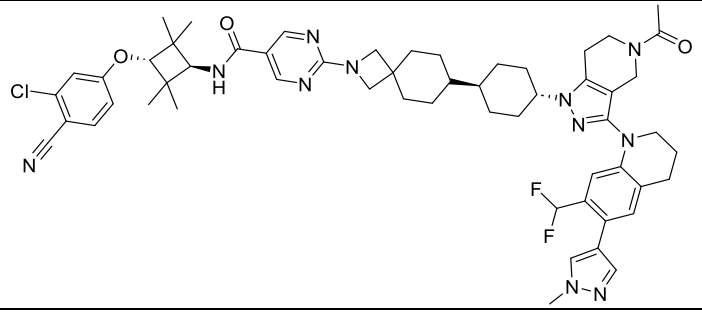
Compuesto	Estructura
340	
341	
342	
343	
344	

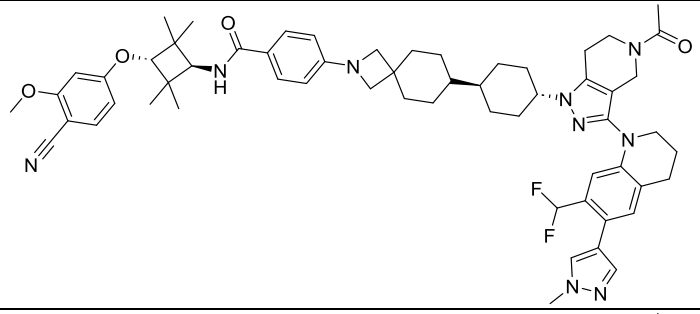
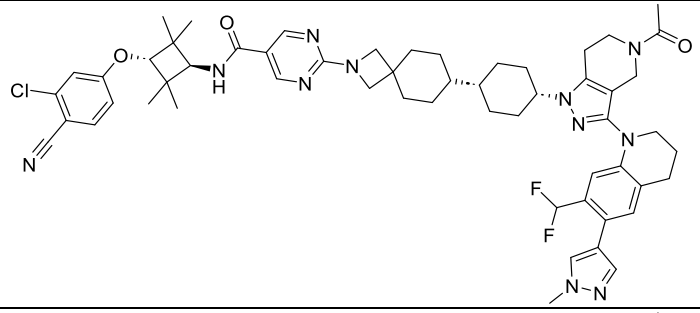
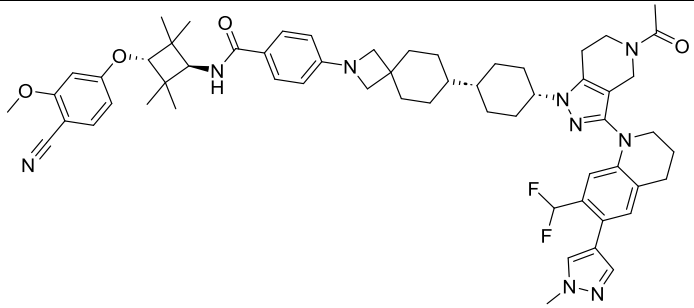
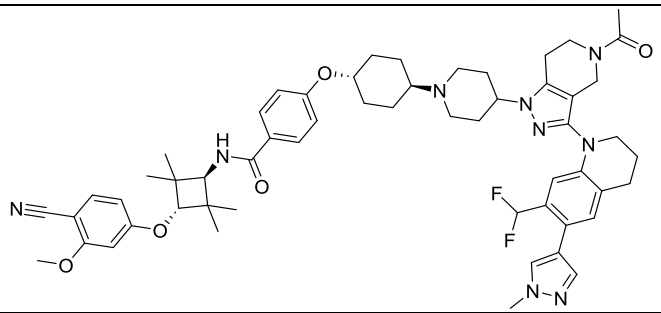
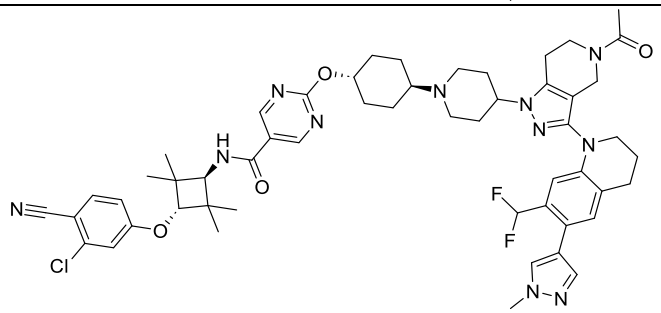
Compuesto	Estructura
345	
346	
347	
348	
349	

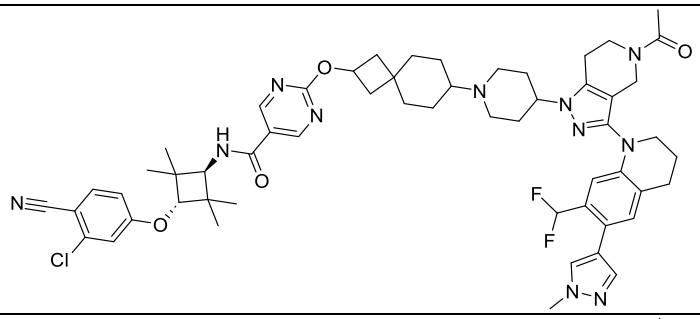
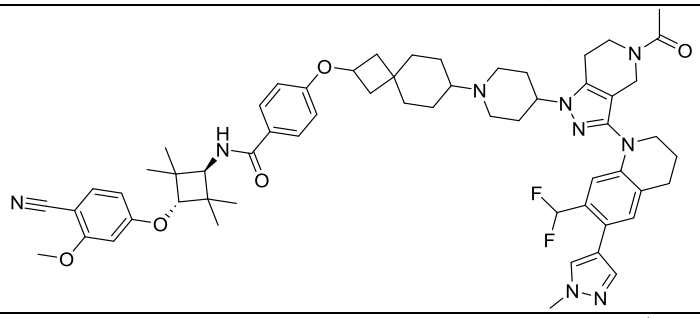
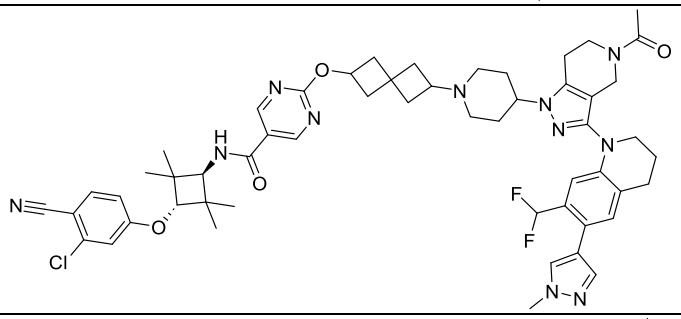
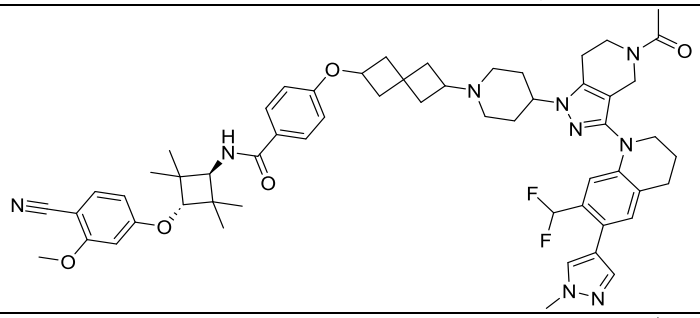
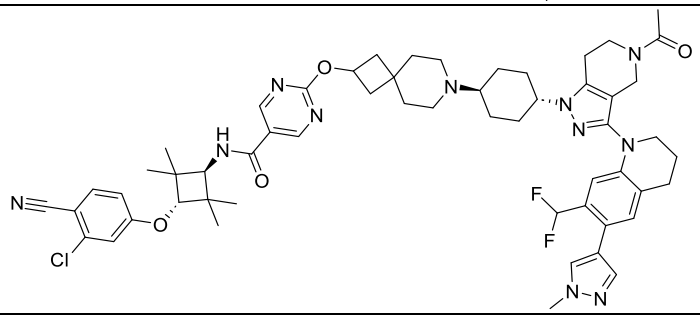
Compuesto	Estructura
350	
355	
356	
357	
360	
362	

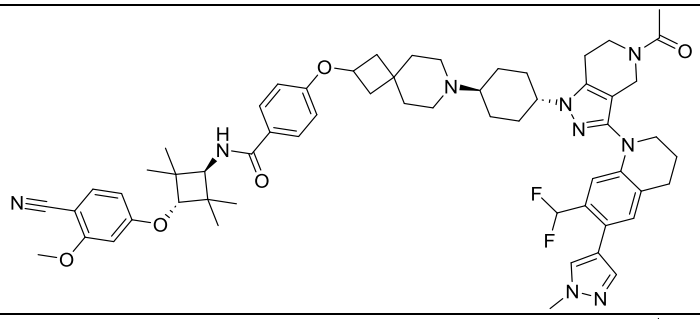
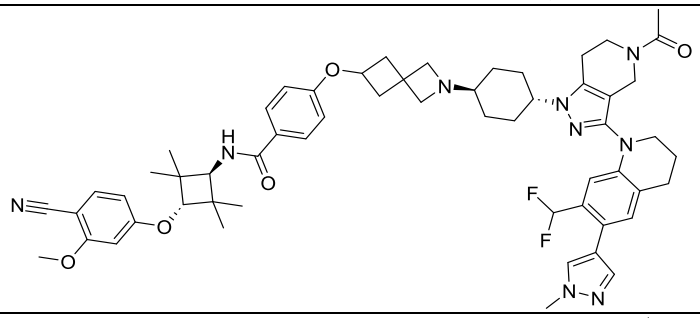
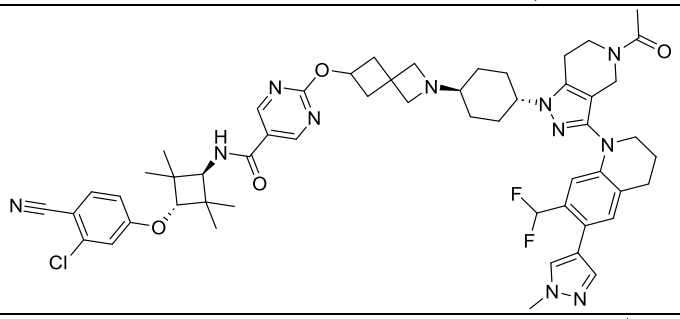
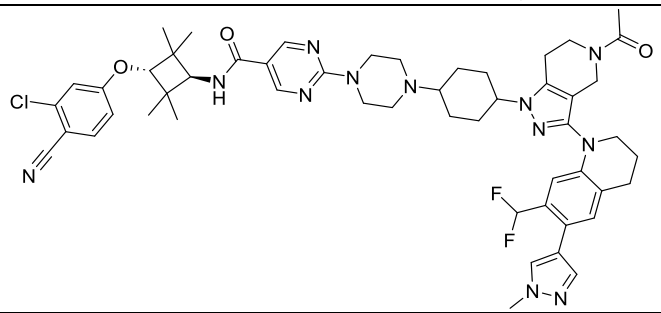
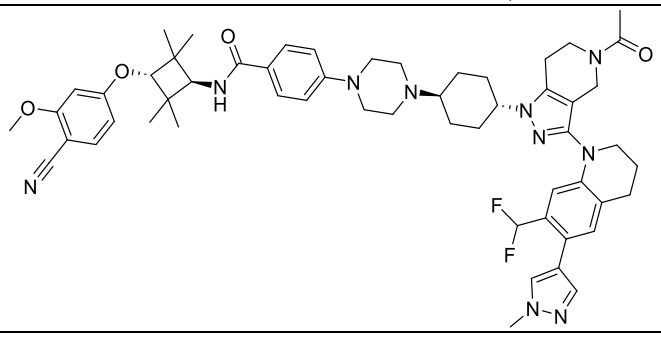
Compuesto	Estructura
363	
364	
365	
366	
367	

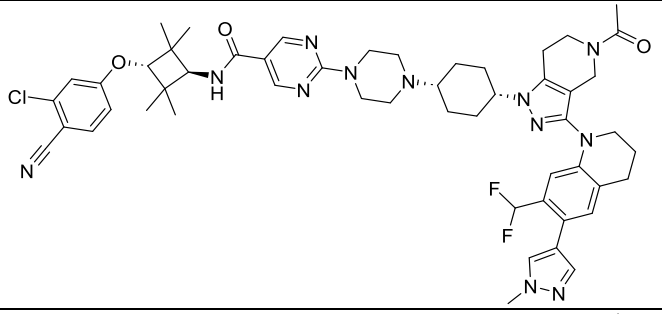
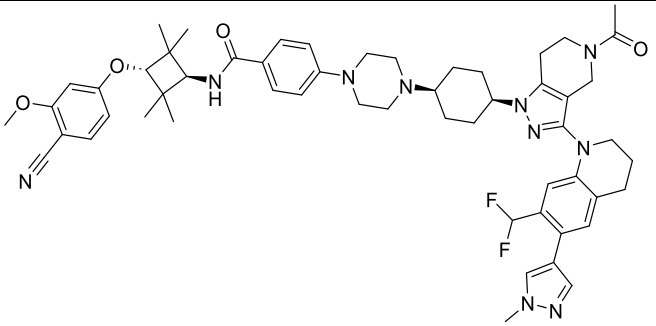
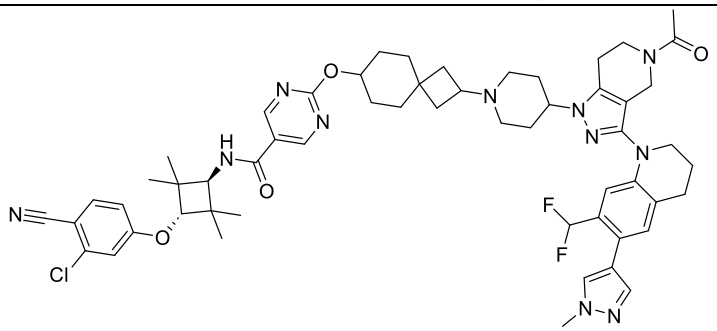
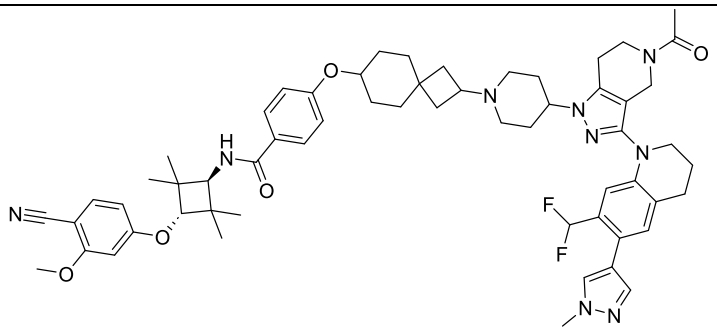
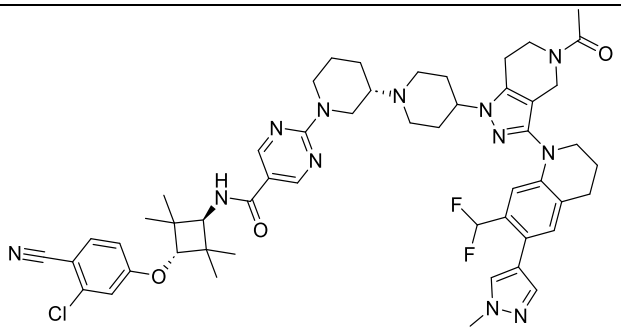
Compuesto	Estructura
368	
369	
370	
371	
372	

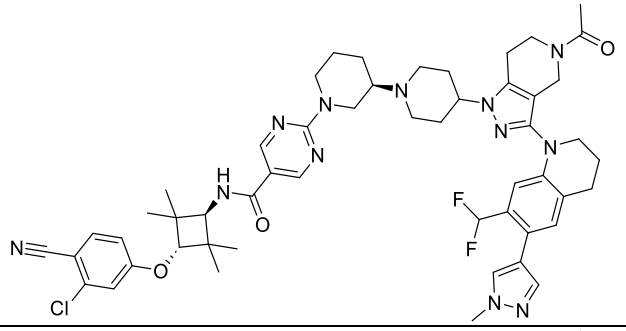
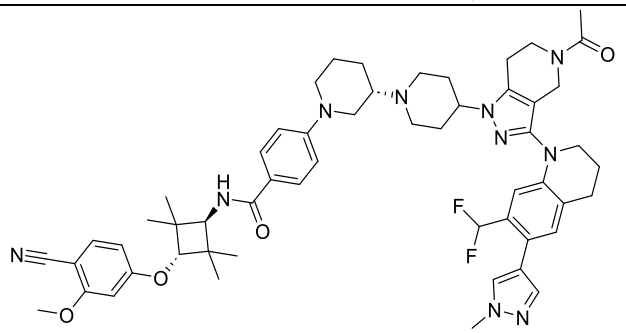
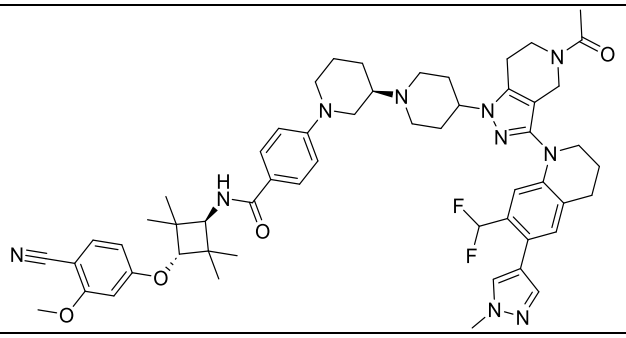
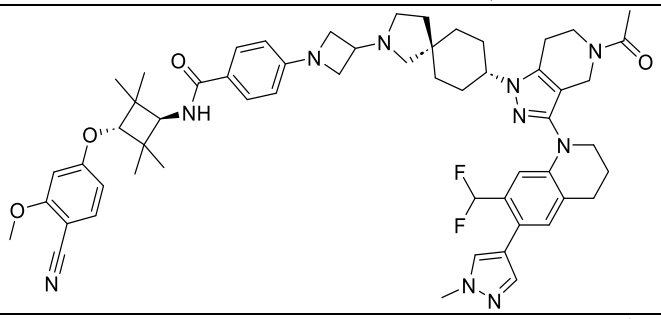
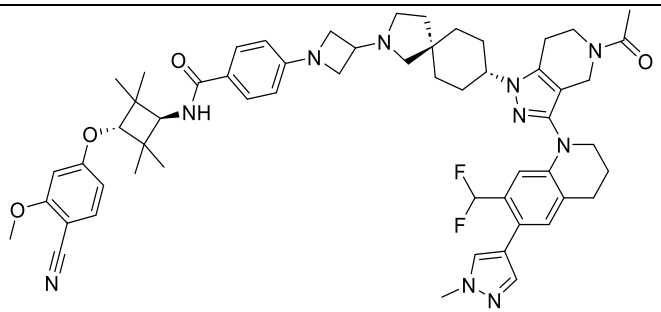
Compuesto	Estructura
373	
374	
375	
376	
377	

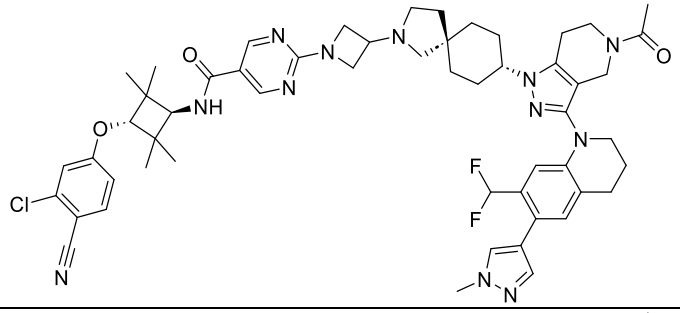
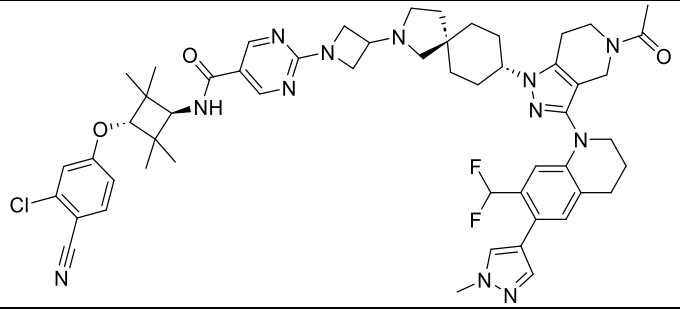
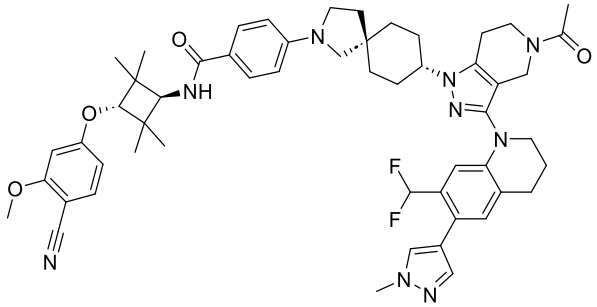
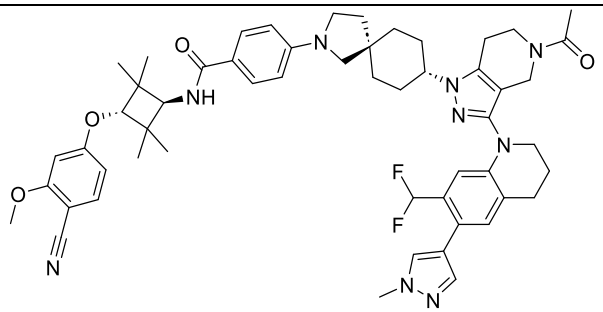
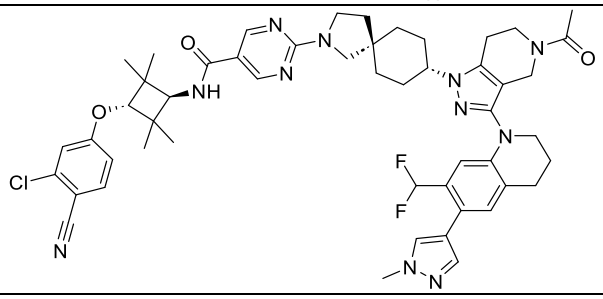
Compuesto	Estructura
378	
379	
380	
381	
382	

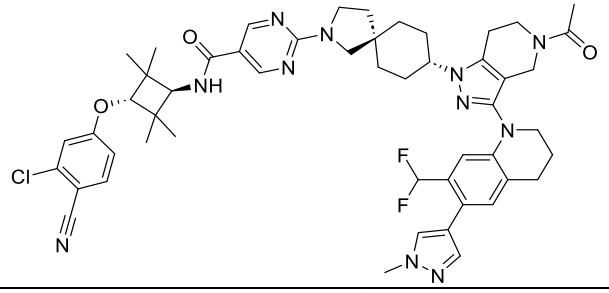
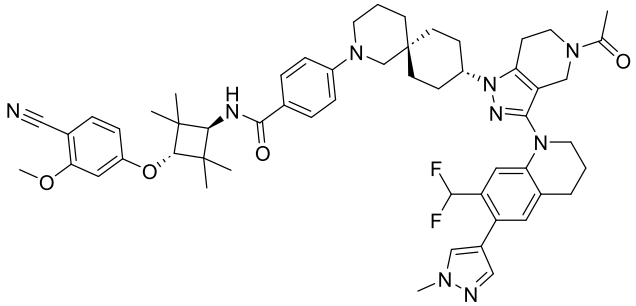
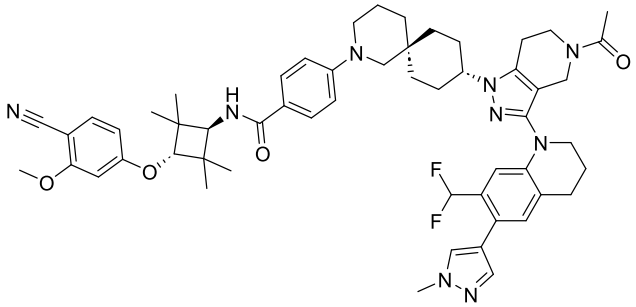
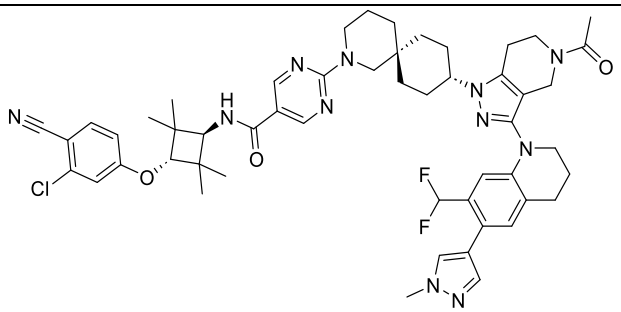
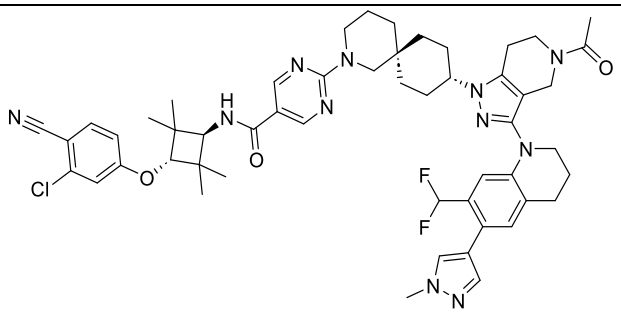
Compuesto	Estructura
383	
384	
385	
386	
387	

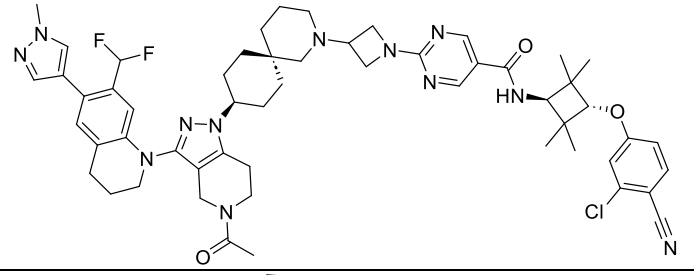
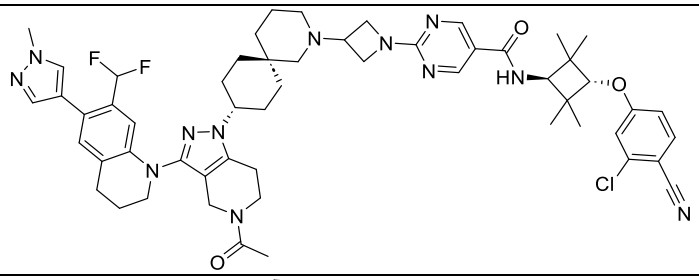
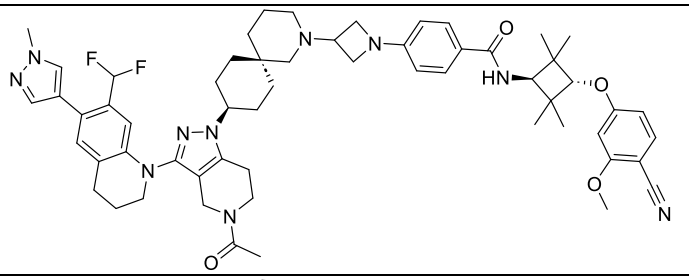
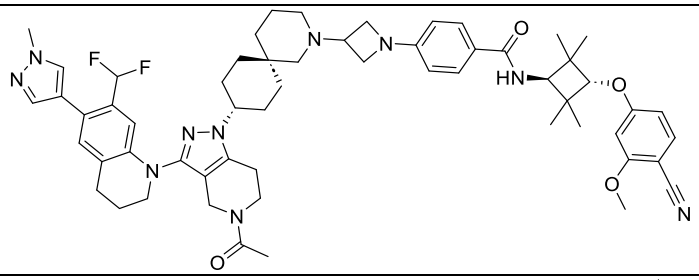
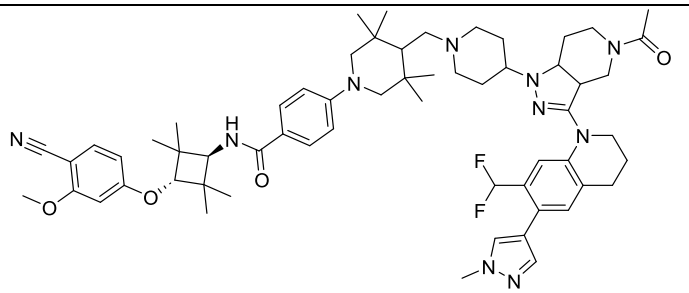
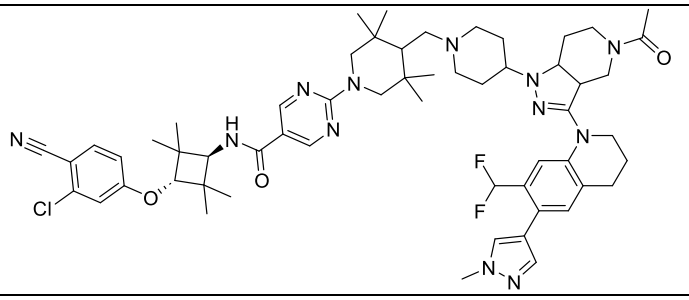
Compuesto	Estructura
388	
389	
390	
391	
392	

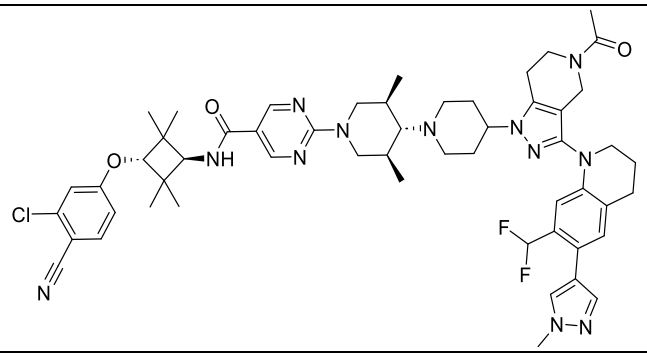
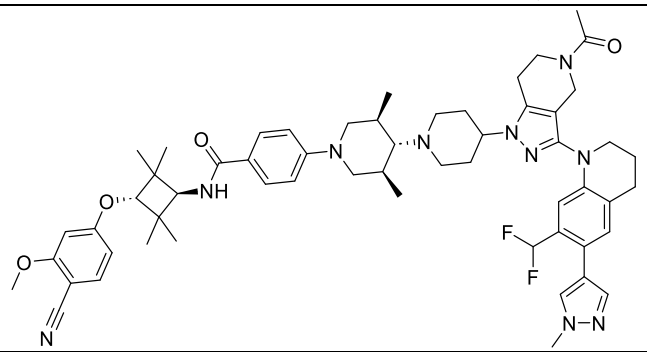
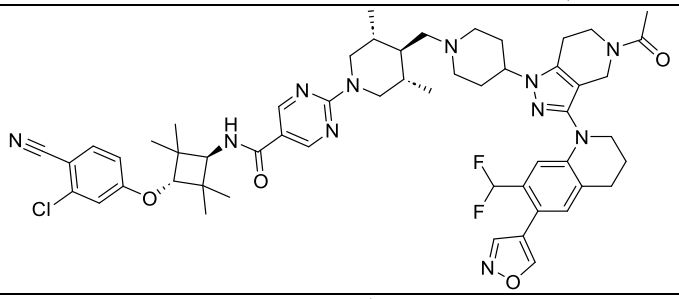
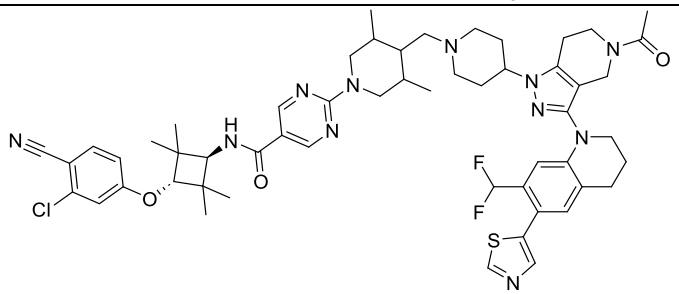
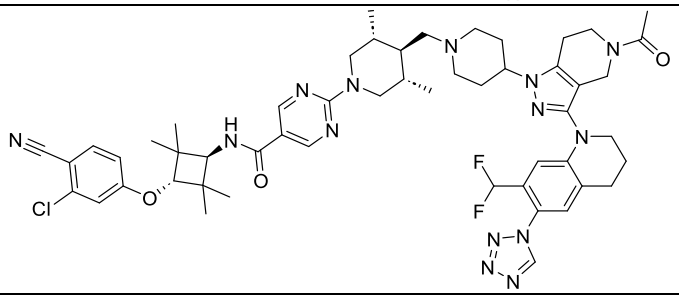
Compuesto	Estructura
393	
394	
395	
396	
397	

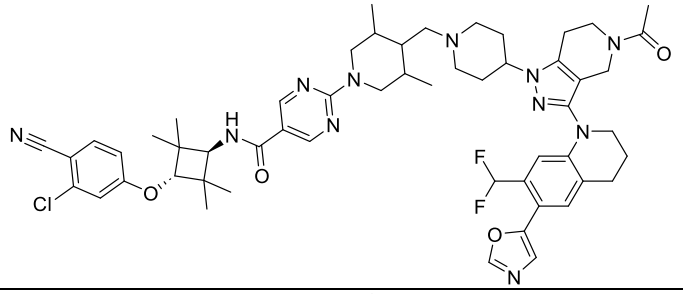
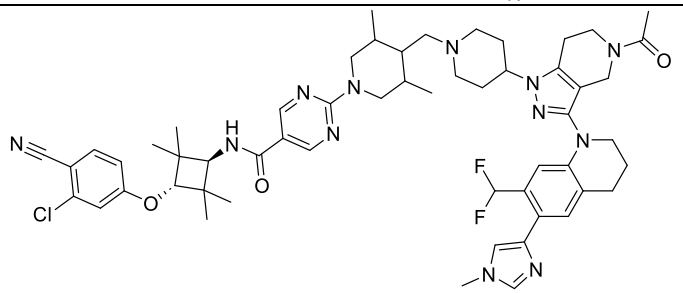
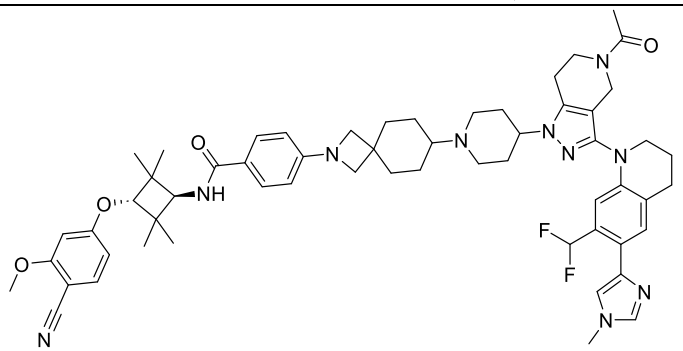
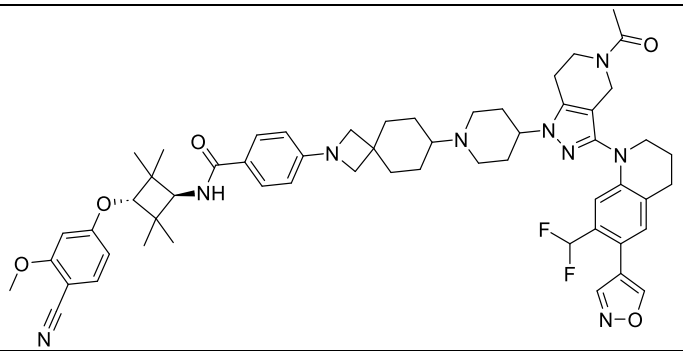
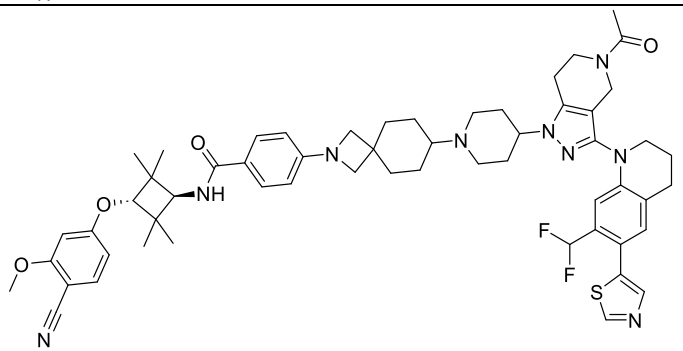
Compuesto	Estructura
398	
399	
400	
401	
402	

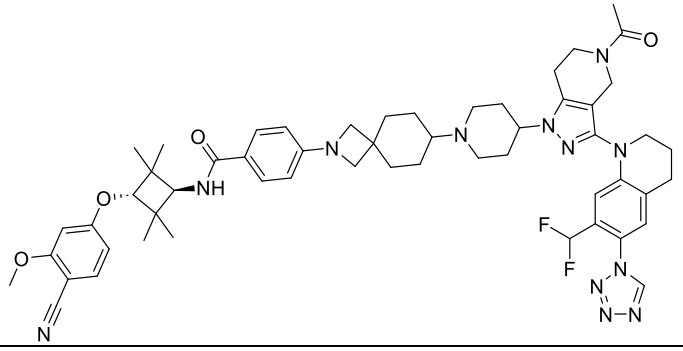
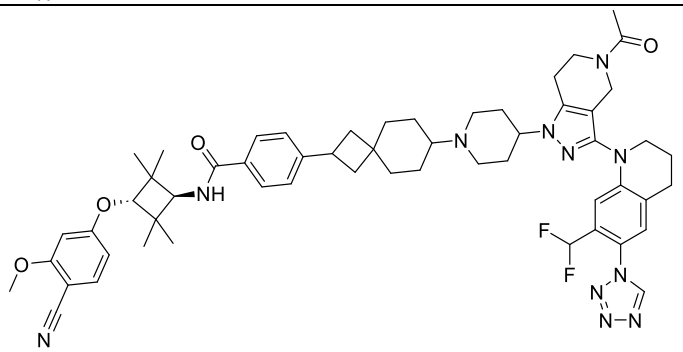
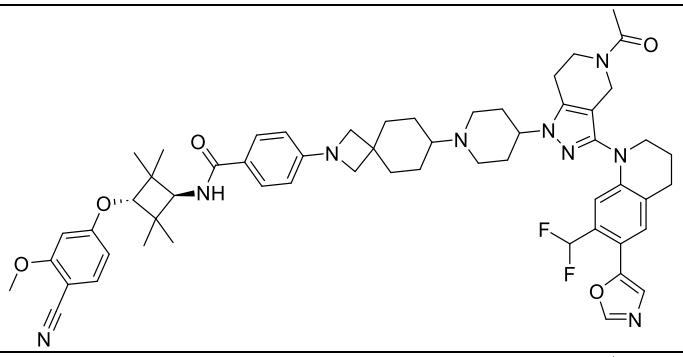
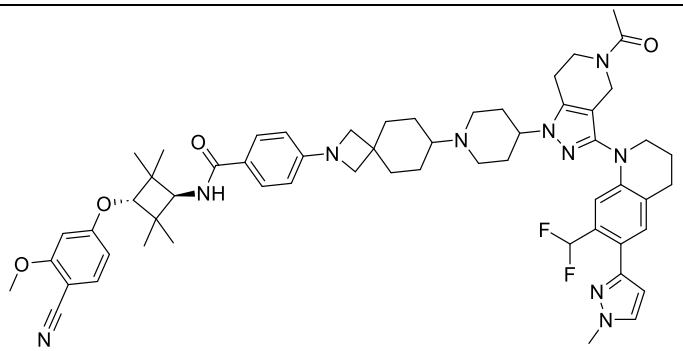
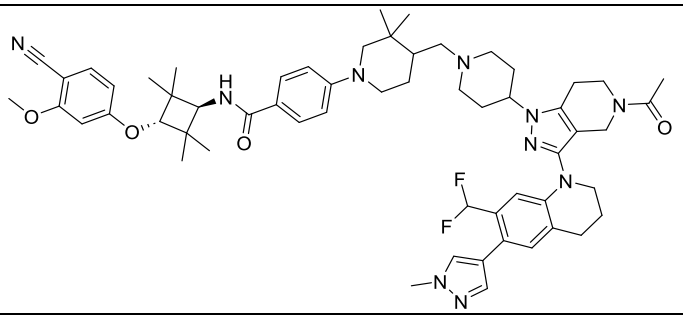
Compuesto	Estructura
403	
404	
405	
406	
407	

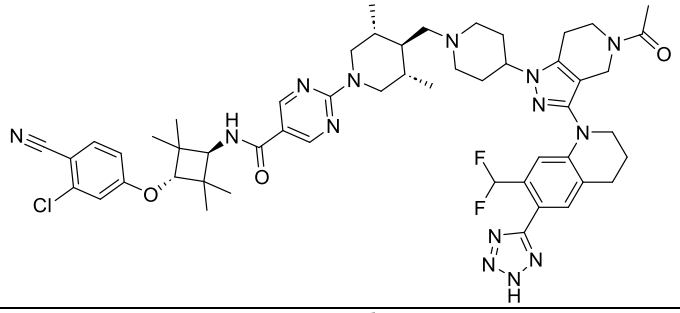
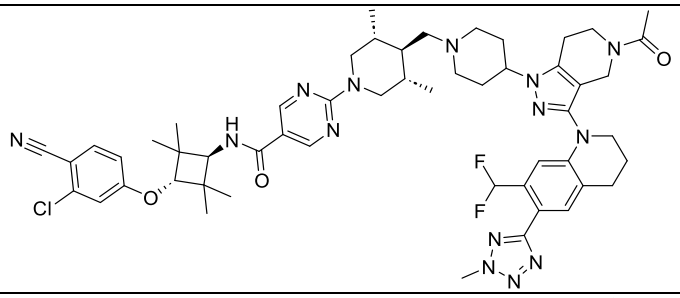
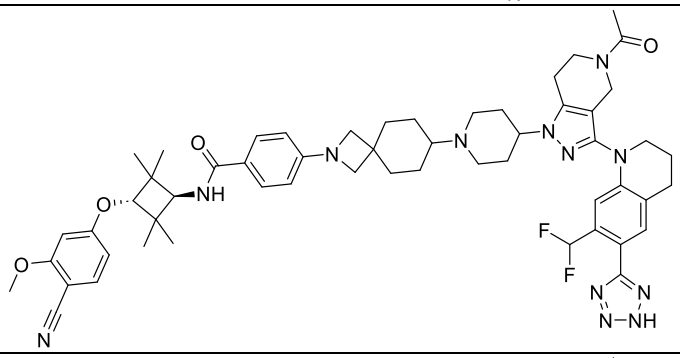
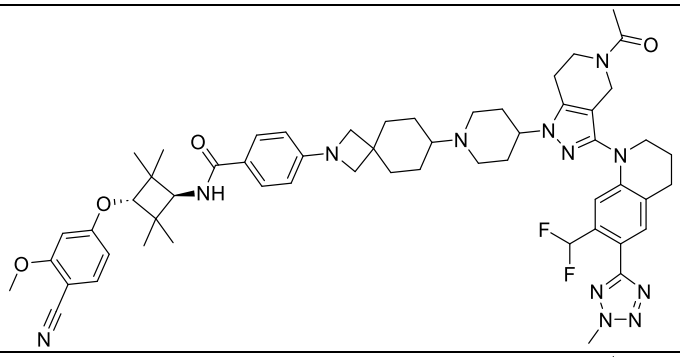
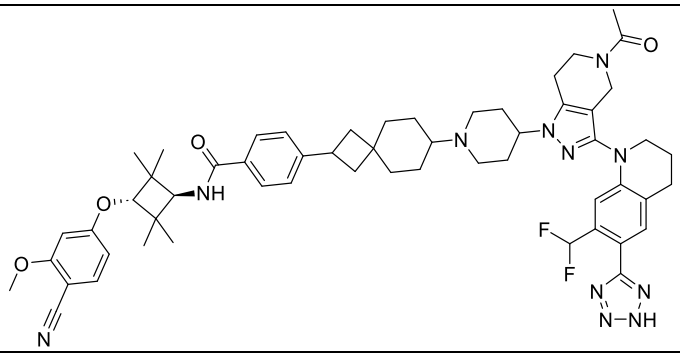
Compuesto	Estructura
408	
409	
410	
411	
412	

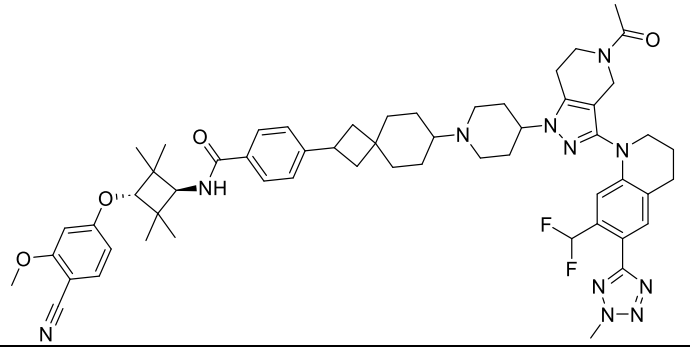
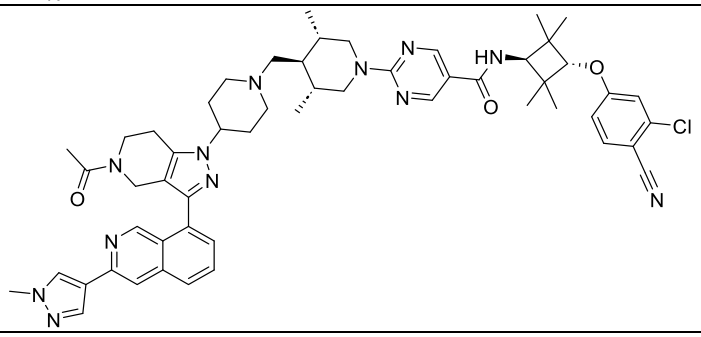
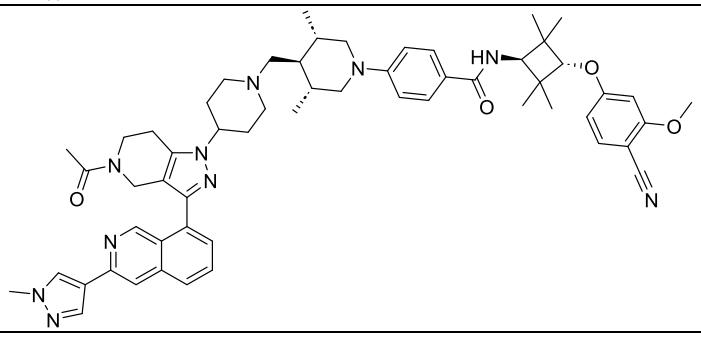
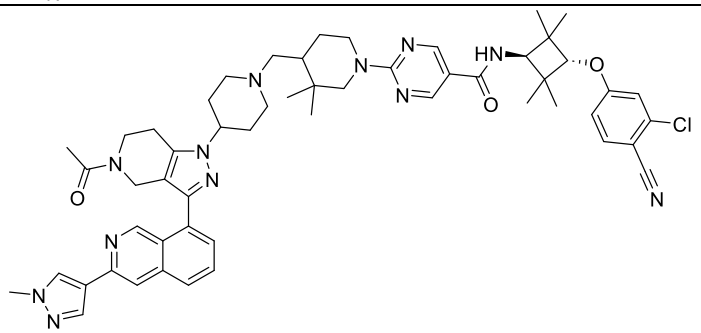
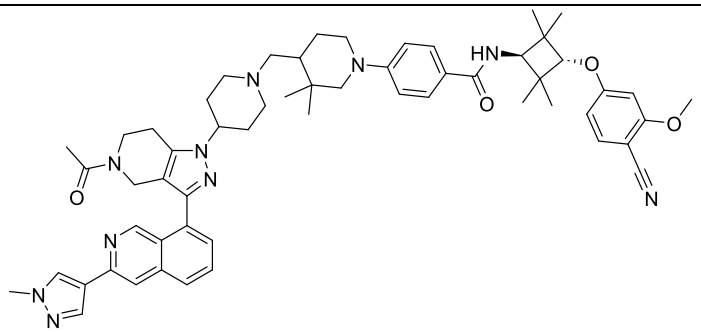
Compuesto	Estructura
413	
414	
415	
416	
417	
418	

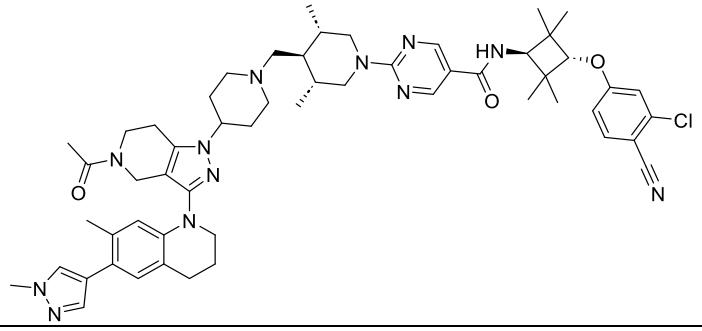
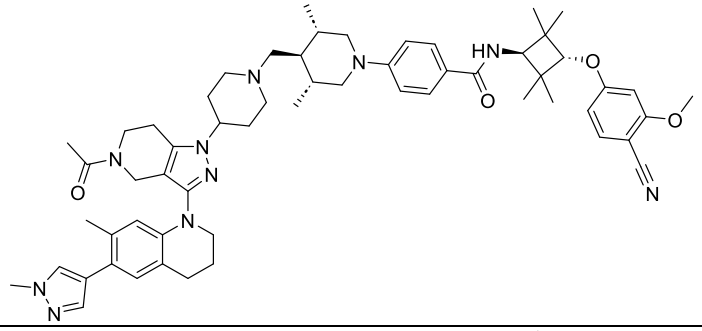
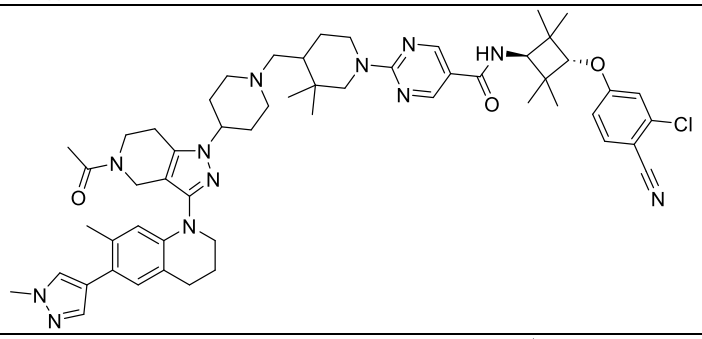
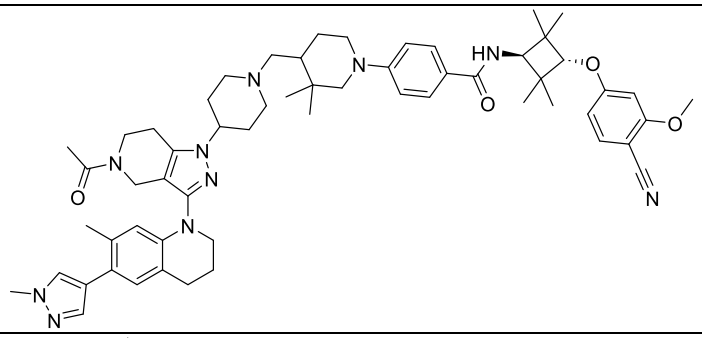
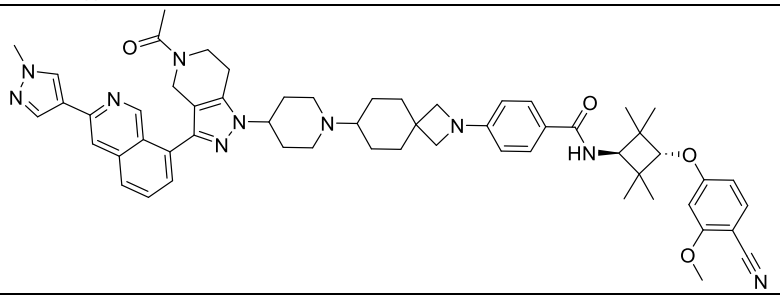
Compuesto	Estructura
419	
420	
421	
422	
423	

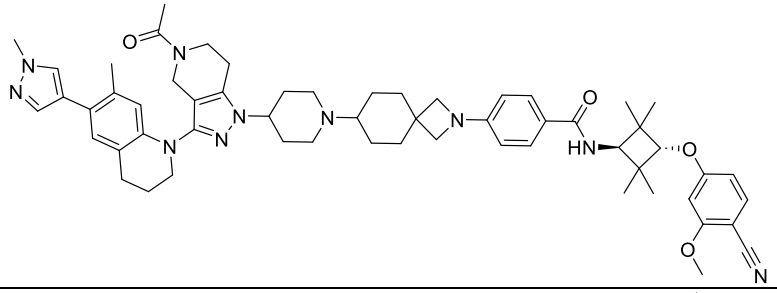
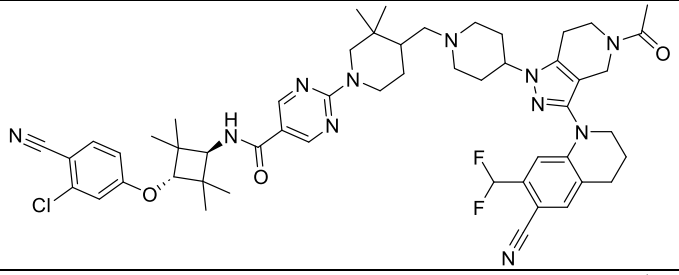
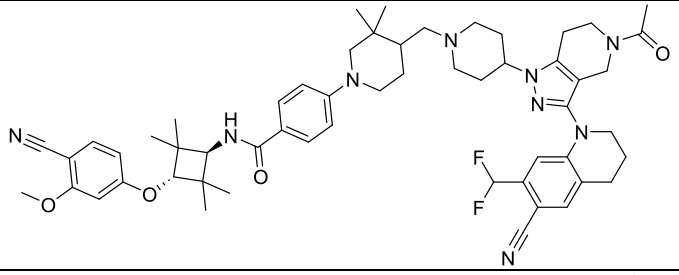
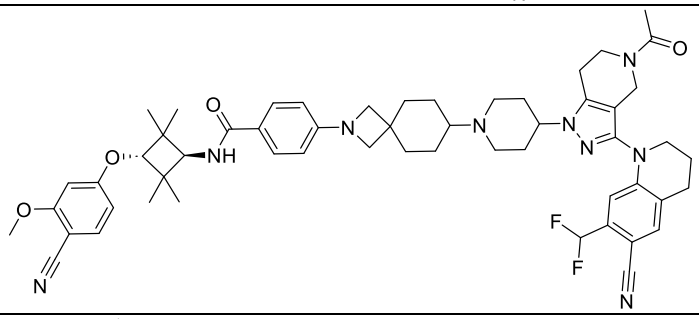
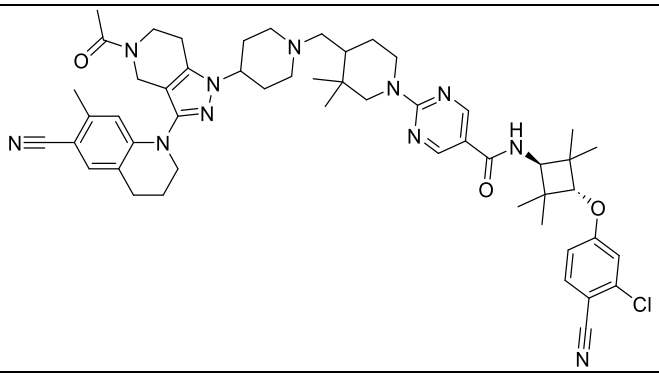
Compuesto	Estructura
424	
425	
426	
427	
428	

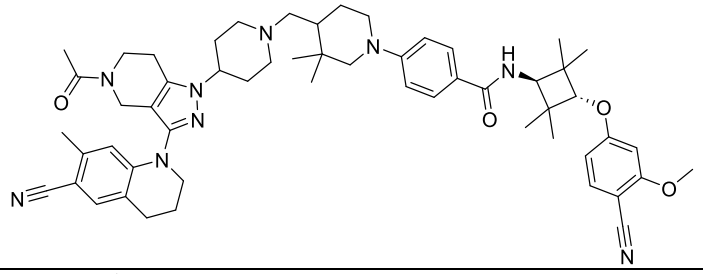
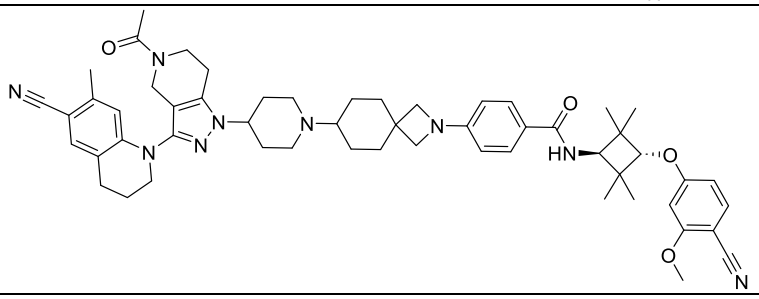
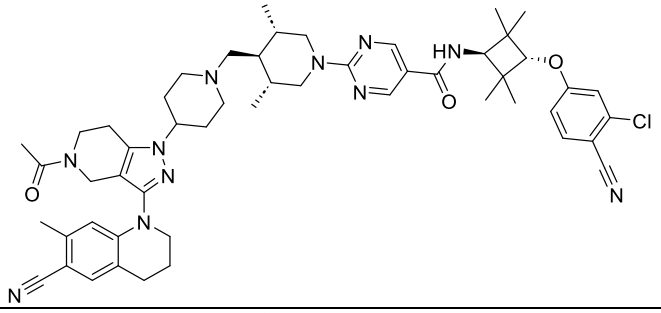
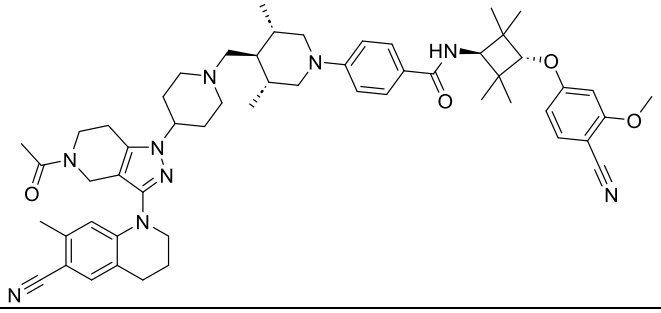
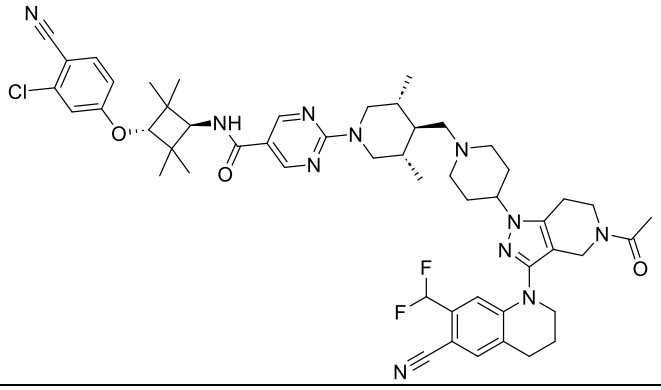
Compuesto	Estructura
429	
430	
431	
432	
433	

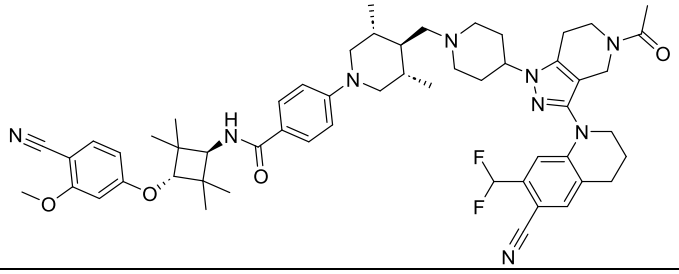
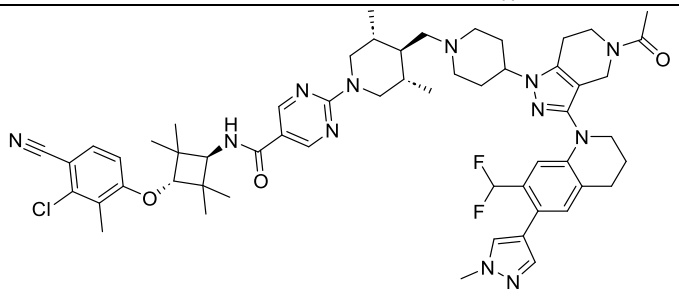
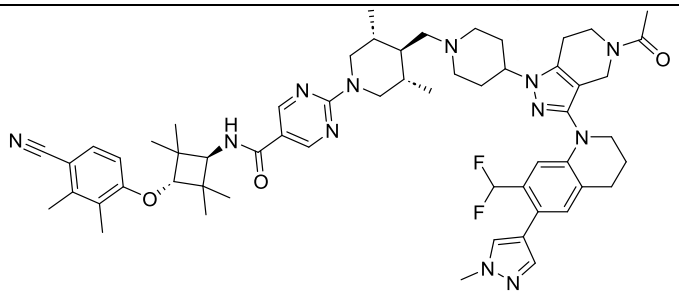
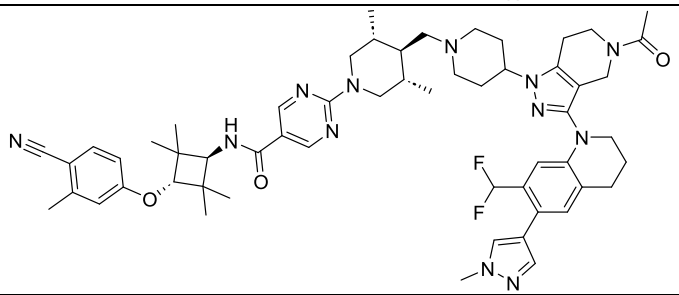
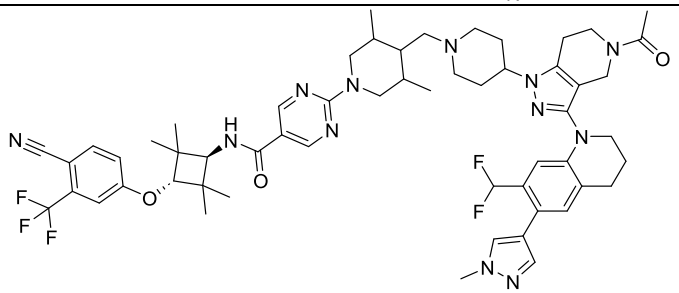
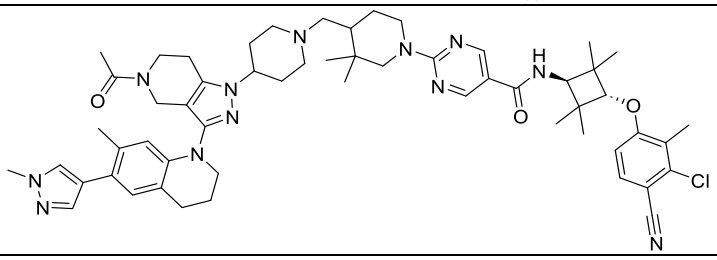
Compuesto	Estructura
434	
435	
436	
437	
438	

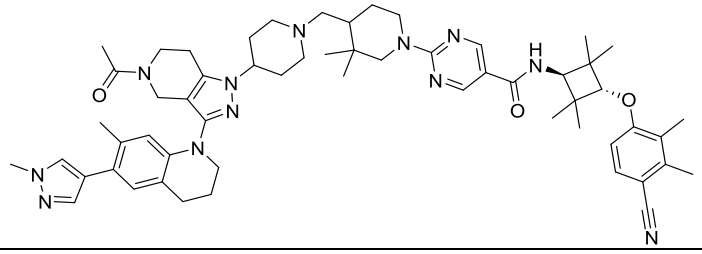
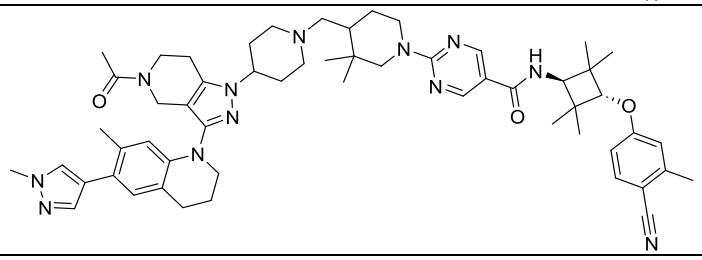
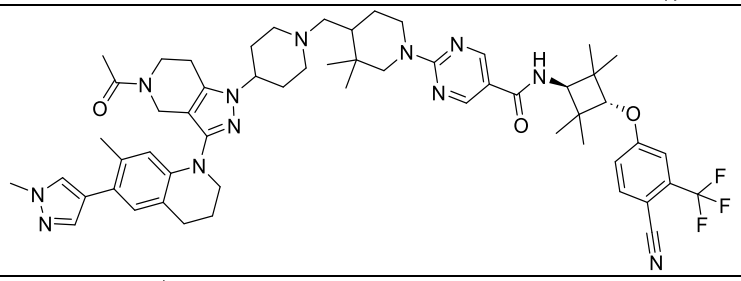
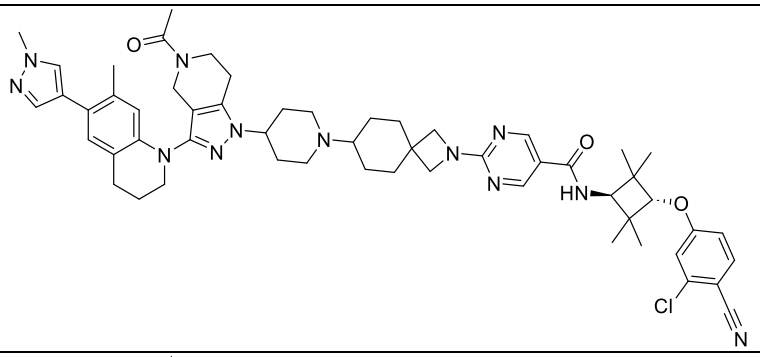
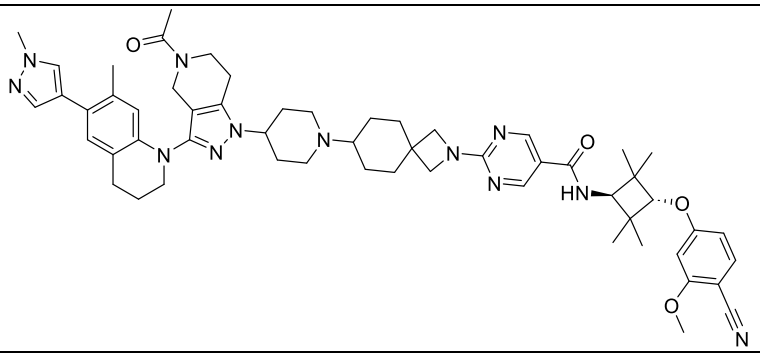
Compuesto	Estructura
439	
440	
441	
442	
443	

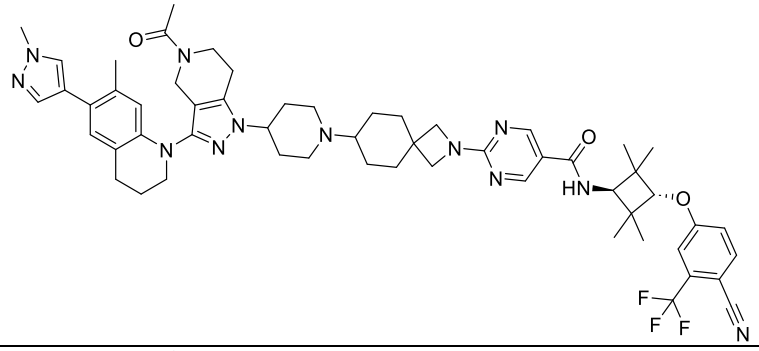
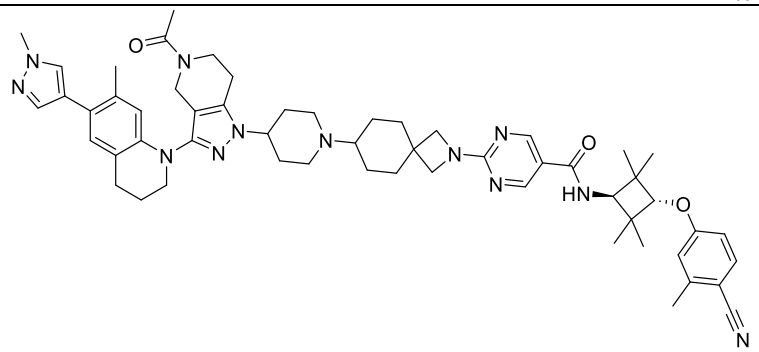
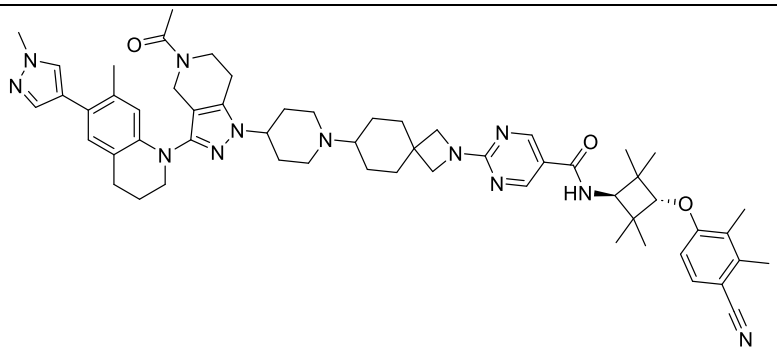
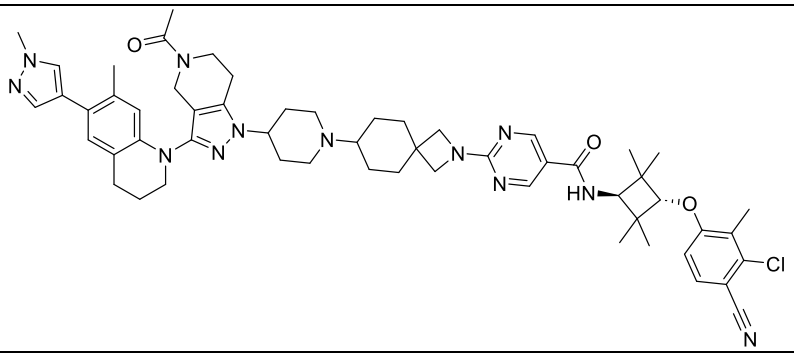
Compuesto	Estructura
444	
445	
446	
447	
448	

Compuesto	Estructura
449	
450	
451	
452	
453	

Compuesto	Estructura
454	
455	
456	
457	
458	

Compuesto	Estructura
459	
460	
461	
462	
463	
464	

Compuesto	Estructura
465	
466	
467	
468	
469	

Compuesto	Estructura
470	
471	
472	
473	

Otras formas de compuestos

[00321] En cierto modo, los compuestos descritos en este documento se presentan en forma de sales farmacéuticamente aceptables. Asimismo, los metabolitos activos de estos compuestos que tengan el mismo tipo de actividad están incluidos en el alcance de la presente divulgación. Además, los compuestos descritos en la presente abarcan formas no solvatadas así como también solvatadas con solventes farmacéuticamente

aceptables, tales como agua, etanol y similares. Las formas solvatadas de los compuestos descritos en la presente también se consideran divulgados en la presente.

[00322] La expresión “farmacéuticamente aceptable”, tal como se utiliza en el presente documento, se refiere a un material, como un excipiente o un diluyente, que no anula la actividad biológica ni las propiedades del compuesto y que es relativamente no tóxico; es decir, el material se administra a un individuo sin causar efectos biológicos indeseables ni interactuar de manera perjudicial con ninguno de los componentes de la composición en la que está contenido.

[00323] La expresión “sal farmacéuticamente aceptable” se refiere a una forma de un agente terapéuticamente activo que consiste en una forma catiónica del agente terapéuticamente activo en combinación con un anión adecuado, o, en otras formas de realización, una forma aniónica del agente terapéuticamente activo en combinación con un catión adecuado. Manual de sales farmacéuticas: propiedades, selección y uso. Unión Internacional de Química Pura y Aplicada, Wiley-VCH 2002. SM Berge, LD Bighley, DC Monkhouse, J. Pharm. Ciencia. 1977, 66, 1-19. PH Stahl y CG Wermuth, editores, *Manual de sales farmacéuticas: propiedades, selección y uso*, Weinheim/Zúrich:Wiley-VCH/VHCA, 2002. Las sales farmacéuticas suelen ser más solubles y se disuelven más rápidamente en los jugos estomacales e intestinales que las sustancias no iónicas, por lo que resultan útiles en formas farmacéuticas sólidas. Además, debido a que su solubilidad suele depender del pH, es posible la disolución selectiva en una u otra parte del tracto digestivo, y esta capacidad puede manipularse como un aspecto de los mecanismos de liberación retardada y sostenida. Además, dado que la molécula formadora de sal puede estar en equilibrio con una forma neutra, se puede regular su paso a través de las membranas biológicas.

[00324] En algunas formas de realización, se obtienen sales farmacéuticamente aceptables mediante la reacción de un compuesto aquí descrito con un ácido. En algunas formas de realización, el compuesto aquí descrito (es decir, en forma de base libre) es básico y reacciona con un ácido orgánico o un ácido inorgánico. Los ácidos inorgánicos incluyen, entre otros, el ácido clorhídrico, el ácido bromhídrico, el ácido sulfúrico, el ácido fosfórico, el ácido nítrico y el ácido metafosfórico. Los ácidos orgánicos incluyen, pero no se limitan a, ácido 1-hidroxi-2-naftoico; ácido 2,2-dicloroacético; ácido 2-hidroxietanosulfónico; ácido 2-oxoglutárico; ácido 4-acetamidobenzoico; ácido 4-aminosalicílico; ácido acético; ácido adípico; ácido ascórbico (L); ácido aspártico (L); ácido bencenosulfónico; ácido benzoico; ácido canfórico (+); ácido canfor-10-sulfónico (+); ácido cáprico (ácido decanoico); ácido caproico (ácido hexanoico); ácido caprílico

(ácido octanoico); ácido carbónico; ácido cinámico; ácido cítrico; ácido ciclámico; ácido dodecilsulfúrico; ácido etano-1,2-disulfónico; ácido etanosulfónico; ácido fórmico; ácido fumárico; ácido galactárico; ácido gentísico; ácido glucoheptónico (D); ácido glucónico (D); ácido glucurónico (D); ácido glutámico; ácido glutárico; ácido glicerofosfórico; ácido glicólico; ácido hipúrico; ácido isobutírico; ácido láctico (DL); ácido lactobiónico; ácido láurico; ácido maleico; ácido málico (-L); ácido malónico; ácido mandélico (DL); ácido metanosulfónico; ácido naftaleno-1,5-disulfónico; ácido naftaleno-2-sulfónico; ácido nicotínico; ácido oleico; ácido oxálico; ácido palmítico; ácido pamoico; ácido fosfórico; ácido propiónico; ácido piroglutámico (-L); ácido salicílico; ácido sebácico; ácido esteárico; ácido succínico; ácido sulfúrico; ácido tartárico (+L); ácido tiociánico; ácido toluenosulfónico (*p*); y ácido undecilénico.

[00325] En algunas formas de realización, se obtienen sales farmacéuticamente aceptables mediante la reacción de un compuesto aquí descrito con una base. En algunas formas de realización, el compuesto aquí descrito es ácido y reacciona con una base. En tales situaciones, un protón ácido del compuesto aquí descrito se reemplaza por un ion metálico, por ejemplo, litio, sodio, potasio, magnesio, calcio o un ion aluminio. En algunos casos, los compuestos descritos en este documento se coordinan con una base orgánica, como por ejemplo, pero sin limitarse a, etanolamina, dietanolamina, trietanolamina, trometamina, meglumina, N-metilglucamina, diciclohexilamina, tris(hidroximetil)metilamina. En otros casos, los compuestos descritos en este documento forman sales con aminoácidos como la arginina, la lisina y otros similares, entre otros. Las bases inorgánicas aceptables que se utilizan para formar sales con compuestos que incluyen un protón ácido incluyen, entre otras, hidróxido de aluminio, hidróxido de calcio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, hidróxido de sodio, hidróxido de litio y similares. En algunas formas de realización, los compuestos aquí descritos se preparan como sal de sodio, sal de calcio, sal de potasio, sal de magnesio, sal de meglumina, sal de N-metilglucamina o sal de amonio.

[00326] Debe entenderse que una referencia a una sal farmacéuticamente aceptable incluye las formas de adición de solvente. Los solvatos contienen cantidades estequiométricas o no estequiométricas de un solvente y, en algunas formas de realización, se forman durante el proceso de cristalización con solventes farmacéuticamente aceptables tales como agua, etanol y similares. Los hidratos se forman cuando el solvente es agua, o los alcoholatos se forman cuando el solvente es alcohol. Los solvatos de los compuestos descritos en la presente pueden prepararse o formarse convenientemente durante los procesos descritos en la presente. Además, los

compuestos proporcionados en la presente pueden existir en formas no solvatadas, así como solvatadas.

[00327] Los métodos y formulaciones descritos en el presente documento incluyen el uso de *N*-óxidos (si procede), o sales farmacéuticamente aceptables de compuestos que tienen la estructura aquí divulgada, así como metabolitos activos de estos compuestos que tienen el mismo tipo de actividad.

[00328] En algunas formas de realización, los sitios de los radicales orgánicos (por ejemplo, grupos alquilo, anillos aromáticos) de los compuestos aquí descritos son susceptibles a diversas reacciones metabólicas. La incorporación de sustituyentes apropiados en los radicales orgánicos reducirá, minimizará o eliminará esta vía metabólica. En determinadas formas de realización, el sustituyente apropiado para disminuir o eliminar la susceptibilidad del anillo aromático a las reacciones metabólicas es, a modo de ejemplo, un halógeno, deuterio, un grupo alquilo, un grupo haloalquilo o un grupo deuteroalquilo.

[00329] En algunas formas de realización, los compuestos descritos en la presente se etiquetan mediante otros medios, que incluyen, entre otros, el uso de cromóforos o porciones fluorescentes, etiquetas bioluminiscentes o etiquetas quimioluminiscentes.

[00330] Los compuestos de la invención también incluyen compuestos marcados de manera isotópica que son idénticos a los descritos en la presente, salvo por el hecho de que uno o más átomos se reemplazan mediante un átomo que tiene una masa atómica o el número másico que se encuentra habitualmente en la naturaleza. Ejemplos de isótopos que pueden incorporarse a los compuestos presentes incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, azufre, flúor, cloro, yodo, fósforo, como por ejemplo, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{32}P y ^{33}P. Ciertos compuestos etiquetados isotópicamente, por ejemplo, aquellos en los que se incorporan isótopos radiactivos tales como ^{3}H y ^{14}C, son útiles en ensayos de distribución de tejido de sustrato y/o fármacos. En un aspecto, la sustitución con isótopos como el deuterio ofrece ciertas ventajas terapéuticas derivadas de una mayor estabilidad metabólica, como, por ejemplo, una mayor *vida media in vivo* o una reducción de los requerimientos de dosis.

[00331] En algunas formas de realización, los compuestos aquí descritos poseen uno o más estereocentros, y cada estereocentro existe de forma independiente en la configuración R o S. En algunas formas de realización, el compuesto aquí descrito existe en la configuración R. En algunas formas de realización, el compuesto aquí descrito existe en la configuración S. Los compuestos descritos en la presente incluyen todas las

formas diastereoméricas, enantioméricas y epiméricas, así como las mezclas correspondientes de estas. Los compuestos presentados en la presente incluyen todos los isómeros cis, trans, syn, anti, entgegen (opuestos) (E) y zusammen (Z), así como las mezclas correspondientes de estos.

[00332] Si se desea, los estereoisómeros individuales se obtienen mediante métodos como la síntesis estereoselectiva y/o la separación de estereoisómeros mediante columnas cromatográficas quirales, o la separación de diastereómeros mediante columnas cromatográficas quirales o no quirales, o la cristalización y recristalización en un disolvente adecuado o una mezcla de disolventes. En algunas formas de realización, los compuestos descritos en la presente se preparan como sus estereoisómeros individuales al hacer reaccionar una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisoméricos, separar los diastereómeros y recuperar los enantiómeros ópticamente puros. En algunas formas de realización, la resolución de enantiómeros individuales se lleva a cabo utilizando derivados diastereoméricos covalentes de los compuestos descritos en el presente documento. En algunas formas de realización, los diastereómeros se separan mediante cromatografía quiral, o preferentemente, mediante técnicas de separación/resolución en función de las diferencias en la solubilidad. En otras formas de realización, la separación de estereoisómeros se realiza mediante cromatografía o mediante la formación de sales diastereoméricas y su posterior separación por recristalización, cromatografía o cualquier combinación de las mismas. Jean Jacques, Andre Collet, Samuel H. Wilen, “Enantiómeros, racematos y resoluciones”, John Wiley And Sons, Inc., 1981. En algunos casos, los estereoisómeros se obtienen mediante síntesis estereoselectiva.

[00333] En algunas formas de realización, los compuestos descritos en el presente documento se analizaron de la siguiente manera: Un “profármaco” se refiere a un agente que se convierte en el fármaco original *in vivo*. Los profármacos suelen ser útiles porque, en algunas situaciones, son más fáciles de administrar que el fármaco original. Por ejemplo, son biodisponibles por vía oral, mientras que el compuesto original no lo es. Además, o como alternativa, el profármaco también presenta una solubilidad mejorada en composiciones farmacéuticas en comparación con el fármaco original. En algunas formas de realización, el diseño de un profármaco aumenta la solubilidad efectiva en agua. Un ejemplo, sin limitación, de un profármaco es un compuesto descrito en el presente documento, que se administra como un éster (el “profármaco”) pero que luego se hidroliza metabólicamente para proporcionar la entidad activa. Otro ejemplo de

profármaco es un péptido corto (poliaminoácido) unido a un grupo ácido, donde el péptido se metaboliza para revelar la parte activa. En ciertas formas de realización, tras la administración *in vivo*, un profármaco se convierte químicamente en la forma biológicamente, farmacéuticamente o terapéuticamente activa del compuesto. En ciertas formas de realización, un profármaco se metaboliza enzimáticamente mediante uno o más pasos o procesos hasta convertirse en la forma biológicamente, farmacéuticamente o terapéuticamente activa del compuesto.

[00334] Los profármacos de los compuestos descritos en el presente documento incluyen, entre otros, ésteres, éteres, carbonatos, tiocarbonatos, derivados de N-acilo, derivados de N-aciloxialquilo, derivados de N-alquiloxiacilo, derivados cuaternarios de aminas terciarias, bases de N-Mannich, bases de Schiff, conjugados de aminoácidos, ésteres de fosfato y ésteres de sulfonato. Véase, por ejemplo, Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 y Method in Enzymology, Widder, K. *et al*., Ed.; Academic, 1985, vol. 42, páginas 309-396; Bundgaard, H. "Design and Application of Prodrugs" en A Textbook of Drug Design and Development, Krosgaard-Larsen y H. Bundgaard, Ed., 1991, Capítulo 5, páginas 113-191; y Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, cada uno de los cuales se incorpora aquí por referencia. En algunas formas de realización, un grupo hidroxilo en los compuestos aquí descritos se utiliza para formar un profármaco, en el que el grupo hidroxilo se incorpora a un éster de aciloxialquilo, éster de alcoxicarboniloxialquilo, éster de alquilo, éster de arilo, éster de fosfato, éster de azúcar, éter, etc. En algunas formas de realización, un grupo hidroxilo en los compuestos aquí descritos es un profármaco en el que el hidroxilo se metaboliza in vivo para proporcionar un grupo ácido carboxílico. En algunas formas de realización, se utiliza un grupo carboxilo para proporcionar un éster o una amida (es decir, el profármaco), que luego se metaboliza in vivo para proporcionar un grupo ácido carboxílico. En algunas formas de realización, los compuestos descritos en el presente documento se preparan como profármacos de éster alquílico.

Terminología específica

[00335] A menos que se indique de otro modo, los siguientes términos que se usan en la memoria descriptiva y las reivindicaciones tienen los significados que se proporcionan a continuación: Además, el uso de la expresión "que incluye", así como de otras formas, tales como "incluye" e "incluido" no es limitativa.

[00336] Tal como se utiliza en el presente documento, C_1-C_x incluye C_1-C_2, C_1-C_3 . . . 2C1C: A modo de ejemplo, un grupo designado como "C_1-C_4" indica que hay de uno a cuatro átomos de carbono en la unidad, es decir, grupos que contienen 1 átomo de

carbono, 2 átomos de carbono, 3 átomos de carbono o 4 átomos de carbono. Así, a modo de ejemplo, "C_1-C_4 alquilo" indica que hay de uno a cuatro átomos de carbono en el grupo alquilo, *es decir*, el grupo alquilo se selecciona entre metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo y *t*-butilo.

[00337] El término "acilo", tal como se usa aquí, se refiere al grupo -C(=O)-R, donde R es alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, heterociclo o cualquier otra porción en la que el átomo unido al carbonilo sea carbono. Un grupo "acetilo" se refiere a un grupo –C(=O)CH_3.

[00338] El término "alquenilo", tal como se utiliza en el presente documento, se refiere a un radical hidrocarbonado de cadena lineal o ramificada que posee uno o más enlaces dobles y contiene de 2 a 20 átomos de carbono. En ciertas formas de realización, el grupo alquenilo incluye de 2 a 6 átomos de carbono. El término "alquileno" se refiere a un radical alquilo divalente. En algunas formas de realización, se selecciona un alquenilo entre etenilo (*es decir,*, vinilo), propenilo (*es decir,*, alilo), butenilo, pentenilo, pentadienilo y similares. Ejemplos no limitativos de un grupo alquenilo incluyen -CH=CH_2, -$C(CH_3)$=CH_2, -CH=$CHCH_3$, -$C(CH_3)$=$CHCH_3$ y –CH_2CH=CH_2.

[00339] El término "alcoxi" se refiere a un grupo (alquilo)-O-, donde alquilo se define aquí. En algunas formas de realización, el grupo alcoxi es un C_1-C_6alcoxi, que se refiere a un grupo (C_1-C_6alquilo)-O-. Algunos ejemplos de grupos alquilo son metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, isobutoxi, sec-butoxi, tert-butoxi, etc.

[00340] Un grupo "alquilo" se refiere a un grupo hidrocarbonado alifático. En algunas formas de realización, el alquilo es un grupo hidrocarbonado alifático de cadena lineal o ramificada que contiene de 1 a 20 átomos de carbono. En ciertas formas de realización, el grupo alquilo incluye de 1 a 10 átomos de carbono. En otras formas de realización, el grupo alcoxi contiene de 1 a 8 átomos de carbono. Algunos ejemplos de radicales alquilo son metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isoamilo, hexilo, octilo, nonilo, y similares. En algunas formas de realización, el arilo es un arilo C_1-C_6. En un aspecto, el grupo alquilo es metilo, etilo, propilo, isopropilo, n-butilo, isobutilo, sec-butilo o t-butilo. El término "alquileno" se refiere a un alquilo divalente, como el metileno (-CH_2-). En algunas formas de realización, el arilo es un arilo C_1-C_6. En algunas formas de realización, el arilo es un arilo C_1-C_4. Los radicales alquileno habituales incluyen, entre otros: metileno (-CH_2-) 1,2-etilo (-CH_2CH_2-), 1,3-propilo (-$CH_2CH_2CH_2$-), 1,4-butilo (-$CH_2CH_2CH_2CH_2$-), y similares.

[00341] El término "amino", tal como se usa aquí, se refiere a -NRR', donde R y R' se seleccionan independientemente entre hidrógeno, alquilo, acilo, heteroalquilo, arilo,

cicloalquilo, heteroarilo y heterocicloalquilo, cualquiera de los cuales puede ser sustituido opcionalmente. Además, R y R' pueden combinarse para formar heterocicloalquilo, cualquiera de los cuales puede ser sustituido opcionalmente. En un aspecto, “amino”, tal como se usa aquí, se refiere a un grupo $-NH_2$.

[00342] El término “alquinilo”, tal como se utiliza en el presente documento, se refiere a un radical hidrocarbonado de cadena lineal o ramificada que posee uno o más enlaces triples y contiene de 2 a 20 átomos de carbono. En ciertas formas de realización, dicho alquinilo comprende de 2 a 6 átomos de carbono. En otras formas de realización, dicho alquinilo comprende de 2 a 4 átomos de carbono. En una realización, un grupo alquenilo tiene la fórmula -C≡CR, donde R se refiere a las porciones restantes del grupo alquinilo. En algunas formas de realización, Re es H o alquilo C1-6. En algunas formas de realización, se selecciona un alquinilo entre etinilo, propinilo, butinilo, pentinilo, hexinilo y similares. Ejemplos no limitativos de un grupo alquinilo incluyen -C≡CH, $-C{\equiv}CCH_3$ - $C{\equiv}CCH_2CH_3$, $-CH_2C{\equiv}CH$. El término “alquinileno” se refiere a un triple enlace carbono-carbono unido en dos posiciones como el etinileno (-C≡C-). Algunos ejemplos de radicales alquinilo son el etinilo, el propinilo, el hidroxipropinilo, el butin-1-ilo, el butin-2-ilo, el pentin-1-ilo, el 3-metilbutin-1-ilo, el hexin-2-ilo, y similares. Salvo que se especifique lo contrario, el término “alquinilo” puede incluir grupos “alquinileno”.

[00343] El término “aromático” se refiere a un anillo planar que tiene un sistema deslocalizado de π electrones que contiene $4n+2$ π electrones, donde n es un número entero. El término “aromático” incluye tanto grupos arilo carbocíclicos (“arilo”, *ej.*, fenilo) como grupos arilo heterocíclicos (o “heteroarilo” o “heteroaromático”) (*ej.*, piridina). El término incluye grupos policíclicos monocíclicos o de anillos fusionados (*es decir,*, anillos que comparten pares adyacentes de átomos de carbono).

[00344] El término “carbocíclico” o “carbociclo” se refiere a un anillo o sistema de anillos donde los átomos que forman la estructura principal del anillo son todos átomos de carbono. De este modo, el término distingue los anillos carbocíclicos de los anillos “heterocíclicos” o “heterociclos”, en los que la estructura del anillo contiene al menos un átomo diferente del carbono. En algunas formas de realización, al menos uno de los dos anillos de un carbociclo bicíclico es aromático. En algunas formas de realización, ambos anillos de un carbociclo bicíclico son aromáticos. Los carbociclos incluyen arilos y cicloalquilos.

[00345] El término “arilo”, tal como se utiliza en el presente documento, se refiere a un sistema aromático carbocíclico que contiene uno, dos o tres anillos, en el cual dichos sistemas de anillos policíclicos están fusionados entre sí. El término "arilo" abarca

radicales aromáticos, tal como, fenilo, naftilo, indenilo, tetrahidronaftilo e indanilo. En un aspecto, el arilo es fenil o un naftilo. En algunas formas de realización, el arilo es un fenilo. En algunas formas de realización, un arilo es un fenilo, naftilo, indanilo, indenilo o tetrahiodronaftilo. En algunas formas de realización, el arilo es un arilo C_6-C_{10}. Dependiendo de su estructura, un grupo arilo es un monorradical o un dirradical (es decir, un grupo arileno).

[00346] Los términos “benzo” y “benz”, tal como se utilizan en el presente documento, se refieren a un sistema de anillos bicíclicos o policíclicos fusionados que se forma con el benceno como uno de los anillos. Algunos ejemplos son el benzofurano, el benzotiofeno y el benzimidazol.

[00347] El término “cicloalquilo”, tal como se utiliza en el presente documento, se refiere a un grupo alquilo monocíclico, bicíclico o tricíclico saturado o parcialmente saturado, en el que cada fragmento cíclico contiene de 3 a 12 miembros de anillo de átomos de carbono y que opcionalmente puede ser un sistema de anillo fusionado de benceno que está opcionalmente sustituido según se define en el presente documento. En algunas formas de realización, los grupos cicloalquilo incluyen grupos que tienen de 3 a 10 átomos de anillo. En ciertas formas de realización, dicho cicloalquilo comprenderá de 5 a 7 átomos de carbono. En ciertas formas de realización, dicho cicloalquilo comprenderá de 3 a 6 átomos de carbono. Algunos ejemplos de estos grupos cicloalquilo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, tetrahidronaftilo, indanilo, octahidronaftilo, 2,3-dihidro-1H-indenilo, adamantly y similares. Los términos “bicíclico” y “tricíclico”, tal como se utilizan en el presente documento, incluyen tanto los sistemas de anillos fusionados, como el decahidronaftaleno y el octahidronaftaleno, como los de tipo multicíclico (multicéntrico), saturados o parcialmente insaturados. Este último tipo de isómero se ejemplifica generalmente con el biciclo[1,1,1]pentano, el alcanfor, el adamantano y el biciclo[3,2,1]octano. En algunas formas de realización, el arilo es un arilo C_3-C_6. En algunas formas de realización, el arilo es un arilo C_3-C_4.

[00348] El término "heterociclo" o "heterocíclico" se refiere a anillos heteroaromáticos (también conocidos como heteroarilos) y anillos heterocicloalquílicos que contienen de uno a cuatro heteroátomos en el/los anillo(s), donde cada heteroátomo en el/los anillo(s) se selecciona entre O, S y N, donde cada grupo heterocíclico tiene de 3 a 10 átomos en su sistema de anillo, y con la condición de que ningún anillo contenga dos átomos de O o S adyacentes. Los grupos heterocíclicos no aromáticos (también conocidos como heterocicloalquilos) incluyen anillos que tienen de 3 a 10 átomos en su sistema de

anillos, y los grupos heterocíclicos aromáticos incluyen anillos que tienen de 5 a 10 átomos en su sistema de anillos. Los grupos heterocíclicos incluyen sistemas de anillos fusionados con benceno. Ejemplos de grupos heterocíclicos no aromáticos son pirrolidinilo, tetrahidrofurano, dihidrofurano, tetrahidrotienilo, oxazolidinonilo, tetrahidropiranilo, dihidropiranilo, tetrahidrotiopiranilo, piperidinilo, morfolinilo, tiomorfolinilo, tioxanilo, piperazinilo, aziridinilo, azetidinilo, oxetanilo, tietanilo, homopiperidinilo, oxepanilo, tiepanilo, oxazepinilo, diazepinilo, tiazepinilo, 1,2,3,6-tetrahidropiridinilo, pirrolin-2-ilo, pirrolin-3-ilo, indolinilo, 2H-piranilo, 4H-piranilo, dioxanilo, 1,3-dioxolanilo, pirazolinilo, ditianilo, ditiolanilo, dihidropiranilo, dihidrotienilo, dihidrofurano, pirazolidinilo, imidazolinilo, imidazolidinilo, 3-azabiciclo[3,1,0]hexanilo, 3-azabiciclo[4,1,0]heptanilo, 3H-indolilo, indolin-2-onilo, isoindolin-1-onilo, isoindolina-1,3-dionilo, 3,4-dihidroisoquinolina-1(2H)-onilo, 3,4-dihidroquinolina-2(1H)-onilo, isoindolina-1,3-ditionilo, benzo[d]oxazol-2(3H)-onilo, 1H-benzo[d]imidazol-2(3H)-onilo, benzo[d]tiazol-2(3H)-onilo y quinolizinilo. Ejemplos de grupos heterocíclicos aromáticos son piridinilo, imidazolilo, pirimidinilo, pirazolilo, triazolilo, pirazinilo, tetrazolilo, furilo, tienilo, isoxazolilo, tiazolilo, oxazolilo, isotiazolilo, pirrolilo, quinolinilo, isoquinolinilo, indolilo, bencimidazolilo, benzofuranilo, cinnolinilo, indazolilo, indolizinilo, ftalazinilo, piridazinilo, triazinilo, isoindolilo, pteridinilo, purinilo, oxadiazolilo, tiadiazolilo, furazanilo, benzofurazanilo, benzotiofenilo, benzotiazolilo, benzoxazolilo, quinazolinilo, quinoxalinilo, naftiridinilo y furopiridinilo. Los grupos anteriores están unidos por C (o enlazados por C) o *N*- cuando sea posible. Por ejemplo, un grupo derivado de pirrol puede ser pirrol-1-ilo (unido a N) o pirrol-3-ilo (unido a C). Además, un grupo derivado del imidazol incluye imidazol-1-ilo o imidazol-3-ilo (ambos unidos a *N*-) o imidazol-2-ilo, imidazol-4-ilo o imidazol-5-ilo (todos unidos a C). Los grupos heterocíclicos incluyen sistemas de anillos fusionados con benceno. Los heterociclos no aromáticos se sustituyen opcionalmente con uno o dos grupos oxo (=O), como la pirrolidin-2-ona. En algunas formas de realización, al menos uno de los dos anillos de un heterociclo bicíclico es aromático. En algunas formas de realización, ambos anillos de un heterociclo bicíclico son aromáticos.

[00349] Los términos “heteroarilo” o, alternativamente, “heteroaromático” se refieren a un grupo arilo que incluye uno o más heteroátomos en el anillo, seleccionados entre nitrógeno, oxígeno y azufre. En algunas formas de realización, el término "heteroarilo", tal como se utiliza en el presente documento, se refiere a un anillo heteromonocíclico insaturado de 3 a 15 miembros, o a un sistema de anillos monocíclicos, bicíclicos o tricíclicos fusionados en el que al menos uno de los anillos fusionados es aromático y

contiene al menos un átomo seleccionado entre N, O y S. En ciertas formas de realización, dicho heteroarilo comprenderá de 1 a 4 heteroátomos como miembros del anillo. En otras formas de realización, dicho heteroarilo comprenderá de 1 a 2 heteroátomos como miembros del anillo. En ciertas formas de realización, dicho heteroarilo comprenderá de 5 a 7 átomos. El término también abarca grupos policíclicos fusionados en los que los anillos heterocíclicos se fusionan con anillos arílicos, en los que los anillos heteroarílicos se fusionan con otros anillos heteroarílicos, en los que los anillos heteroarílicos se fusionan con anillos heterocicloalquílicos o en los que los anillos heteroarílicos se fusionan con anillos cicloalquílicos. Ejemplos de grupos heteroarílicos incluyen pirrolilo, imidazolilo, pirazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, triazolilo, furilo, tienilo, oxazolilo, isoxazolilo, oxadiazolilo, tiazolilo, tiadiazolilo, isotiazolilo, indolilo, isoindolilo, indolizinilo, bencimidazolilo, quinolilo, isoquinolilo, quinoxalinilo, quinazolinilo, indazolilo, benzotriazolilo, benzodioxolilo, benzopiranilo, benzoxazolilo, benzoxadiazolilo, benzotiazolilo, benzotiadiazolilo, benzofuranilo, benzotienilo, cromonilo, cumarina, benzopiranilo, tetrahidroquinolinilo, tetrazolopiridazinilo, tetrahidroisoquinolinilo, tienopiridinilo, furopiridinilo, pirrolopiridinilo y similares. Entre los grupos heterocíclicos tricíclicos ejemplares se incluyen el carbazolilo, el bencidolilo, el fenantrolinilo, el dibenzofuranilo, el acridinilo, el fenantridinilo, el xantenilo y similares. En algunas formas de realización, un heteroarilo contiene de 0 a 4 átomos de N en el anillo. En algunas formas de realización, un heteroarilo contiene de 1 a 4 átomos de nitrógeno en el anillo. En algunas formas de realización, un heteroarilo contiene 1 átomo de O en el anillo. En algunas formas de realización, un heteroarilo contiene 1 átomo de S en el anillo. En algunas formas de realización, un heteroarilo contiene de 1 a 4 átomos de N, de 0 a 1 átomo de O y de 0 a 1 átomo de S en el anillo. En algunas formas de realización, haloalquilo es haloalquil C_1-C_9. En algunas formas de realización, el arilo es un arilo C_1-C_5. En algunas formas de realización, el heteroarilo es un heteroarilo de 5 a 6 miembros. En algunas formas de realización, el arilo es un arilo C_6-C_9.

[00350] Un grupo “heterocicloalquilo” se refiere a un grupo cicloalquilo que incluye al menos un heteroátomo seleccionado entre nitrógeno, oxígeno y azufre. En algunas formas de realización, el término “heterocicloalquilo”, tal como se utiliza en el presente documento, se refiere a un grupo heterocíclico, bicíclico o tricíclico saturado, parcialmente insaturado o totalmente insaturado (pero no aromático) que contiene al menos un heteroátomo como miembro del anillo, donde cada uno de dichos heteroátomos puede seleccionarse independientemente entre nitrógeno, oxígeno y

azufre. En ciertas formas de realización, dicho heterocicloalquilo comprenderá de 1 a 4 heteroátomos como miembros del anillo. En otras formas de realización, dicho heterocicloalquilo comprenderá de 1 a 2 heteroátomos como miembros del anillo. En ciertas formas de realización, dicho heterocicloalquilo comprenderá de 3 a 8 miembros de anillo en cada anillo. En otras formas de realización, dicho heterocicloalquilo comprenderá de 3 a 7 miembros de anillo en cada anillo. En otras formas de realización, dicho heterocicloalquilo comprenderá de 5 a 6 miembros de anillo en cada anillo. Los términos “heterocicloalquilo” y “heterociclo” incluyen sulfonas, sulfóxidos, N-óxidos de miembros de anillos de nitrógeno terciarios y sistemas de anillos fusionados carbocíclicos y benzo; además, ambos términos también incluyen sistemas en los que un anillo heterocíclico está fusionado a un grupo arilo, como se define en el presente documento, o a un grupo heterocíclico adicional. Ejemplos de grupos heterocíclicos incluyen aziridinilo, azetidinilo, 1,3-benzodioxolilo, dihidroisoindolilo, dihidroisoquinolinilo, dihidrocinnolinilo, dihidrobenzodioxinilo, dihidro[1,3]oxazolo[4,5-b]piridinilo, benzotiazolilo, dihidroindolilo, dihidropiridinilo, 1,3-dioxanilo, 1,4-dioxanilo, 1,3-dioxolanilo, isoindolinilo, morfolinilo, piperazinilo, pirrolidinilo, tetrahidropiridinilo, piperidinilo, tiomorfolinilo y similares. Los grupos heterocíclicos pueden sustituirse opcionalmente, a menos que esté específicamente prohibido. En algunas formas de realización, el heterocicloalquilo es un (C_2–C_{10})heterocicloalquilo. En algunas formas de realización, el heterocicloalquilo es un (C_4–C_{10})heterocicloalquilo. En algunas formas de realización, el heterocicloalquilo es bicíclico. En algunas formas de realización, un heterocicloalquilo es monocíclico y es un anillo de 3, 4, 5, 6, 7 u 8 miembros. En algunas formas de realización, un heterocicloalquilo es monocíclico y es un anillo de 3, 4, 5 o 6 miembros. En algunas formas de realización, un heterocicloalquilo es monocíclico y es un anillo de 3 o 4 miembros. En algunas formas de realización, un heterocicloalquilo contiene 1-2 átomos de N en el anillo. En algunas formas de realización, un heterocicloalquilo contiene 1-2 átomos de O. En algunas formas de realización, un heterocicloalquilo contiene 1 átomo de S. En algunas formas de realización, un heterocicloalquilo contiene de 0 a 2 átomos de N, de 0 a 2 átomos de O y de 0 a 1 átomo de S en el anillo.

[00351] El término “carbamato”, tal como se utiliza en el presente documento, se refiere a un éster del ácido carbámico (-NHCOO-) que puede unirse a la molécula principal desde el extremo nitrogenado o ácido, y que puede sustituirse opcionalmente según se define en el presente documento.

[00352] El término “carboxilo” o “carboxi”, tal como se usa aquí, se refiere a -C(=O)OH

o al anión “carboxilato” correspondiente, como el que se encuentra en una sal de ácido carboxílico.

[00353] El término “oxo”, como se usa en la presente, se refiere a un grupo “=O”.

[00354] El término “éster”, tal como se utiliza en el presente documento, se refiere a un grupo carboxilo que une dos fragmentos enlazados por átomos de carbono.

[00355] El término “éter”, tal como se utiliza en el presente documento, se refiere a un grupo oxi que une dos fragmentos enlazados por átomos de carbono.

[00356] El término “halo” o “halógeno” se refiere a flúor, cloro, bromo o yodo. En algunas formas de realización, el halo es flúor, cloro o bromo.

[00357] El término “haloalquilo”, tal como se utiliza en el presente documento, se refiere a un radical alquilo con el significado definido anteriormente, en el que uno o más hidrógenos son reemplazados por un halógeno. En concreto, se incluyen los radicales monohaloalquilo, dihaloalquilo y polihaloalquilo. Un radical monohaloalquilo, por ejemplo, puede tener un átomo de yodo, bromo, cloro o flúor dentro del radical. Los radicales dihalogenados y polihalogenados pueden tener dos o más átomos de halógeno iguales o una combinación de radicales halógenos diferentes. Ejemplos de radicales haloalquilo incluyen fluorometilo, difluorometilo, trifluorometilo, clorometilo, diclorometilo, triclorometilo, pentafluoroetilo, heptafluoropropilo, difluoroclorometilo, diclorofluorometilo, difluoroetilo, difluoropropilo, dicloroetilo y dicloropropilo. El término “haloalquileno” se refiere a un grupo haloalquilo unido en dos o más posiciones. Algunos ejemplos son el fluorometileno (-CFH-), el difluorometileno (-CF_2 -), el clorometileno (-CHCl-) y similares. En algunas formas de realización, haloalquilo es haloalquil C_1-C_6. En algunas formas de realización, haloalquilo es haloalquil C_1-C_4.

[00358] El término “haloalcoxi”, tal como se utiliza en el presente documento, se refiere a un grupo haloalquilo unido a la molécula principal a través de un átomo de oxígeno. En un aspecto, el haloalcoxi es un C_1-C_6haloalcoxi, que se refiere a un grupo (C_1-C_6haloalquilo)-O-. En otro aspecto, el haloalcoxi es un C_1-C_4haloalcoxi, que se refiere a un grupo (C_1-C_4haloalquilo)-O-.

[00359] El término “heteroalquilo” se refiere a un alquilo en el que uno o más átomos de carbono son reemplazados por un heteroátomo. En algunas formas de realización, “heteroalquilo” se refiere a un alquilo en el que uno o más átomos de carbono se reemplazan con uno o más heteroátomos que se seleccionan independientemente entre NH, -N(alquilo), O, S, S(=O) y $S(=O)_2$. La unión del/de los heteroátomo(s) al resto del compuesto se produce en los átomos de carbono del heteroalquilo. En algunas formas de realización, pueden ser consecutivos hasta dos heteroátomos, como por ejemplo, -

CH_2-NH-OCH_3. En algunas formas de realización, “heteroalquilo” es un “alcoxialquilo”, “alquiltioalquilo” o “alquilaminoalquilo”. “Alcoxialquilo” se refiere a un alquilo en el que un átomo de hidrógeno es reemplazado por un grupo alcoxi, según se define en el presente documento. En algunas formas de realización, un alcoxialquilo es un (C_1-C_6alcoxi)-C_1-C_6alquilo. Los grupos alcoxialquilo típicos incluyen, entre otros, -CH_2OCH_3, -$CH_2CH_2OCH_3$, -$CH_2CH_2CH_2OCH_3$, -$CH_2CH_2CH_2CH_2OCH_3$, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_2CH_3$, -$CH_2CH_2CH_2OCH_2CH_3$, -$CH_2CH_2CH_2CH_2OCH_2CH_3$, y similares. “Alquiltioalquilo” se refiere a un alquilo en el que un átomo de hidrógeno es reemplazado por un grupo alquiltio, tal como se define en el presente documento. En algunas formas de realización, un alcoxialquilo es un (C_1-C_6 alquiltio)-C_1-C_6alquilo. Los grupos alcoxialquilo típicos incluyen, pero no se limitan a, -CH_2SCH_3, -$CH_2CH_2SCH_3$, -$CH_2CH_2CH_2SCH_3$, -$CH_2CH_2CH_2CH_2SCH_3$, -$CH_2SCH_2CH_3$, -$CH_2CH_2SCH_2CH_3$, -$CH_2CH_2CH_2SCH_2CH_3$, -$CH_2CH_2CH_2CH_2SCH_2CH_3$, y similares. “Alquilaminoalquilo” se refiere a un alquilo en el que un átomo de hidrógeno es reemplazado por un grupo alquilamino, tal como se define en el presente documento. En algunas formas de realización, un alcoxialquilo es un (C_1-C_6alquilamino)-C_1-C_6alquilo. Los grupos alcoxialquilo típicos incluyen, pero no se limitan a, -CH_2NHCH_3, -$CH_2CH_2NHCH_3$, -$CH_2CH_2CH_2NHCH_3$, -$CH_2CH_2CH_2CH_2NHCH_3$, -$CH_2NHCH_2CH_3$, -$CH_2CH_2NHCH_2CH_3$, -$CH_2CH_2CH_2NHCH_2CH_3$, -$CH_2CH_2CH_2CH_2NHCH_2CH_3$, y similares.

[00360] El término “hidroxilo”, o “hidroxilo”, tal como se utiliza aquí se refiere a -OH.

[00361] El término “hidroxialquilo”, tal como se utiliza en el presente documento, se refiere a un grupo hidroxilo unido a la molécula principal a través de un grupo alquilo. En algunas formas de realización, el arilo es un arilo C_1-C_4. Los radicales alquileno habituales incluyen, entre otros: metileno (-CH_2-) 1,2-etilo (-CH_2CH_2-), 1,3-propilo (-$CH_2CH_2CH_2$-), 1,4-butilo (-$CH_2CH_2CH_2CH_2$-), y similares.

[00362] La expresión “cadena lineal de átomos” se refiere a la cadena recta más larga de átomos seleccionados independientemente entre el carbono, el nitrógeno, el oxígeno y el azufre.

[00363] El término “oxo”, como se usa en la presente, se refiere a un grupo “=O”.

[00364] El término “oxo”, como se usa en la presente, se refiere a un grupo “=O”.

[00365] Los términos “sulfonato”, “ácido sulfónico” y “sulfónico”, tal como se utilizan en el presente documento, se refieren al grupo -SO_3H y a su anión, ya que el ácido sulfónico se utiliza en la formación de sales.

[00366] El término “oxo”, como se usa en la presente, se refiere a un grupo “=O”.

[00367] El término “oxo”, como se usa en la presente, se refiere a un grupo “=O”.

[00368] El término “sulfonilo”, tal como se usa aquí, se refiere a un grupo -$S(=O)_2$-, -$S(=O)_2$R o -$S(=O)_2$R-, con R como se define aquí.

[00369] Cualquier definición aquí contenida puede utilizarse en combinación con cualquier otra definición para describir un grupo estructural compuesto. Por convención, el elemento final de cualquier definición de este tipo es el que se adjunta a la parte principal. Por ejemplo, el grupo compuesto alquilamido representaría un grupo alquilo unido a la molécula principal a través de un grupo amido, y el término alcoxialquilo representaría un grupo alcoxi unido a la molécula principal a través de un grupo alquilo.

[00370] Cuando se define un grupo como "nulo", lo que se quiere decir es que dicho grupo está ausente.

[00371] En algunas formas de realización, el término “sustituido opcionalmente” o “sustituido” significa que el grupo de referencia está sustituido opcionalmente con uno o más grupos adicionales seleccionados individual e independientemente de halógeno, -CN, -NH_2, -NH(alquilo), -N(alquilo)$_2$, -OH, -CO_2H, -CO_2alquilo, -C(=O)NH_2, -C(=O)NH(alquilo), -C(=O)N(alquilo)$_2$, -$S(=O)_2NH_2$, -$S(=O)_2$NH(alquilo), -$S(=O)_2$N(alquilo)$_2$, alquilo, cicloalquilo, fluoroalquilo, heteroalquilo, alcoxi, fluoroalcoxi, heterocicloalquilo, arilo, heteroarilo, ariloxi, alquiltio, ariltio, alquilsulfóxido, arilsulfóxido, alquilsulfona y arilsulfona. En otras formas de realización, los sustituyentes opcionales se seleccionan independientemente de halógeno, -CN, -NH_2, -NH(CH_3), -N(CH_3)$_2$, -OH, -CO_2H, -CO_2(C_1-C_4alquilo), -C(=O)NH_2, -C(=O)NH(C_1-C_4alquilo), -C(=O)N(C_1-C_4alquilo)$_2$, -$S(=O)_2NH_2$, -$S(=O)_2$NH(C_1-C_4alquilo), -$S(=O)_2$N(C_1-C_4alquilo)$_2$, C_1-C_4alquilo, C_3-C_6cicloalquilo, C_1-C_4fluoroalquilo, C_1-C_4heteroalquilo, C_1-C_4alcoxi, C_1-C_4fluoroalcoxi, -SC_1-C_4alquilo, -S(=O)C_1-C_4alquilo y -$S(=O)_2C_1$-C_4alquilo. En algunas formas de realización, los sustituyentes opcionales se seleccionan independientemente entre halógeno, -CN, -NH_2, -OH, -NH(CH_3), -N(CH_3)$_2$, -CH_3, -CH_2CH_3, -CHF_2, -CF_3, -OCH_3, -$OCHF_2$ y -OCF_3. En algunas formas de realización, los grupos sustituidos se sustituyen por uno o dos de los grupos precedentes. En algunas formas de realización, un sustituyente opcional en un átomo de carbono alifático (acíclico o cíclico) incluye oxo (=O).

[00372] El término “enlace” se refiere a una unión covalente entre dos átomos, o dos grupos funcionales cuando los átomos unidos por el enlace se consideran parte de una subestructura mayor. Un bono puede ser simple, doble o triple, a menos que se especifique lo contrario. En el dibujo de una molécula, una línea discontinua entre dos átomos indica que puede haber o no un enlace adicional en esa posición.

[00373] El término “enfermedad” o “trastorno”, tal como se utiliza en el presente

documento, se refiere a cualquier afección que afecte el funcionamiento normal del cuerpo, como una anomalía funcional o una alteración que perjudique el funcionamiento normal.

[00374] El término “terapia combinada” se refiere a la administración de dos o más agentes terapéuticos para tratar una afección o trastorno terapéutico descrito en la presente divulgación.

[00375] La expresión "terapéuticamente eficaz" tiene como objetivo calificar la cantidad de ingredientes activos utilizados en el tratamiento de una enfermedad o trastorno o en la consecución de un resultado clínico.

[00376] El término "terapéuticamente aceptable" se refiere a aquellos compuestos (o sales, profármacos, tautómeros, formas zwitteriónicas, etc.) que son adecuados para su uso en contacto con los tejidos de los pacientes sin toxicidad, irritación ni respuesta alérgica excesivas, que presentan una relación beneficio/riesgo razonable y que son eficaces para el uso previsto.

[00377] En el presente documento, "tratar", "tratamiento" y términos similares significan mejorar una enfermedad, de manera que se reduzca, mejore o elimine su causa, su progresión, su gravedad o uno o más de sus síntomas, o que se altere de manera beneficiosa la enfermedad en un sujeto. En ciertas formas de realización, la referencia a "tratar" o "tratamiento" de un sujeto en riesgo de desarrollar una enfermedad, o en riesgo de que la enfermedad progrese a un estado peor, incluye la profilaxis. La prevención de una enfermedad puede implicar una protección completa contra la enfermedad o bien la prevención de su progresión. La prevención de enfermedades también puede significar prevenir la progresión de una enfermedad a una etapa posterior.

[00378] El término “paciente” es generalmente sinónimo del término “sujeto” e incluye a todos los mamíferos, incluidos los seres humanos. Entre los ejemplos de pacientes se incluyen humanos, primates no humanos como chimpancés y otras especies de simios y monos; ganado como vacas, cabras, ovejas, cerdos y conejos, y animales de compañía como perros, gatos, conejos y caballos. Preferentemente, el sujeto es un ser humano.

Composiciones y formulaciones farmacéuticas

[00379] Las formulaciones pueden prepararse mediante cualquier método adecuado, normalmente mezclando uniformemente el/los compuesto/s activo/s con líquidos o excipientes sólidos finamente divididos, o ambos, en las proporciones requeridas y, si es necesario, dando a la mezcla resultante la forma deseada.

[00380] En los comprimidos y cápsulas para administración oral se pueden utilizar excipientes convencionales, como agentes aglutinantes, rellenos, agentes humectantes aceptables, lubricantes para la compresión y desintegrantes. Las preparaciones líquidas para administración oral pueden presentarse en forma de soluciones, emulsiones, suspensiones acuosas o oleosas y jarabes. Como alternativa, las preparaciones orales pueden presentarse en forma de polvo seco que puede reconstituirse con agua u otro vehículo líquido adecuado antes de su uso. A las preparaciones líquidas se les pueden añadir aditivos adicionales como agentes suspensivos o emulsionantes, vehículos no acuosos (incluidos aceites comestibles), conservantes, aromatizantes y colorantes. Las formas farmacéuticas parenterales pueden prepararse disolviendo el compuesto aquí proporcionado en un vehículo líquido adecuado y esterilizando la solución por filtración antes de llenar y sellar un vial o ampolla apropiados. Estos son solo algunos ejemplos de los muchos métodos apropiados y bien conocidos en la técnica para la preparación de formas farmacéuticas.

[00381] Un compuesto de la presente invención puede formularse en composiciones farmacéuticas utilizando técnicas bien conocidas por los expertos en la materia. Se conocen en la técnica otros excipientes farmacéuticamente aceptables, además de los aquí mencionados; por ejemplo, véase Remington, The Science and Practice of Pharmacy, 20.ª edición, 2000, Lippincott Williams & Wilkins, (Editores: Gennaro *et*. *al*.).

[00382] Los compuestos aquí descritos, junto con un adyuvante, excipiente o diluyente convencional, pueden presentarse en forma de formulaciones farmacéuticas y dosis unitarias, y emplearse como sólidos, tales como comprimidos o cápsulas rellenas, o líquidos, tales como soluciones, suspensiones, emulsiones, elixires, geles o cápsulas rellenas con los mismos, todos para uso oral, o en forma de soluciones inyectables estériles para uso parenteral (incluido el subcutáneo). Dichas composiciones farmacéuticas y sus formas farmacéuticas unitarias pueden comprender ingredientes convencionales en proporciones convencionales, con o sin compuestos o principios activos adicionales, y dichas formas farmacéuticas unitarias pueden contener cualquier cantidad eficaz adecuada del ingrediente activo, acorde con el rango de dosis diaria previsto.

[00383] Para su administración oral, la composición farmacéutica puede presentarse en forma de, por ejemplo, comprimido, cápsula, suspensión o líquido. La composición farmacéutica se elabora preferiblemente en forma de unidad de dosificación que contiene una cantidad determinada del principio activo. Ejemplos de dichas unidades de dosificación son cápsulas, comprimidos, polvos, gránulos o suspensiones, con aditivos

convencionales como lactosa, manitol, almidón de maíz o almidón de patata; con aglutinantes como celulosa cristalina, derivados de celulosa, goma arábiga, almidón de maíz o gelatinas; con desintegrantes como almidón de maíz, almidón de patata o carboximetilcelulosa sódica; y con lubricantes como talco o estearato de magnesio. El principio activo también puede administrarse mediante inyección en forma de una composición en la que, por ejemplo, se puede utilizar solución salina, dextrosa o agua como vehículo farmacéuticamente aceptable.

[00384] Los compuestos aquí descritos, o sus sales, solvatos o hidratos, pueden utilizarse como ingredientes activos en composiciones farmacéuticas. El término "ingrediente activo", definido en el contexto de una "composición farmacéutica", se refiere a un componente de una composición farmacéutica que proporciona el efecto farmacológico principal, a diferencia de un "ingrediente inactivo", que generalmente se considera que no proporciona ningún beneficio farmacéutico.

[00385] La dosis al utilizar los compuestos aquí descritos puede variar dentro de límites amplios y, como es habitual y bien sabido por el médico u otro profesional clínico, debe adaptarse a las condiciones individuales de cada caso. Depende, por ejemplo, de la naturaleza y la gravedad de la enfermedad a tratar, del estado del paciente, del compuesto empleado o de si se trata de una enfermedad aguda o crónica, o si se realiza profilaxis, o de si se administran otros compuestos activos además de los aquí descritos. Las dosis representativas incluyen, pero no se limitan a, aproximadamente 0,001 mg a aproximadamente 5000 mg, aproximadamente 0,001 mg a aproximadamente 2500 mg, aproximadamente 0,001 mg a aproximadamente 1000 mg, aproximadamente 0,001 mg a aproximadamente 500 mg, aproximadamente 0,001 mg a aproximadamente 250 mg, aproximadamente 0,001 mg a 100 mg, aproximadamente 0,001 mg a aproximadamente 50 mg y aproximadamente 0,001 mg a aproximadamente 25 mg. Se pueden administrar varias dosis durante el día, especialmente cuando se considera que se necesitan cantidades relativamente grandes, por ejemplo, 2, 3 o 4 dosis. Dependiendo de cada persona y según lo considere apropiado el profesional sanitario, puede ser necesario ajustar las dosis descritas en este documento, tanto al alza como a la baja.

[00386] La cantidad del compuesto, o una sal activa o derivada de este, requerida para su uso en el tratamiento variará no sólo con la sal particular seleccionada, sino también con la vía de administración, la naturaleza de la afección que se está tratando y la edad y condición del paciente, y será en última instancia a discreción del médico o clínico que lo atiende. En general, un experto en la materia entiende cómo extrapolar *in vivo* datos obtenidos en un sistema modelo, típicamente un modelo animal, a otro, como un ser

humano. En algunos casos, estas extrapolaciones pueden basarse simplemente en el peso del modelo animal en comparación con otro, como un mamífero, preferiblemente un ser humano; sin embargo, con mayor frecuencia, estas extrapolaciones no se basan simplemente en pesos, sino que incorporan una variedad de factores. Entre los factores representativos se incluyen el tipo, la edad, el peso, el sexo, la dieta y la condición médica del paciente, la gravedad de la enfermedad, la vía de administración, consideraciones farmacológicas como la actividad, la eficacia, los perfiles farmacocinéticos y toxicológicos del compuesto en particular empleado, si se utiliza un sistema de administración de fármacos, si se está tratando una enfermedad aguda o crónica, o si se está realizando profilaxis, o si se administran otros compuestos activos además de los aquí proporcionados y como parte de una combinación de fármacos. La pauta posológica para el tratamiento de una enfermedad con los compuestos y/o composiciones aquí descritos se selecciona de acuerdo con diversos factores, como se ha mencionado anteriormente. Por lo tanto, el régimen de dosificación real empleado puede variar ampliamente y, por consiguiente, puede desviarse del régimen de dosificación preferido, y un experto en la materia reconocerá que se pueden probar dosis y regímenes de dosificación fuera de estos rangos típicos y, cuando sea apropiado, se pueden utilizar en los métodos aquí descritos.

[00387] Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones, por ejemplo, soluciones de agua o de agua-propilenglicol. Por ejemplo, las preparaciones líquidas para inyección parenteral pueden formularse como soluciones en solución acuosa de polietilenglicol. Las preparaciones inyectables, por ejemplo, suspensiones oleaginosas o acuosas inyectables estériles, se pueden formular de acuerdo con el estado de la técnica conocido usando agentes de dispersión, agentes humectantes y/o agentes de suspensión adecuados.

[00388] Las formulaciones acuosas aptas para uso oral pueden prepararse disolviendo o suspendiendo el componente activo en agua y añadiendo colorantes, aromatizantes, agentes estabilizantes y espesantes adecuados, según se desee.

[00389] También se incluyen preparados en forma sólida que están destinados a ser convertidos, poco antes de su uso, en preparados en forma líquida para su administración oral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones. Estos preparados pueden contener, además del componente activo, colorantes, aromatizantes, estabilizantes, tampones, edulcorantes artificiales y naturales, dispersantes, espesantes, agentes solubilizantes y similares.

[00390] Para su administración tópica en la epidermis, los compuestos aquí descritos

pueden formularse en forma de ungüentos, cremas o lociones, o como un parche transdérmico.

[00391] Las pomadas y cremas pueden formularse, por ejemplo, con una base acuosa u oleosa, a la que se le añaden agentes espesantes y/o gelificantes adecuados. Las lociones pueden formularse con una base acuosa u oleosa y, por lo general, también contendrán uno o más agentes emulsionantes, estabilizantes, dispersantes, suspensivos, espesantes o colorantes.

[00392] Las preparaciones farmacéuticas se presentan preferiblemente en dosis unitarias. De esta forma, la preparación se subdivide en dosis unitarias que contienen las cantidades adecuadas del componente activo. La forma farmacéutica unitaria puede ser una preparación envasada, cuyo envase contiene cantidades discretas de la preparación, como por ejemplo comprimidos, cápsulas y polvos envasados en viales o ampollas. Asimismo, la forma farmacéutica unitaria puede ser una cápsula, un comprimido, un pastilla o una pastilla para chupar, o bien puede ser la cantidad adecuada de cualquiera de estas envasadas.

Métodos de tratamiento, métodos de dosis y regímenes de tratamiento

[00393] En una modalidad, los compuestos aquí descritos, o una sal farmacéuticamente aceptable de los mismos, se utilizan en la preparación de medicamentos para el tratamiento de enfermedades o afecciones en mamíferos. Los métodos para tratar cualquiera de las enfermedades o afecciones descritas en el presente documento en un mamífero que necesite dicho tratamiento, implican la administración de composiciones farmacéuticas que incluyan al menos un compuesto divulgado en el presente documento, o una sal farmacéuticamente aceptable, un metabolito activo, un profármaco o un solvato farmacéuticamente aceptable de este, en cantidades terapéuticamente efectivas a dicho mamífero.

[00394] En ciertas formas de realización, las composiciones que contienen el/los compuesto(s) descrito(s) en el presente documento se administran para tratamientos profilácticos y/o terapéuticos. En aplicaciones terapéuticas, las composiciones se administran a un paciente que ya tiene una enfermedad o afección, en una cantidad suficiente para curar o al menos interrumpir parcialmente al menos uno de los síntomas de la enfermedad o afección. En algunas formas de realización, las cantidades eficaces para su uso dependen de la gravedad y el transcurso de la enfermedad o afección, tratamiento previo, el estado de salud del paciente, peso y respuesta a los fármacos y/o el criterio del médico tratante. Las dosis terapéuticamente efectivas se determinan opcionalmente mediante métodos que incluyen, entre otros, un ensayo clínico de

escalada de dosis y/o de determinación de la dosis.

[00395] En aplicaciones profilácticas, las composiciones que contienen los compuestos descritos en este documento se administran a un paciente susceptible o en riesgo de padecer una enfermedad, trastorno o afección en particular. Dicha cantidad se define como una “cantidad o dosis profilácticamente eficaz”. En este uso, las cantidades precisas también dependen del estado de salud del paciente, el peso y similares. Cuando se usan en un paciente, las cantidades eficaces para este uso dependerán de la gravedad y curso de la enfermedad, trastorno o afección, tratamiento previo, el estado de salud del paciente y la respuesta a los fármacos y el criterio del médico tratante. En un aspecto, los tratamientos profilácticos incluyen la administración a un mamífero que previamente haya experimentado al menos un síntoma de la enfermedad que se está tratando y que actualmente se encuentre en remisión, de una composición farmacéutica que comprenda un compuesto divulgado en el presente documento, o una sal farmacéuticamente aceptable de este, con el fin de prevenir la reaparición de los síntomas de la enfermedad o afección.

[00396] En ciertos casos en los que la condición del paciente no mejora, a discreción del médico, se administran los compuestos de forma crónica, es decir, durante un período prolongado, incluso durante toda la vida del paciente, con el fin de aliviar, controlar o limitar los síntomas de la enfermedad o afección del paciente.

[00397] Una vez que las condiciones del paciente mejoraron, se administra una dosis de mantenimiento, en caso de ser necesaria. Posteriormente, en formas de realización específicas, las dosis o la frecuencia de administración, o ambas, se reduce, como una función de los síntomas, a un nivel en el cual la enfermedad, trastorno o afección mejorada se retiene. En algunas formas de realización, sin embargo, el paciente requiere tratamiento intermitente a largo plazo ante cualquier recaída de los síntomas.

[00398] La cantidad de un agente determinado que corresponde a dicha cantidad varía según factores, tales como el compuesto particular, el estado de la enfermedad y su gravedad, la identidad (por ejemplo, peso, sexo) del sujeto o huésped que necesita el tratamiento, pero puede, no obstante, determinarse de acuerdo con las circunstancias particulares que rodean el caso, que incluyen, por ejemplo, el agente específico que se administra, la vía de administración, la afección que se trata y el sujeto o huésped que se trata.

[00399] En general, sin embargo, las dosis empleadas para el tratamiento en adultos suelen estar en el rango de 0,01 mg a 2000 mg por día. En una forma de realización, la dosis deseada se presenta convenientemente en una sola dosis o en dosis divididas

administradas de manera simultánea (o en un período más breve) o en intervalos adecuados, por ejemplo, como dos, tres, cuatro o más subdosis por día.

[00400] En una modalidad, las dosis diarias apropiadas para el compuesto aquí descrito, o una sal farmacéuticamente aceptable de este, son de aproximadamente 0,01 a aproximadamente 50 mg/kg de peso corporal. En algunas formas de realización, la dosis diaria o la cantidad de principio activo en la forma farmacéutica son inferiores o superiores a los rangos indicados en el presente documento, en función de diversas variables relacionadas con el régimen de tratamiento individual. En diversas formas de realización, las dosis diarias y unitarias se modifican en función de una serie de variables que incluyen, entre otras, la actividad del compuesto utilizado, la enfermedad o afección a tratar, el modo de administración, las necesidades del sujeto individual, la gravedad de la enfermedad o afección que se está tratando y el criterio del médico.

[00401] La toxicidad y la eficacia terapéutica de dichos regímenes terapéuticos se determinan mediante procedimientos farmacéuticos estándar en cultivos celulares o animales de experimentación, incluyendo, entre otros, la determinación de la LD_{50} y la ED_{50}. La proporción de dosis entre efectos tóxicos y terapéuticos es el índice terapéutico, que se puede expresar como la proporción DL_{50}/DE_{50}. En ciertas formas de realización, los datos obtenidos de ensayos de cultivo celular y estudios en animales se utilizan para formular el rango de dosis diaria terapéuticamente eficaz y/o la cantidad de dosis unitaria terapéuticamente eficaz para su uso en mamíferos, incluidos los seres humanos. En algunas formas de realización, la cantidad de dosis diaria de los compuestos descritos en el presente documento se encuentra dentro de un rango de concentraciones circulantes que incluyen la ED_{50} con toxicidad mínima. En ciertas formas de realización, el rango de dosis diaria y/o la cantidad de dosis unitaria varían dentro de este rango dependiendo de la forma farmacéutica empleada y la vía de administración utilizada.

[00402] En cualquiera de los aspectos mencionados anteriormente, existen otras formas de realización en las que la cantidad efectiva del compuesto divulgado en el presente documento, o una sal farmacéuticamente aceptable de este, se administra: (a) sistémicamente al mamífero; y/o (b) oralmente al mamífero; y/o (c) intravenosamente al mamífero; y/o (d) por inyección al mamífero; y/o (e) tópicamente al mamífero; y/o (f) de forma no sistémica o local al mamífero.

[00403] En cualquiera de los aspectos mencionados anteriormente, existen otras formas de realización que comprenden administraciones únicas de la cantidad efectiva del compuesto, incluidas otras formas de realización en las que (i) el compuesto se

administra una vez al día; o (ii) el compuesto se administra al mamífero varias veces en el transcurso de un día.

[00404] En cualquiera de los aspectos mencionados anteriormente, existen otras formas de realización que comprenden múltiples administraciones de la cantidad efectiva del compuesto, incluidas otras formas de realización en las que (i) el compuesto se administra de forma continua o intermitente: como en una sola dosis; (ii) el tiempo entre múltiples administraciones es cada 6 horas; (iii) el compuesto se administra al mamífero cada 8 horas; (iv) el compuesto se administra al mamífero cada 12 horas; (v) el compuesto se administra al mamífero cada 24 horas. En otras formas de realización alternativas, el método comprende un periodo de descanso farmacológico, durante el cual se suspende temporalmente la administración del compuesto o se reduce temporalmente la dosis administrada; al finalizar dicho periodo, se reanuda la administración del compuesto. En una modalidad, la duración del período de descanso farmacológico varía de 2 días a 1 año.

[00405] En ciertos casos, es apropiado administrar al menos un compuesto aquí descrito, o una sal farmacéuticamente aceptable de este, en combinación con uno o más agentes terapéuticos.

[00406] Como se usan a lo largo de la presente divulgación, las siguientes expresiones, a menos que se indique lo contrario, se deben entender de acuerdo con los siguientes significados:

ACN o MeCN	acetonitrilo
Ac	acetilo
Ac_2O	anhídrido acético
AcOH	ácido acético
AIBN	azobisisobutironitrilo
BINAP	2,2'-bis(difenilfosfin)-1,1'-dinaftaleno
Bn	bencilo
BOC o Boc	*ter*-butil carbamato
Boc_2O	di-ter-butil descarbonato o anhídrido Boc
BPO	peróxido de benzoilo
BrettPhos Pd G3	[(2-diciclohexilfosfino-3,6-dimetoxi-2′,4′,6′-triisopropil-1,1′-bifenil)-2-(2′-amino-1,1′-bifenil)]paladio(II) metansulfonato metansulfonato
t-Bu	*ter*-butilo
C Phos Pd G3	[(2-diciclohexilfosfino-2′,6′-bis(N,N-dimetilamino)-1,1′-

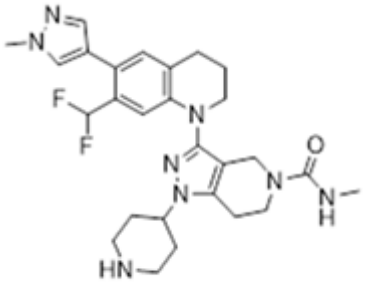
	bifenil)-2-(2′-amino-1,1′-bifenil)] paladio(II) metansulfonato
Cy	cicliclohexilo
DBA o dba	dibencilidenacetona
DBU	1,8-diazabiciclo[5,4,0]undec-7-eno
DCE	dicloroetano ($ClCH_2CH_2Cl$)
DCM	diclorometano (CH_2Cl_2)
DIPEA o DIEA	diisopropiletilamina
DMAP	4-(*N,N*-dimetilamino)piridina
DMF	dimetilformamida
DMA	*N,N*-dimetilacetamida
DMSO	dimetilsulfóxido
Dppf	1,1'-bis(difenilfosfino)ferroceno
EEDQ	2-etoxi-1-etoxicarbonil-1,2-dihidroquinolina
eq	equivalentes
Et	etilo
Et2O	dietiléter
EtOH	etanol
EtOAc	acetato de etilo
FA	ácido fórmico
HATU	hexafluorofosfato de 3-óxido de 1-[bis(dimetilamino)metilen]-1H-1,2,3-triazolo[4,5-b]piridinio
HPLC	cromatografía de líquidos de alto rendimiento
H_2O	agua
K_2CO_3	carbonato de potasio
LAH	anhídrido de litio y aluminio
LCMS	cromatografía de líquidos-espectrometría de masas
Me	metilo
MeOH	metanol
MS	espectrometría de masas
MsCl	cloruro de mesilo
Na_2CO_3	carbonato de sodio
$NaBH(OAc)_3$	triacetoxiborohidruro de sodio
NaH	hidruro de sodio

Na_2SO_4	sulfato de sodio
NBS	N-bromo succinamida
NMP	N-metil-pirrolidin-2-ona
NMR	resonancia magnética nuclear
$Pd(dppf)Cl_2$	(1,1'-bis(difenilfosfino)ferrocen)paladio(II) dicloruro
Ph	fenilo
Pin	pinacolato
Prep-HPLC	cromatografía de líquidos de alta resolución preparativa
i-Pr	*iso*-propilo
RP-HPLC	cromatografía de líquidos de alta presión de fase inversa
RuPhos Pd G3	(2-diciclohexilfosfino-2',6'-diisopropoxi-1,1'-bifenil)[2-(2'-amino-1,1'-bifenil)]paladio(II) metansulfonato
TBS	*ter*-butildimetilsililo
TFA	ácido trifluoroacético
TEA	trietilamina
THF	tetrahidrofurano
TsCl	cloruro de tosilo
TLC	cromatografía de capa fina

EJEMPLOS

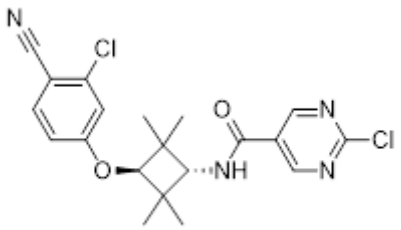
[00407] Los siguientes ejemplos se proporcionan solo a fines ilustrativos, y no se pretende que limiten el alcance de la presente divulgación.

[00408] Las moléculas de TCB se prepararon de acuerdo con los métodos descritos en WO 2022/42707 A1.



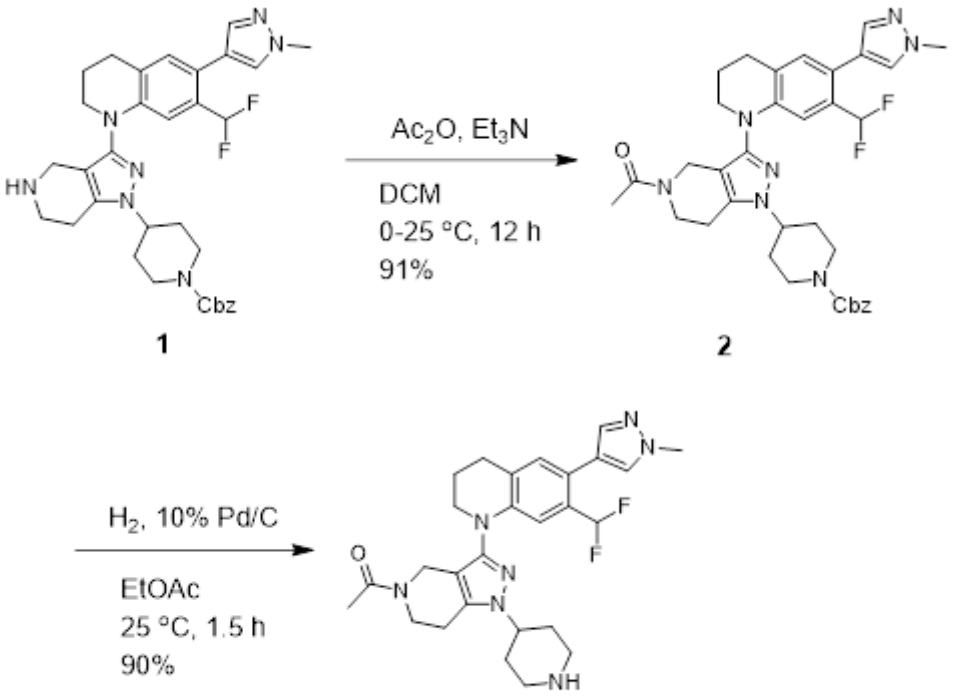
Compuesto A

[00409] El **compuesto B** se preparó según el procedimiento descrito en Journal of Medicinal Chemistry, 2023, 66, 7, 4784 – 4801.



Compuesto B

[00410] El compuesto **480c** se preparó de acuerdo con el siguiente esquema:



Compuesto C

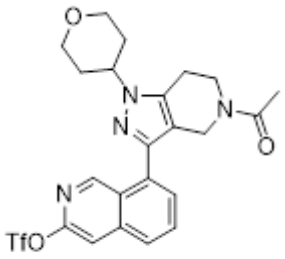
[00411] Las moléculas de TCB se prepararon de acuerdo con los métodos descritos en WO 2022/42707 A1.

[00412] A una solución de 4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-4,5,6,7-tetrahidropirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de bencilo (0,250 g, 349 µmol, 1,0 eq, TFA) en DCM (0,5 ml) se añadieron TEA (106 mg, 1,05 mmol, 146 µl, 3,0 eq) y Ac_2O (53,5 mg, 524 µmol, 49,2 µl, 1,5 eq) a 0 °C. La mezcla se agitó a 25 °C durante 12 h. La mezcla se vertió en agua helada (20 ml). La fase acuosa se extrajo con acetato de etilo (15 ml x 3). La capa orgánica combinada se lavó con salmuera (10 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante *prep*-TLC (sílice, diclorometano/alcohol metílico = 10/1). El compuesto 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-

1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de bencilo (0,21 g, 316 µmol, 91 % de rendimiento) se obtuvo como un sólido amarillo claro. LC-MS: MS (ESI$^+$): t_R = 0,980 min, m/z = 644,3 [M + H$^+$]

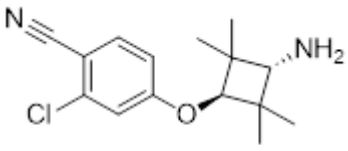
[00413] Pd/C (0,110 g, 10 % Pd sobre carbono, p/p) se agregó a un matraz de fondo redondo de un solo cuello de 100 ml bajo N_2, y luego se agregó EtOAc (10 ml) a 25 °C bajo N_2. Después de la adición, se agregó 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de bencilo (0,210 g, 326 µmol, 1,0 eq) bajo N_2. La suspensión se desgasificó y se purgó con H_2 3 veces. La mezcla se agitó bajo H_2 (15 psi) a 25 °C durante 1,5 h. La mezcla de reacción se filtró y se lavó con MeOH (20 ml x 3). La mezcla de reacción se concentró para proporcionar un residuo. El crudo se usó para la siguiente etapa sin purificación adicional. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (0,15 g, 294 µmol, 90 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI$^+$): t_R = 0,429 min, m/z = 510,3 [M + H$^+$]

[00414] Las moléculas de TCB se prepararon de acuerdo con los métodos descritos en WO 2017/205538 A1.



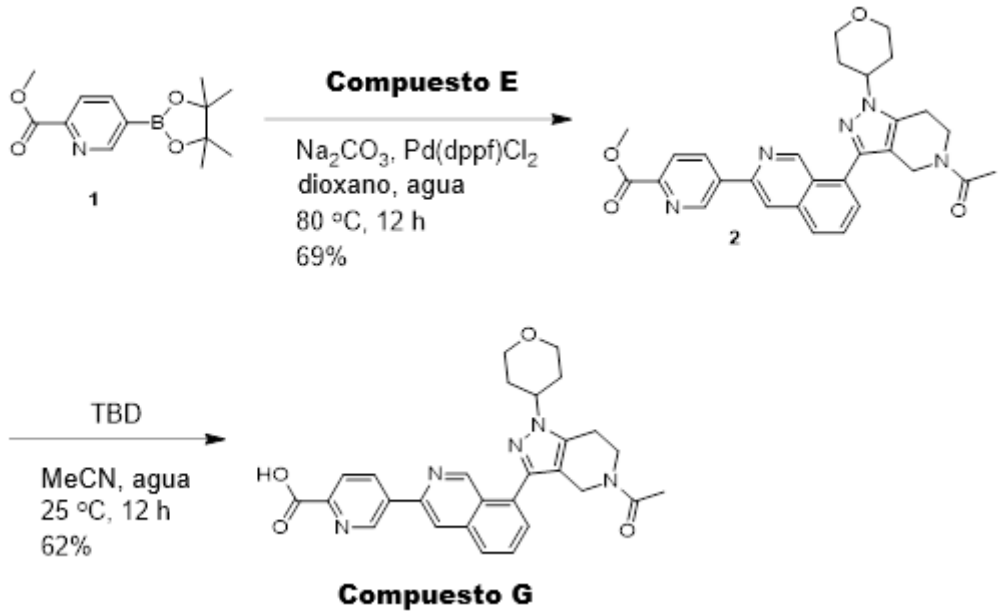
Compuesto E

[00415] El **compuesto F** se preparó según el procedimiento descrito en Journal of Medicinal Chemistry, 2023, 66, 7, 4784 – 4801.



Compuesto F

[00416] El compuesto **480c** se preparó de acuerdo con el siguiente esquema:

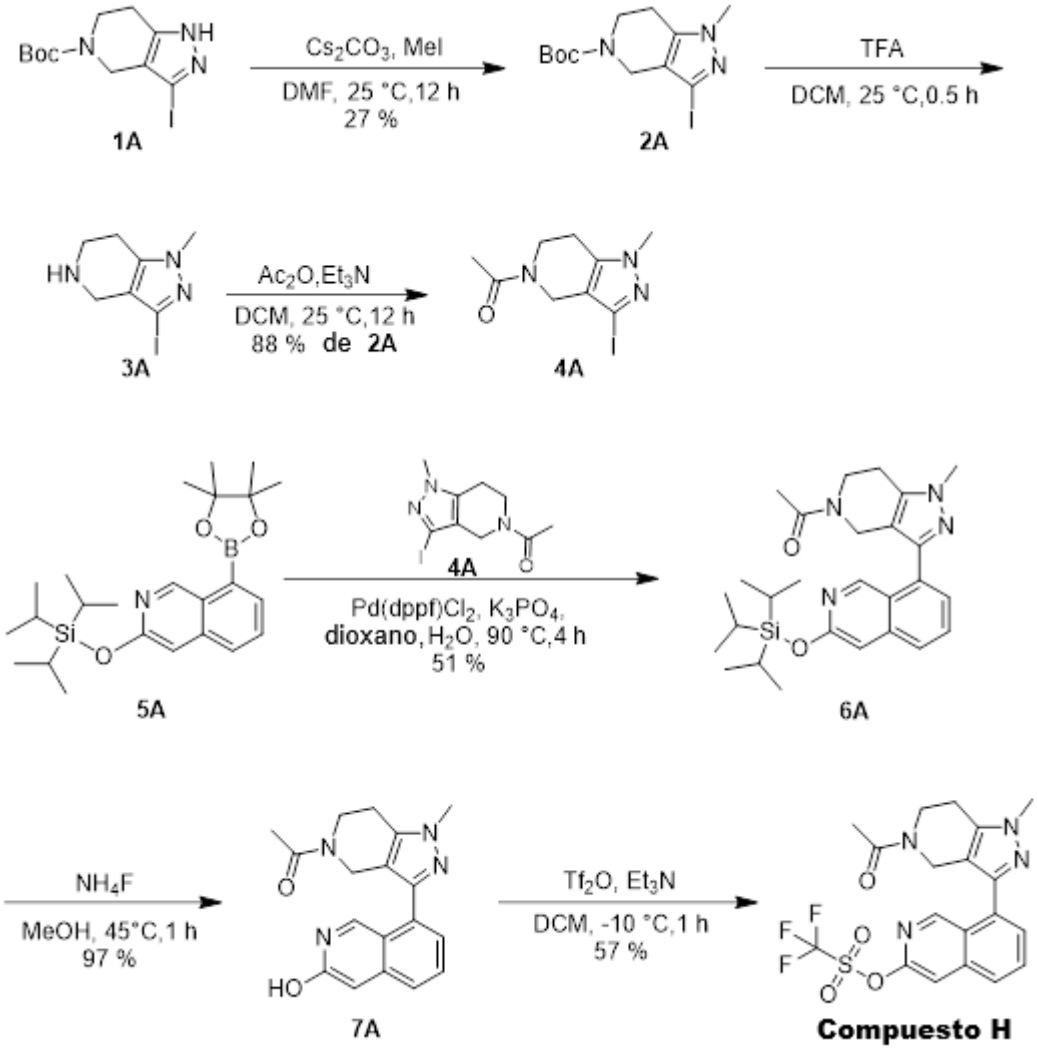


[00417] A una solución de 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina-2-carboxilato de metilo (0,15 g, 570,13 µmol, 1 eq) y Na_2CO_3 (120,86 mg, 1,14 mmol, 2 eq) y $Pd(dppf)Cl_2$ (41,72 mg, 57,01 µmol, 0,1 eq) en dioxano (5 ml) y H_2O (0,5 ml) se agregó [8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil] trifluorometanosulfonato (299 mg, 570 µmol, 1,0 eq). La mezcla de reacción se agitó a 80 °C durante 12 h. La mezcla de reacción se vertió en H_2O (100 ml) y se extrajo dos veces con EtOAc. Los orgánicos combinados se lavaron con salmuera (200 ml × 2), se secaron en Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 0/1, éter de petróleo/acetato de etilo = 1/1, producto 1 Rf = 1). El compuesto metil 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carboxilato (0,20 g, 390,95 µmol, 68 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,468 min, m/z = 512,2 [$M + H^+$]

[00418] A una solución de metil 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carboxilato (0,20 g, 391 µmol, 1,0 eq) en MeCN (3 ml) y H_2O (1 ml) se agregó 3,4,6,7,8,9-hexahidro-2H-pirimido[1,2-a]pirimidina (109 mg, 782 µmol, 2,0 eq). La mezcla resultante se agitó a 25 °C durante 12 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 2). La capa orgánica combinada se lavó con salmuera (100 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(HCl)-ACN]; gradiente: 13 %-43 % B durante 10 min). El compuesto ácido 5-[8-(5-acetil-1-

tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carboxílico (0,12 g, 241 µmol, 62 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI$^+$): t_R = 0,477 min, m/z = 498,3 [M + Na$^+$]

[00419] El compuesto **480c** se preparó de acuerdo con el siguiente esquema:



[00420] La síntesis de **5A** fue reportada en WO2021/231174 A1.

[00421] Una mezcla de ter-butil 3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridina-5-carboxilato (15,0 g, 42,96 mmol, 1 eq), Cs_2CO_3 (41,9 g, 128,88 mmol, 3,0 eq) en DMF (150 ml) se desgasificó y se purgó con N_2 durante 3 veces, y luego se agregó MeI (9,15 g, 64,44 mmol, 4,01 ml, 1,5 eq), la mezcla se agitó a 25 °C durante 1 2 h bajo N_2. La mezcla de reacción se diluyó con agua (1000 ml) y se extrajo con acetato de etilo (300 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (300 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de

petróleo/acetato de etilo = 10/1 a 2/1). El compuesto ter-butil 3-iodo-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato (4,3 g, 11,84 mmol, 27 % de rendimiento) se obtuvo como un sólido blanco.

[00422] RMN (400 MHz, DMSO-d6) δ = 4,09 (s, 1H), 3,69 (s, 1H), 3,59 (d, J = 5,6 Hz, 1H), 2,64 (d, J = 5,6 Hz, 1H), 1,41 (s, 9H)

[00423] **LC-MS:** MS (ESI$^+$): t_R = 0,521 min, m/z = 364,1 [M + H$^+$]

[00424] A una solución de 3-iodo-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato de ter-butilo (4,30 g, 11,84 mmol, 1,0 eq) en DCM (20 ml) se le agregó TFA (15,35 g, 134,62 mmol, 10 ml, 11,3 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se concentró al vacío para obtener el producto crudo. El compuesto 3-iodo-1-metil-4,5,6,7-tetrahidropirazolo[4,3-c]piridina (4,46 g) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[00425] **LC-MS:** MS (ESI$^+$): t_R = 0,218 min, m/z = 263,1 [M + H$^+$]

[00426] A una solución de 3-iodo-1-metil-4,5,6,7-tetrahidropirazolo[4,3-c]piridina (4,46 g, 11,83 mmol, 1,0 eq) en DCM (40 ml) se añadieron Et_3N (3,59 g, 35,48 mmol, 4,94 ml, 3,0 eq) y Ac_2O (1,81 g, 17,74 mmol, 1,67 ml, 1,5 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se concentró al vacío para obtener el producto crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 0/1). El compuesto 1-(3-iodo-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il)etanona (3,20 g, 10,49 mmol, 88 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00427] **LC-MS:** MS (ESI$^+$): t_R = 0,378 min, m/z = 306,1 [M + H$^+$]

[00428] Una mezcla de 1-(3-iodo-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il)etanona (3,00 g, 9,83 mmol, 1,0 eq), triisopropil-[[8-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3-isoquinolil]oxi]silano (7,00 g, 11,46 mmol, 1,1 eq), $Pd(dppf)Cl_2$ (359 mg, 491,62 µmol, 0,05 eq), K_3PO_4 (7,30 g, 34,41 mmol, 3,5 eq) y agua (50 ml) en dioxano (80 ml) fue desgasificado y purgado con N_2 durante 3 veces, y luego la mezcla se agitó a 90 °C durante 4 h bajo N_2. La mezcla de reacción se inactivó con agua helada (100 ml) y se extrajo con DCM (100 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 100/1 a 20/1). El compuesto 1-[1-metil-3-(3-triisopropilsililoxi-8-isoquinolil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (2,43 g, 5,08 mmol, 51 % de rendimiento) se obtuvo como un sólido blanco.

[00429] **LC-MS:** MS (ESI$^+$): t_R = 0,893 min, m/z = 479,3 [M + H$^+$]

[00430] A una solución de 1-[1-metil-3-(3-triisopropilsililoxi-8-isoquinolil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (2,43 g, 5,08 mmol, 1,0 eq) en MeOH (20 ml) se agregó NH_4F (1,88 g, 50,76 mmol, 10,0 eq). La mezcla se agitó a 45 °C durante 1 h. La mezcla de reacción se filtró y se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano : metanol = 50/1 a 10/1). El compuesto 1-[3-(3-hidroxi-8-isoquinolil)-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (1,6 g, 4,96 mmol, 97 % de rendimiento) se obtuvo como un sólido amarillo.

[00431] 1H NMR (400 MHz, DMSO-d6) δ 10,97 (br. s, 1H), 9,44 – 9,21 (m, 1H), 7,70 – 7,63 (m, 1H), 7,63 – 7,55 (m, 1H), 7,28 – 7,17 (m, 1H), 6,90 – 4,48 (m, 2H), 3,89 – 3,72 (m, 2H), 2,92 – 2,71 (m, 2H), 2,14 – 1,94 (m, 3H).

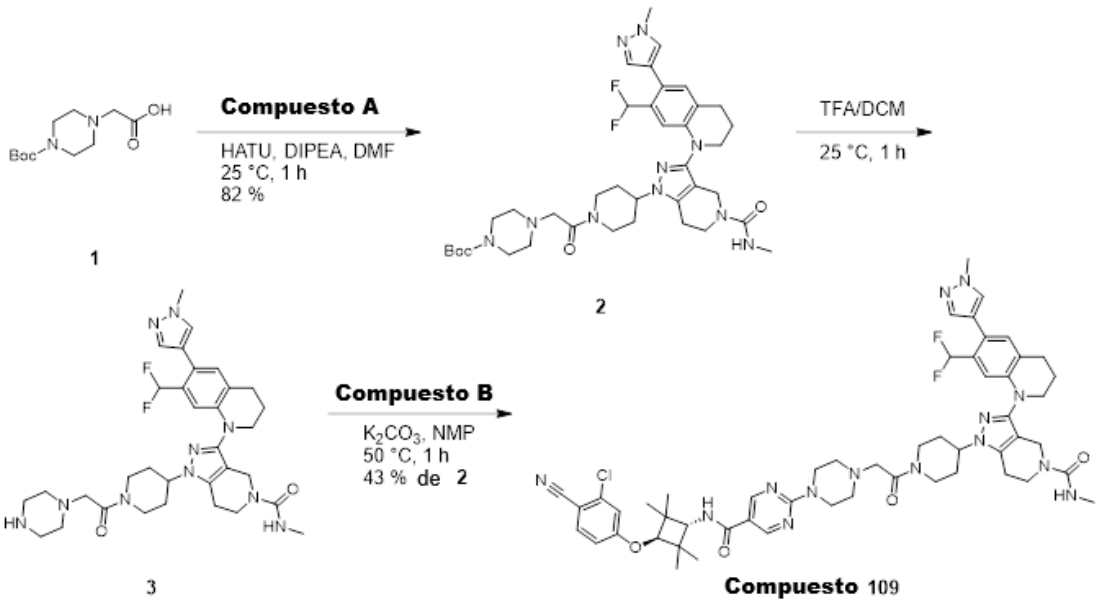
[00432] **LC-MS:** MS (ESI^+): t_R = 0,368 min, m/z = 323,2 [M + H^+]

[00433] A una solución de 1-[3-(3-hidroxi-8-isoquinolil)-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (1,60 g, 4,96 mmol, 1,0 eq) en DCM (20 ml) se agregó Et_3N (1,51 g, 14,89 mmol, 2,07 ml, 3,0 eq) y Tf_2O (2,10 g, 7,45 mmol, 1,23 ml, 1,5 eq). La mezcla de reacción se agitó a 45 oC durante 1 h. La mezcla de reacción se inactivó con agua (20 ml) y se extrajo con acetato de etilo (20 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 50/1 a 10/1). El compuesto [8-(5-acetil-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil] trifluorometanosulfonato (1,3 g, 2,86 mmol, 57 % de rendimiento) se obtuvo como un sólido amarillo.

[00434] 1H NMR (400 MHz, DMSO-d6) δ 9,82 – 9,76 (m, 1H), 8,21 (s, 1H), 8,14 – 7,09 (m, 1H), 8,04 – 7,96 (m, 1H), 7,82 – 7,71 (m, 1H), 3,89 – 3,76 (m, 2H), 2,93 (d, J = 5,8 Hz, 2H), 1,98 (s, 3H).

[00435] **LC-MS:** MS (ESI^+): t_R = 0,521 min, m/z = 455,2 [M + H^+]

[00436] **Ejemplo 1**: Síntesis de 1-[1-[2-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazin-1-il]acetil]-4-piperidilo]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 109**)

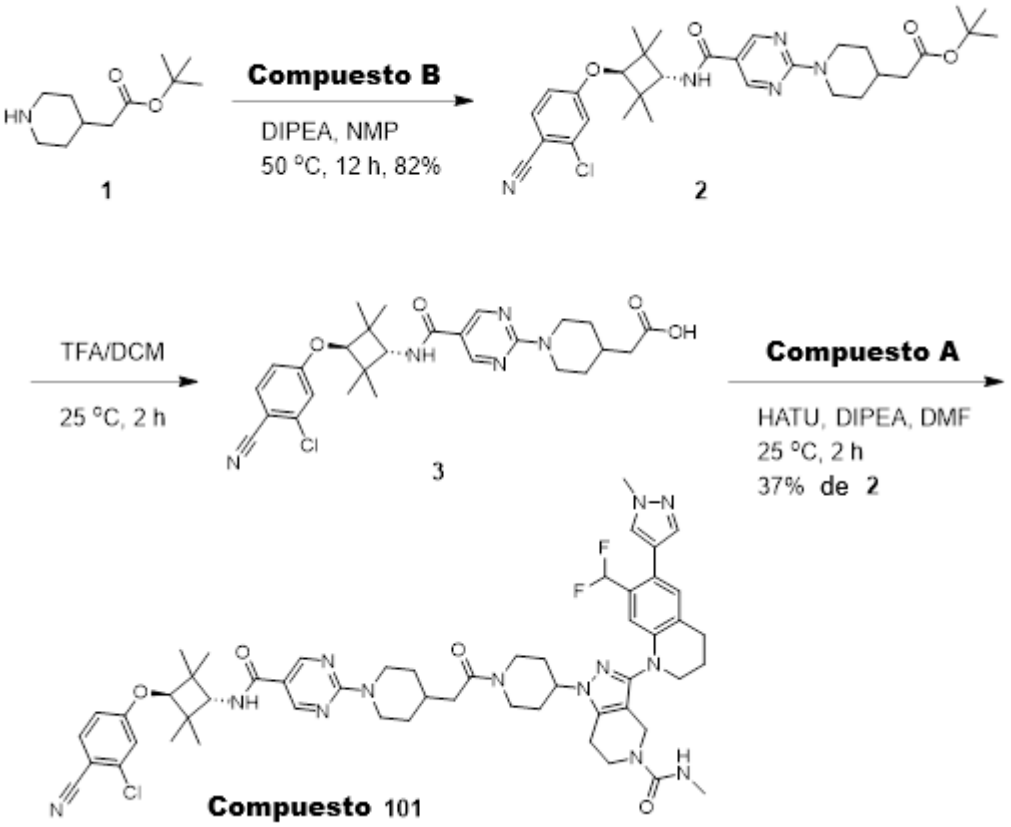


[00437] A una mezcla de 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (110 mg, 209 µmol, 1,0 eq) y ácido 2-(4-tertbutoxicarbonilpiperazin-1-il)acético (76 mg, 314 µmol, 1,5 eq) en DMF (2 ml) se le agregó DIPEA (135 mg, 1,05 mmol, 5,0 eq) y HATU (159 mg, 419 µmol, 2,0 eq), la mezcla se agitó a 25 °C durante 1 h. La mezcla de reacción se diluyó con agua (15 ml) y se extrajo con EtOAc (15 ml * 3). Las capas orgánicas combinadas se concentraron para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 18 %-48 % B durante 10 min) para obtener ter-butil 4-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazina-1-carboxilato (130 mg, 82 % de rendimiento). LC-MS: MS (ESI^+): t_R = 0,828 min, m/z = 751,5 [$M + H^+$]

[00438] A una mezcla de ter-butil 4-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazina-1-carboxilato (130 mg, 173 µmol, 1,0 eq) en DCM (3 ml) se le agregó TFA (1,54 g, 13,4 mmol, 1 ml, 77,7 eq), la mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró para obtener un residuo. El compuesto 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-(2-piperazin-1-ilacetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (112 mg) se obtuvo como un sólido marrón y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,650 min, m/z = 651,3 [$M + H^+$]

[00439] A una mezcla de 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-(2-piperazin-1-ilacetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (112 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (72 mg, 172 µmol, 1,0 eq) en NMP (2 ml) se agregó K_2CO_3 (118 mg, 860 µmol, 5,0 eq), la mezcla se agitó a 50 °C durante 1 h. La mezcla se filtró y concentró para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 31 %-61 % B durante 10 min) para dar 1-[1-[2-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazin-1-il]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 109**, 170 mg, 43 % de rendimiento en dos pasos). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8,70 (s, 2 H), 7,65-7,55 (m, 1 H), 7,52 (s, 1 H), 7,40 (s, 1 H), 7,15-7,05 (m, 1 H), 6,98-6,90 (m, 1 H), 6,86 (s, 1 H), 6,85-6,75 (m, 1 H), 6,70-6,30 (m, 1 H), 6,10-6,00 (m, 1 H), 4,75-4,58 (m, 1 H), 4,55-4,40 (m, 1 H), 4,35-4,10 (m, 3 H), 4,10-4,00 (m, 5 H), 4,00-3,90 (m, 5 H), 3,85-3,68 (m, 2 H), 3,75-3,65 (m, 2 H), 3,60-3,45 (m, 2 H), 3,30-3,15 (m, 1 H), 3,05-2,80 (m, 6 H), 2,79-2,65 (m, 5 H), 2,30-2,15 (m, 2 H), 2,14-1,90 (m, 5 H), 1,40-1,10 (m, 12 H).LC-MS:MS (ESI$^+$): t_R = 1,933 min, m/z= 1033,7 [M+H$^+$].

[00440] Ejemplo 2: Síntesis de 1-[1-[2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 101**)



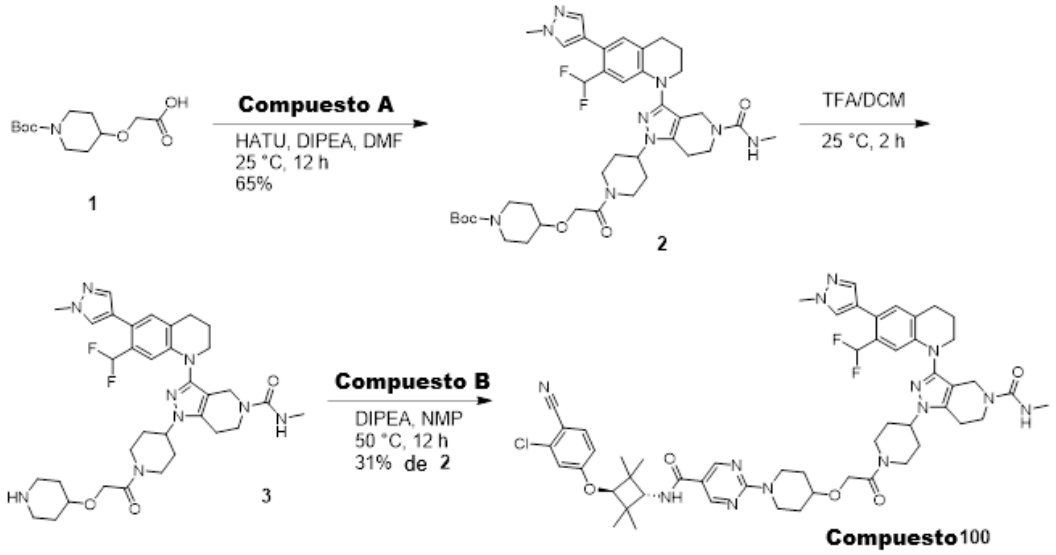
[00441] A una solución de 2-(4-piperidilo)acetato de ter-butilo (48,0 mg, 238 µmol, 1,0 eq) en NMP (1 ml) se le agregó DIPEA (92,5 mg, 715,47 µmol, 0,13 ml, 3,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (100 mg, 238 µmol, 1,0 eq). La mezcla resultante se agitó a 50 °C durante 12 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó mediante *prep*-TLC (sílice, DCM/MeOH = 10/1). El compuesto ter-butil 2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]acetato (123 mg, 196 µmol, 82 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,720 min, m/z = 582,6 [$M + H^+$]

[00442] A una solución de 2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidilo]acetato de ter-butilo (43,0 mg, 73,9 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (733 mg, 6,43 mmol, 480 µl, 87,1 eq). La mezcla se agitó a 25 °C durante 2 h. La mezcla se concentró al vacío. El compuesto ácido 2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]acético (38 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional. LC-

MS: MS (ESI^+): t_R = 0,999 min, m/z = 526,2 [M + H^+]

[00443] A una solución de ácido 2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]acético (38 mg), HATU (33 mg, 86 µmol, 1,2 *equiv*) en DMF (0,5 ml) se agregó 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (42 mg, 81 µmol, 1,1 eq) y DIPEA (28 mg, 0,22 mmol, 0,04 ml, 3,0 eq). La mezcla resultante se agitó a 25 °C durante 2 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 60 %-90 % B durante 10 min). El compuesto 1-[1-[2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 101**, 29 mg, 27 µmol, 37 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. ^1H (400 MHz, $CDCl_3$) δ = 8,69 (s, 2H), 7,57 (d, J = 8,8 Hz, 1H), 7,54 (s, 1H), 7,41 (s, 1H), 7,05 (s, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,87 (s, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,55 (t, J = 55,6 Hz, 1H), 5,93 (d, J = 8,3 Hz, 1H), 4,86 (br d, J = 13,2 Hz, 2H), 4,76 (br d, J = 13,2 Hz, 1H), 4,40 (q, J = 4,4 Hz, 1H), 4,19 - 4,10 (m, 2H), 4,08 - 4,00 (m, 2H), 4,00 - 3,93 (m, 5H), 3,86 - 3,75 (m, 2H), 3,71 (q, J = 5,2 Hz, 2H), 3,25 - 3,14 (m, 1H), 3,05 - 2,94 (m, 2H), 2,88 (br t, J = 5,6 Hz, 2H), 2,79 (d, J = 4,8 Hz, 4H), 2,75 (br t, J = 5,2 Hz, 2H), 2,35 - 2,27 (m, 2H), 2,27 - 1,87 (m, 10H), 1,26 (s, 9H), 1,25 (s ancho, 6H), 1,22 (s, 6H). LC-MS: MS (ESI^+): t_R = 2,016 min, m/z = 975,7 [M + H^+]

[00444] Ejemplo 3: Síntesis de 1-[1-[2-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]oxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 100**)

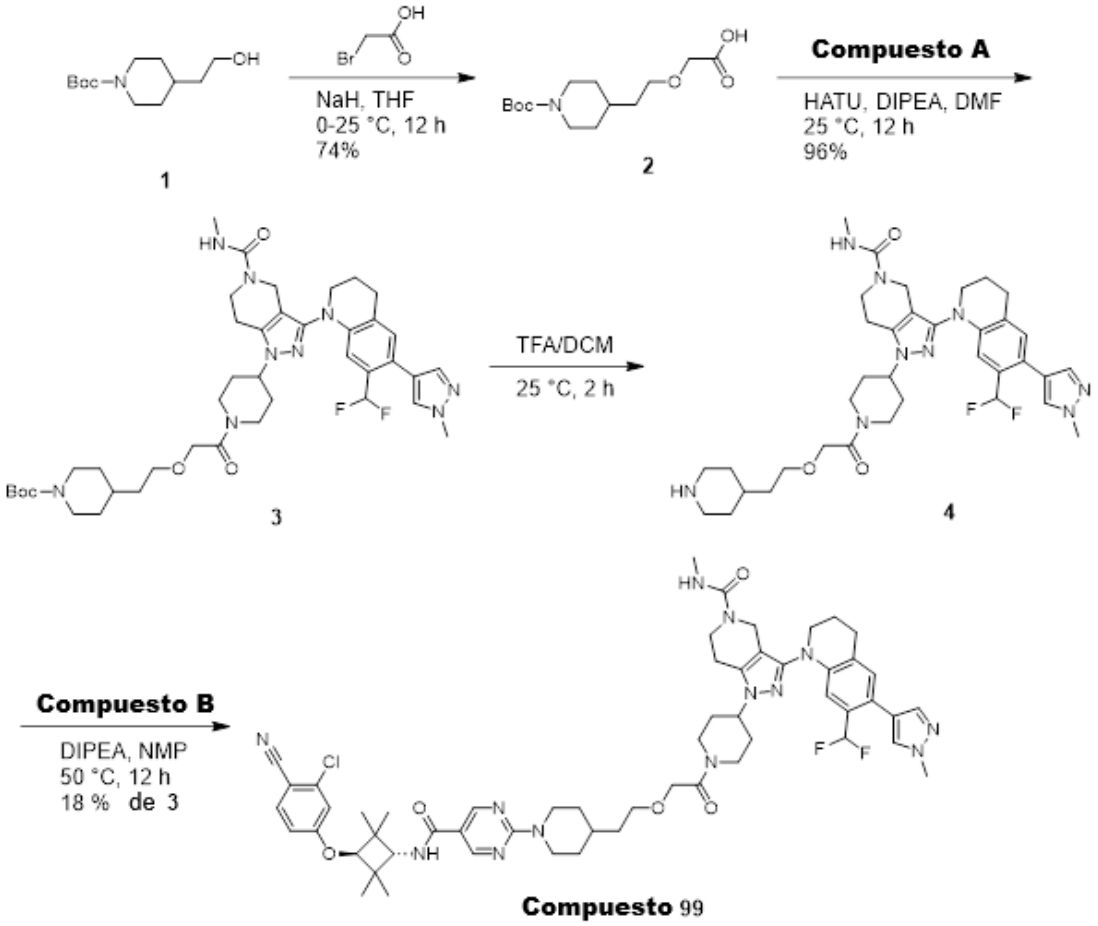


[00445] A una solución de ácido 2-[(1-terc-butoxicarbonil-4-piperidil)oxi]acético (74,0 mg, 286 µmol, 1,5 eq) y 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (100 mg, 191 µmol, 1,0 eq) en DMF (1 ml) se le añadieron HATU (87 mg, 229 µmol, 1,2 eq) y DIPEA (74 mg, 572 µmol, 100 µl, 3,0 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se vertió en agua fría (20 ml). La fase acuosa se extrajo con acetato de etilo (15 ml x 3). La fase orgánica combinada se lavó con salmuera (10 ml x 2), se secó con Na_2SO_4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante *prep*-HPLC (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 40 %-70 % B durante 10 min) para dar ter-butil 4-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etoxi]piperidina-1-carboxilato (100 mg, 65 % de rendimiento) se obtuvo como un sólido blanquecino. LC-MS: MS (ESI^+): t_R = 0,570 min, m/z = 766,6 [M + H^+]

[00446] A una solución de ter-butil 4-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etoxi]piperidina-1-carboxilato (100 mg, 131 µmol, 1,0 eq) en DCM (4 ml) se le agregó TFA (1,5 g, 13,5 mmol, 1 ml, 103,1 eq). La mezcla de reacción se agitó a 25 °C durante 2 h. La mezcla se concentró hasta secarse. El compuesto 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-[2-(4-piperidiloxi)acetil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (100 mg) se obtuvo como un sólido marrón y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,786 min, m/z = 666,4 [M + H^+]

[00447] A una solución de 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-[2-(4-piperidiloxi)acetil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (100 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (65 mg, 154 µmol, 1,2 eq) en NMP (1 ml) se agregó DIPEA (50 mg, 385 µmol, 67 µl, 3,0 eq). La mezcla se agitó a 50 °C durante 12 h. La mezcla de reacción se diluyó con agua (15 ml) y se extrajo con EtOAc (20 ml × 3). Las capas orgánicas combinadas se concentraron a presión reducida. El residuo se purificó mediante *prep*-HPLC (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-60 % B durante 10 min) para dar 1-[1-[2-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]oxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 100**, 43 mg, rendimiento del 31 % en dos pasos). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8,70 (s, 2H), 7,61 - 7,52 (m, 2H), 7,41 (s, 1H), 7,04 (s, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,86 (s, 1H), 6,83 - 6,78 (m, 1H), 6,71 - 6,38 (m, 1H), 5,97 (d, J = 8,4 Hz, 1H), 4,68 (d, J = 12,8 Hz, 1H), 4,46 - 4,37 (m, 1H), 4,36 - 4,24 (m, 4H), 4,23 - 4,10 (m, 3H), 4,05 (s, 1H), 4,00 - 3,93 (m, 5H), 3,85 - 3,65 (m, 5H), 3,64 - 3,53 (m, 2H), 3,29 - 3,14 (m, 1H), 2,87 (m, 3H), 2,82 - 2,77 (m, 3H), 2,74 (m, 2H), 2,28 - 1,93 (m, 8H), 1,73 - 1,66 (m, 2H), 1,25 (s, 6H), 1,22 (s, 6H) LC-MS: MS (ESI+): t_R = 2,706 min, m/z = 1048,6 [M + H+]

[00448] Ejemplo 4: Síntesis de 1-[1-[2-[2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]etoxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 99**)



[00449] A una solución de NaH (349 mg, 60 % p/p, 8,7 mmol, 3,0 eq) en THF (7 ml) se le agregó 4-(2-hidroxietil)piperidina-1-carboxilato de ter-butilo (2,0 g, 8,7 mmol, 3,0 eq) a 0 °C y se agitó a 0 °C durante 0,5 h. A continuación, se agregó gota a gota ácido 2-bromoacético (404 mg, 2,9 mmol, 209 µl, 1,0 eq) en THF (1 ml) a 0 °C. La mezcla resultante se agitó a 25 °C durante 11,5 h. La reacción se detuvo añadiendo gota a gota una solución acuosa saturada de NH_4Cl (2 ml) a 0 °C. La mezcla se extrajo con acetato de etilo (15 ml x 3). La fase acuosa se ajustó a pH 6 con HCl (1 M) y luego se liofilizó para obtener un residuo. El crudo se usó para la siguiente etapa sin purificación adicional. El compuesto ácido 2-[2-(1-terc-butoxicarbonil-4-piperidil)etoxi]acético (620 mg, 74 % de rendimiento) se obtuvo como una goma amarilla. LC-MS: MS (ES^+): t_R = 0,842 min, m/z = 310,1 [M + Na]

[00450] A una solución de ácido 2-[2-(1-terc-butoxicarbonil-4-piperidil)etoxi]acético (115 mg, 400 µmol, 3,0 eq) y HATU (61 mg, 160 µmol, 1,2 eq) en DMF (1 ml) se le añadieron DIPEA (52 mg, 400 µmol, 70 µl, 3,0 eq) y 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (70 mg, 133 µmol, 1,0 eq) en DMF (1 ml). La mezcla se agitó

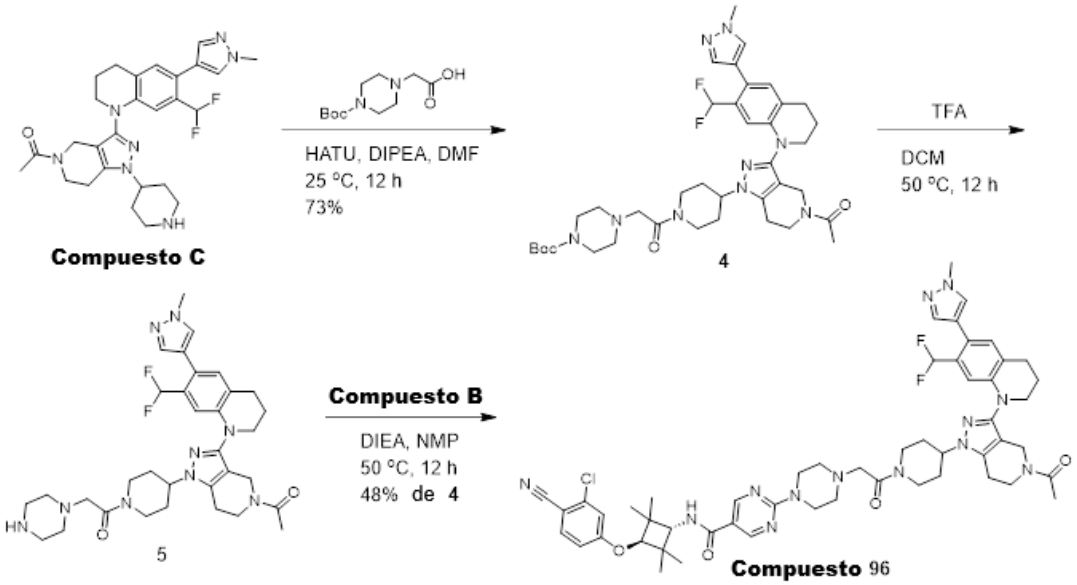
a 25 °C durante 12 h. La mezcla se vertió en agua con hielo (15 ml). La fase acuosa se extrajo con acetato de etilo (10 ml x 3). La capa orgánica combinada se lavó con salmuera (10 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante *prep*-TLC (sílice, DCM/MeOH = 15/1). El compuesto ter-butil 4-[2-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etoxi]etil]piperidina-1-carboxilato (120 mg, 128 µmol, 96 % de rendimiento) se obtuvo como un aceite amarillo. LC-MS: MS (ESI^+): t_R = 0,970 min, m/z = 794,4 [M + H^+]

[00451] A una solución de ter-butil 4-[2-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etoxi]etil]piperidina-1-carboxilato (120 mg, 151 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (768 mg, 6,73 mmol, 0,5 ml, 44,5 eq). La mezcla se agitó a 25 °C durante 2 h. La mezcla se concentró para obtener un residuo. El compuesto 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-[2-[2-(4-piperidil)etoxi]acetil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (100 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,493 min, m/z = 694,4 [M + H^+]

[00452] A una solución de 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-[2-[2-(4-piperidil)etoxi]acetil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (100 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (78 mg, 186 µmol, 1,5 eq) en NMP (1 ml) se agregó DIPEA (48 mg, 371 µmol, 65 µl, 3,0 eq). La mezcla se agitó a 50 °C durante 12 h. Después de enfriar a 25 °C, la mezcla se vertió en agua helada (20 ml) y se extrajo con DCM (15 ml × 3). La fase orgánica combinada se lavó con salmuera (10 ml x 3), se secó con Na_2SO_4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 58 %-88 % B durante 10 min). El compuesto 1-[1-[2-[2-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]etoxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 99**, 25 mg, 18 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. ^{1}H NMR (400 MHz, CLOROFORMO-d) δ = 8,67 (d, J = 7,8 Hz, 1H), 7,06 - 7,00 (m, 2H), 6,97 - 6,85 (m, 1H), 6,83 - 6,79 (m, 4H), 6,70 (br d, J = 7,6 Hz, 1H), 4,88 - 4,77 (m, 1H), 4,68 (s, 1H), 4,40 - 4,09 (m, 4H), 4,05 - 3,96 (m, 1H), 3,86 - 3,75 (m, 2H), 3,73 (s, 1H), 3,61 (s, 1H), 3,20 (s, 2H), 3,00 - 2,90 (m,

2H), 2,85 (s, 1H), 2,81 - 2,69 (m, 6H), 2,24 - 1,92 (m, 2H), 1,88 - 1,72 (m, 4H), 1,64 - 1,61 (m, 4H), 1,25 - 1,22 (m, 2H). LC-MS: MS (ESI$^+$): t_R = 2,55 min, m/z = 1076,7 [M + H$^+$]

[00453] **Ejemplo 5**: Síntesis de 2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 96**)

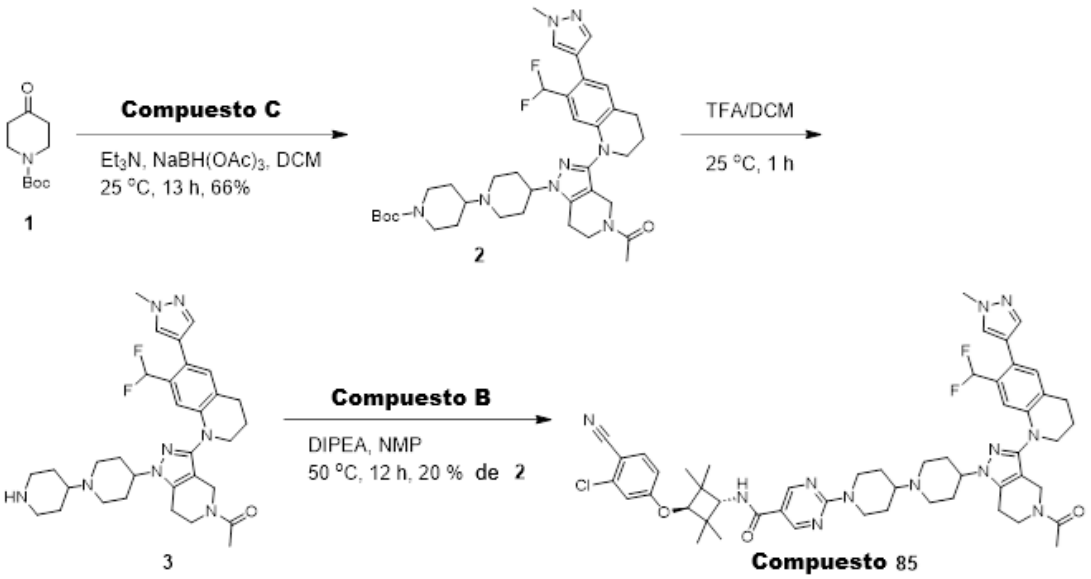


[00454] A una solución de ácido 2-(4-tert-butoxicarbonilpiperazin-1-il)acético (71,9 mg, 294 µmol, 1,5 eq) en DMF (1 ml) se le agregó HATU (119 mg, 314 µmol, 1,6 eq) y se agitó a 25 °C durante 0,5 h. Se añadieron 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg, 196 µmol, 1,0 eq) y Et_3N (59,6 mg, 589 µmol, 81,9 µl, 3,0 eq) a la mezcla de reacción anterior y se agitó a 25 °C durante 11,5 h. La mezcla se vertió en agua helada (15 ml). La fase acuosa se extrajo con acetato de etilo (10 ml x 3). La capa orgánica combinada se lavó con salmuera (10 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 18 %-48 % B durante 10 min). El compuesto ter-butil 4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazina-1-carboxilato (105 mg, 143 µmol, 73 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI$^+$): t_R = 0,521 min, m/z = 736,6 [M + H$^+$]

[00455] A una solución de ter-butil 4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazina-1-carboxilato (105 mg, 143 µmol, 1 eq) en DCM (1 ml) se le agregó TFA (2,69 g, 23,6 mmol, 1,75 ml, 165 eq) y se agitó a 25 °C durante 1 h. La mezcla se concentró para obtener un residuo. El compuesto 1-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-piperazin-1-il-etanona (0,12 g) se obtuvo como un sólido marrón y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,474 min, m/z = 636,5 [M + H^+]

[00456] A una solución de 1-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-piperazin-1-il-etanona (0,12 g) en NMP (1 ml) se agregó DIEA (103 mg, 800 µmol, 139 µl, 5,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (67,1 mg, 160 µmol, 1,0 *eq*). La mezcla de reacción se agitó a 50 °C durante 12 h. Una vez completada (monitoreada mediante TLC), la mezcla se inactivó con agua helada (20 ml) y se extrajo con EtOAc (15 x 50 ml). La capa orgánica combinada se lavó con salmuera (10 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 28 %-58 % B durante 10 min). El compuesto 2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 96**, 81,04 mg, 77,29 µmol, 48 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8,69 (s, 2 H) 7,57 (d, *J*=8,8 Hz, 1 H) 7,48 - 7,54 (m, 1 H) 7,35 - 7,42 (m, 1 H) 7,27 (s, 1 H) 6,98 - 7,06 (m, 1 H) 6,96 (d, *J*=2,4 Hz, 1 H) 6,85 - 6,91 (m, 1 H) 6,80 (m, 1 H) 6,32 - 6,68 (m, 1 H) 6,01 (d, *J*=8,4 Hz, 1 H) 4,62 - 4,77 (m, 1 H) 4,19 - 4,34 (m, 2 H) 4,10 - 4,18 (m, 3 H) 4,05 (s, 1 H) 3,94 (m, 6 H) 3,83 - 3,92 (m, 1 H) 3,64 - 3,80 (m, 4 H) 3,16 - 3,38 (m, 3 H) 2,72 - 2,92 (m, 5 H) 2,61 (m, 4 H) 2,20 - 2,34 (m, 1 H) 2,17 (s, 1 H) 1,97 - 2,08 (m, 6 H) 1,25 (s, 6 H) 1,20 - 1,23 (m, 6 H). LC-MS: MS (ESI^+): t_R = 1,97 min, m/z = 1018,7 [M + H^+]

[00457] **Ejemplo 6**: Síntesis de 2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 85**)



[00458] A una solución de 4-oxopiperidina-1-carboxilato de ter-butilo (235 mg, 1,18 mmol, 4,0 eq), 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (150 mg, 294 µmol, 1,0 eq) en DCM (3 ml) se agregó Et_3N (109 mg, 1,0 mmol, 0,15 ml, 3,7 *equiv*) a 25 °C durante 1 h. Luego se agregó $NaBH(OAc)_3$ (312 mg, 1,47 mmol, 5,0 eq). La mezcla de reacción se agitó a 20 °C durante 12 h. La reacción se diluyó con agua (10 ml) y se extrajo con DCM (10 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó mediante *prep*-TLC (sílice, DCM/MeOH = 10/1). El compuesto ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]piperidina-1-carboxilato (138 mg, 195 µmol, 66 % de rendimiento) se obtuvo como un aceite amarillo. LC-MS: MS (ESI^+): t_R = 0,813 min, m/z = 693,5 [M + H^+]

[00459] A una solución de ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]piperidina-1-carboxilato (80,0 mg, 115 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (768 mg, 6,73 mmol, 0,5 ml, 58 eq). La mezcla se agitó a 25 °C durante 2 h. La mezcla se concentró al vacío. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(4-piperidil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (81 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,457 min, m/z = 593,5 [M + H^+]

[00460] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(4-piperidil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-

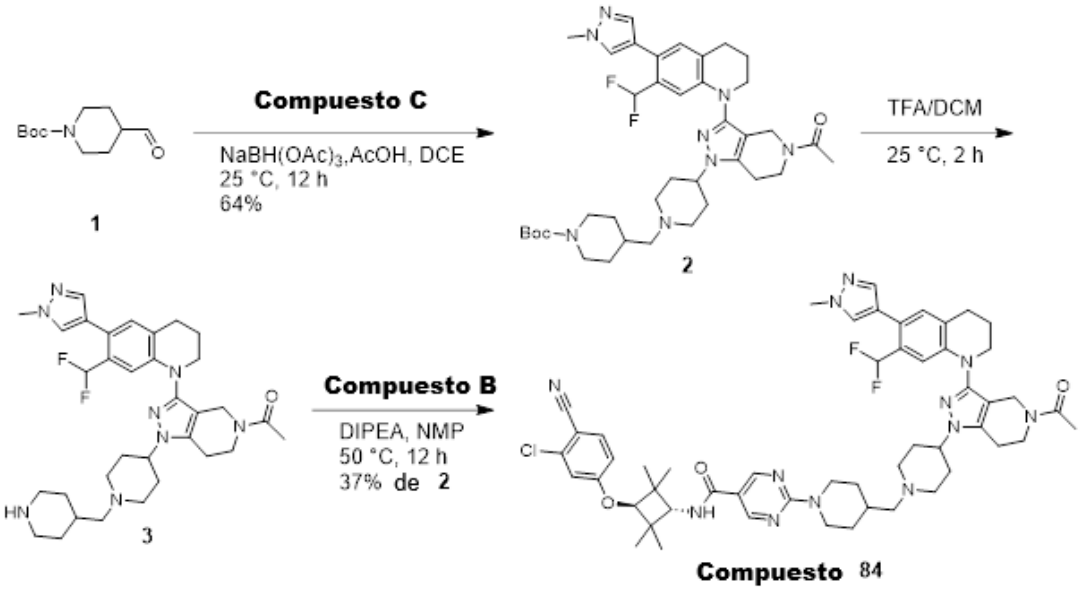
il]etanona (81 mg) en NMP (0,5 ml) se le agregó 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (48 mg, 115 µmol, 1,0 eq) y DIPEA (45,0 mg, 344 µmol, 60,0 uL, 3,0 eq). La mezcla resultante se agitó a 50 °C durante 12 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 28 %-58 % B durante 10 min). El compuesto 2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 85**, 23,2 mg, 23,7 µmol, 20 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino. ^{1}H NMR (DMSO-$_{d6}$) δ = 8,79-8,13 (m, 1H), 7,90-8,49 (m, 1H), 7,79-7,71 (m, 1H), 7,21 (d, *J*=2,4 Hz, 1H), 7,11-7,49 (m, 1H), 7,01 (dd, J=2,4, 8,8 Hz, 1H), 6,80-4,75 (m, 1H), 4,20-4,14 (m, 1H), 4,11-6,66 (m, 1H), 4,07-4,02 (m, 1H), 3,86-3,67 (m, 1H), 3,63-3,55 (m, 1H), 3,30-3,09 (m, 3H), 3,06-2,92 (m, 1H), 2,90 (s, 3H), 2,77-2,70 (m, 3H), 2,20-2,03 (m, 1H), 2,02-1,88 (m, 1H), 1,65-1,42 (m, 1H), 1,30-1,24 (m, 1H), 1,22 (br s, 1H). LC-MS: MS (ESI$^+$): t_R = 2,016 min, m/z = 975,7 [M + H$^+$]

[00461] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 6.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS [M + H$^+$]/2**
276	2-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-3-azaespiro[5,5]undecan-3-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,71 (s, *J* =9,6 Hz, 2H), 7,57 (d, *J* =8,8 Hz, 1 H), 7,54-7,53 (m, 1H), 7,42-7,41 (m, 1H), 7,10 (s, 1H), 6,97-6,96 (m, 1H), 6,91-6,90 (m, 1H), 6,81 (dd, 1H, *J* =2,4, 8,8 Hz), 6,54-6,40 (m, 1H), 5,92 (d, *J* =8 Hz, 1 H), 4,28-4,14 (m, 3H), 4,13 (s, 1H), 3,96 (s, 3H), 3,95-3,90 (m, 6H), 3,74-3,73 (m, 3H), 2,89-2,88 (m, 2H), 2,85-2,83 (m, 1H), 2,75-2,73 (m, 1H), 2,25-2,23 (m, 1H), 2,22-2,20 (m, 2H), 2,19-2,18(m, 1H), 2,15-2,13 (m, 3H), 1,96-1,94 (m, 2H), 1,80-1,75(m, 2H), 1,75-1,73 (m, 2H), 1,49-1,48	480,9

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS [M + H^+]/2
		(m, 2H), 1,30-1,25 (m, 2H), 1,25 (s, 6H), 1,22 (s, 6H)	

[00462] **Ejemplo 7**: Síntesis de 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 84**)



[00463] A una solución de 4-formilpiperidina-1-carboxilato de ter-butilo (63 mg, 294 µmol, 1,5 eq) y 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg, 196 µmol, 1,0 eq) en DCM (3 ml) se añadieron AcOH (18 mg, 294 µmol, 17 µl, 1,5 eq) y $NaBH(OAc)_3$ (125 mg, 589 µmol, 3,0 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla se vertió en agua helada (20 ml). La capa acuosa se extrajo con DCM (15 ml x 3). La fase orgánica combinada se lavó con salmuera (10 ml x 2), se secó con Na_2SO_4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante *prep*-HPLC (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 20 %-50 % B durante 10 min) para dar ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]piperidina-1-carboxilato (90 mg, 125 µmol, 64 % de rendimiento) se obtuvo como un sólido blanquecino. LC-MS: MS (ESI^+): t_R = 0,529 min, m/z = 707,5 [M + H^+]

[00464] A una solución de ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-

4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]piperidina-1-carboxilato (90 mg, 127 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (921 mg, 8,1 mmol, 600 µl, 63,4 eq). La mezcla se agitó a 25 °C durante 2 h. La mezcla se concentró para obtener un residuo. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(4-piperidilmetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (70 mg) se obtuvo como un sólido marrón y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,747 min, m/z = 607,5 [M + H^+]

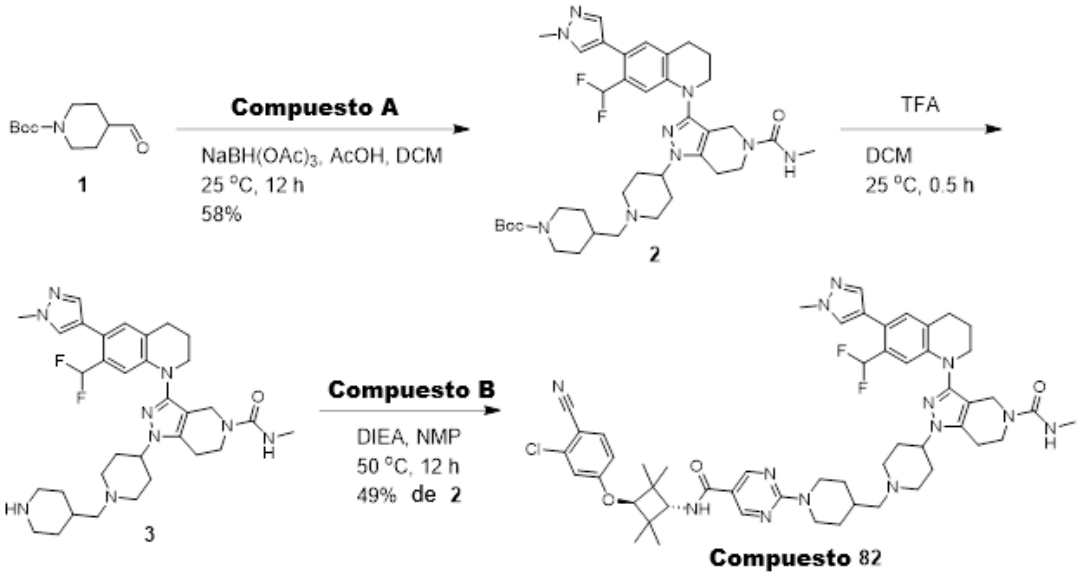
[00465] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(4-piperidilmetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (70 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (58 mg, 138 µmol, 1,2 eq) en NMP (1 ml) se agregó DIPEA (45 mg, 346 µmol, 60 µl, 3,0 eq). La mezcla se agitó a 50 °C durante 12 h. La mezcla de reacción se diluyó con agua (15 ml) y se extrajo con EtOAc (20 ml × 3). Las capas orgánicas combinadas se concentraron a presión reducida. El residuo se purificó mediante *prep*-HPLC (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-60 % B durante 10 min) para dar 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 84**, 43 mg, 43 µmol, 37 % de rendimiento en dos pasos). ^{1}H (400 MHz, $CDCl_3$) δ = 8,70 (s, 2H), 7,60 - 7,50 (m, 2H), 7,44 - 7,35 (m, 1H), 7,09 - 6,94 (m, 2H), 6,91 - 6,85 (m, 1H), 6,83 - 6,77 (m, 1H), 6,72 - 6,34 (m, 1H), 5,93 (d, J = 8,4 Hz, 1H), 4,85 (m, 2H), 4,73 (s, 4H), 4,26 (s, 1H), 4,17 - 4,07 (m, 2H), 4,04 (s, 1H), 3,99 - 3,86 (m, 5H), 3,78 - 3,66 (m, 3H), 3,12 - 2,70 (m, 8H), 2,33 - 2,23 (m, 4H), 2,21 - 2,13 (m, 3H), 2,10 - 2,01 (m, 4H), 1,99 - 1,95 (m, 1H), 1,25 (s, 6H), 1,22 (s, 6H), 1,20 - 1,10 (m, 2H). LC-MS (ESI, m/z): 989,6 [M+H]

[00466] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 7.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
264	4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-4-metoxi-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-	δ = 7,69 (d, J = 8,8 Hz, 2H), 7,53 (d, J = 7,2 Hz, 1H), 7,45 (d, J = 8,4 Hz, 1H), 7,40 (d, J = 6,8 Hz, 1H), 7,08 - 6,97 (m, 1H), 6,97 - 6,82 (m, 3H), 6,69 - 6,38 (m, 3H), 6,15 (br d, J = 8,0 Hz, 1H), 4,27 (s, 1H), 4,18 -	1013,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	tetrametilciclobutil]benzamida	4,11 (m, 2H), 4,05 (s, 1H), 3,95 (d, J = 2,0 Hz, 3H), 3,92 (s, 3H), 3,91 - 3,87 (m, 1H), 3,78 - 3,65 (m, 3H), 3,51 (br d, J = 12,4 Hz, 2H), 3,26 (s, 3H), 3,22 - 3,11 (m, 3H), 2,91 - 2,78 (m, 3H), 2,74 (br t, J = 5,6 Hz, 1H), 2,69 - 2,49 (m, 3H), 2,34 - 2,24 (m, 2H), 2,17 (s, 2H), 2,11 - 2,00 (m, 5H), 1,94 (br d, J = 12,8 Hz, 5H), 1,77 - 1,69 (m, 2H), 1,25 (d, J = 12,4 Hz, 12H)	

[00467] Ejemplo 8: Síntesis de 1-[1-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]metil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 82**)



[00468] A una solución de 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (80,0 mg, 153 µmol, 1,0 eq) y 4-formilpiperidina-1-carboxilato de ter-butilo (65,1 mg, 305,0 µmol, 2,0 eq) en DCM (4 ml) se agregó AcOH (18,3 mg, 305 µmol, 17,5 µl, 2,0 eq) y se agitó a 25 °C durante 0,5 h. Se agregó $NaBH(OAc)_3$ (129 mg, 610 µmol, 4,0 eq) a la mezcla de reacción anterior. La mezcla se agitó a 25 °C durante 12 h. La reacción se detuvo mediante la adición de una solución acuosa saturada de $NaHCO_3$ (30 ml) a 0 °C**,**

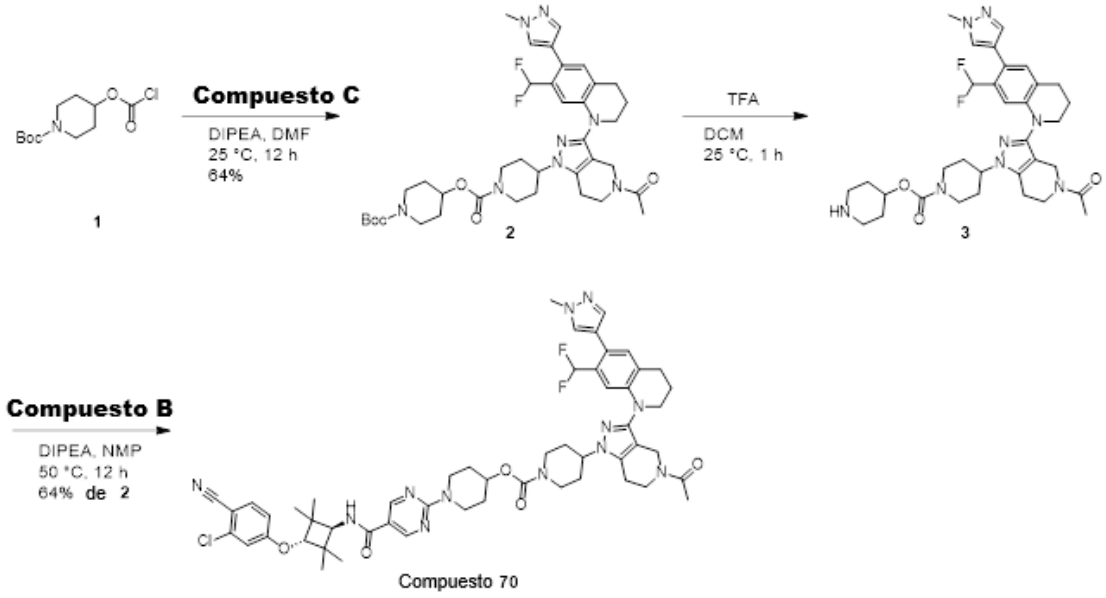
y luego se extrajo con DCM/MeOH (10:1, 30 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante *prep*-HPLC (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 20 %-50 % B durante 10 min). El compuesto ter-butil 4-[[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]piperidina-1-carboxilato (64,0 mg, 88,7 µmol, 58 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,795 min, m/z = 722,4 [$M + H^+$]

[00469] A una solución de ter-butil 4-[[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]piperidina-1-carboxilato (79,0 mg, 109 µmol, 1,0 eq) en DCM (2 ml) se le agregó TFA (1 ml). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se concentró al vacío. El crudo se usó para la siguiente etapa sin purificación adicional. El compuesto 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-(4-piperidilmetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (80 mg) se obtuvo como un aceite amarillo. LC-MS: MS (ESI^+): t_R = 0,687 min, m/z = 622,4 [$M + H^+$]

[00470] A una solución de 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-[1-(4-piperidilmetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (80 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (54,7 mg, 131 µmol, 1,2 eq) en NMP (0,5 ml) se le agregó DIPEA (0,1 ml). La mezcla de reacción se agitó a 50 °C durante 12 h. La mezcla se concentró hasta secarse. El residuo se purificó posteriormente mediante *prep*-HPLC (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto 1-[1-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]metil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 82**, 54,4 mg, 53,6 µmol, 49 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. ^1H (400 MHz, $CDCl_3$): δ = 8,70 (s, 2H), 8,38 - 8,36 (m, 1H), 7,62 - 7,51 (m, 2H), 7,41 (s, 1H), 7,04 (s, 1H), 6,98 - 6,95 (m, 1H), 6,87 (s, 1H), 6,83 - 6,78 (m, 1H), 6,55 (m, J = 55,6 Hz, 1H), 5,98 - 5,91 (m, 1H), 4,85 (m, J = 13,2 Hz, 2H), 4,46 - 4,39 (m, 1H), 4,13 (m, J = 8,1 Hz, 1H), 4,04 (s, 1H), 3,98 (s, 2H), 3,96 (s, 3H), 3,78 (m, J = 5,6 Hz, 2H), 3,75 - 3,70 (m, 2H), 3,12 - 3,04 (m, 2H), 2,95 (m, J = 11,9 Hz, 2H), 2,87 (m, J = 6,2 Hz, 2H), 2,80 - 2,77 (m,

3H), 2,75 (m, *J* = 5,4 Hz, 2H), 2,34 - 2,28 (metros, 3H), 2,20 (m, 1H), 2,10 - 2,03 (m, 3H), 2,03 - 1,90 (m, 7H), 1,23 (m, *J* = 13,7 Hz, 11H), 1,20 - 1,11 (m, 2H) LC-MS: MS (ESI$^+$): t_R = 2,000 min, m/z = 1004,6 [M + H$^+$]

[00471] Ejemplo 9: Síntesis de [1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidilo] 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (**Compuesto 70**)



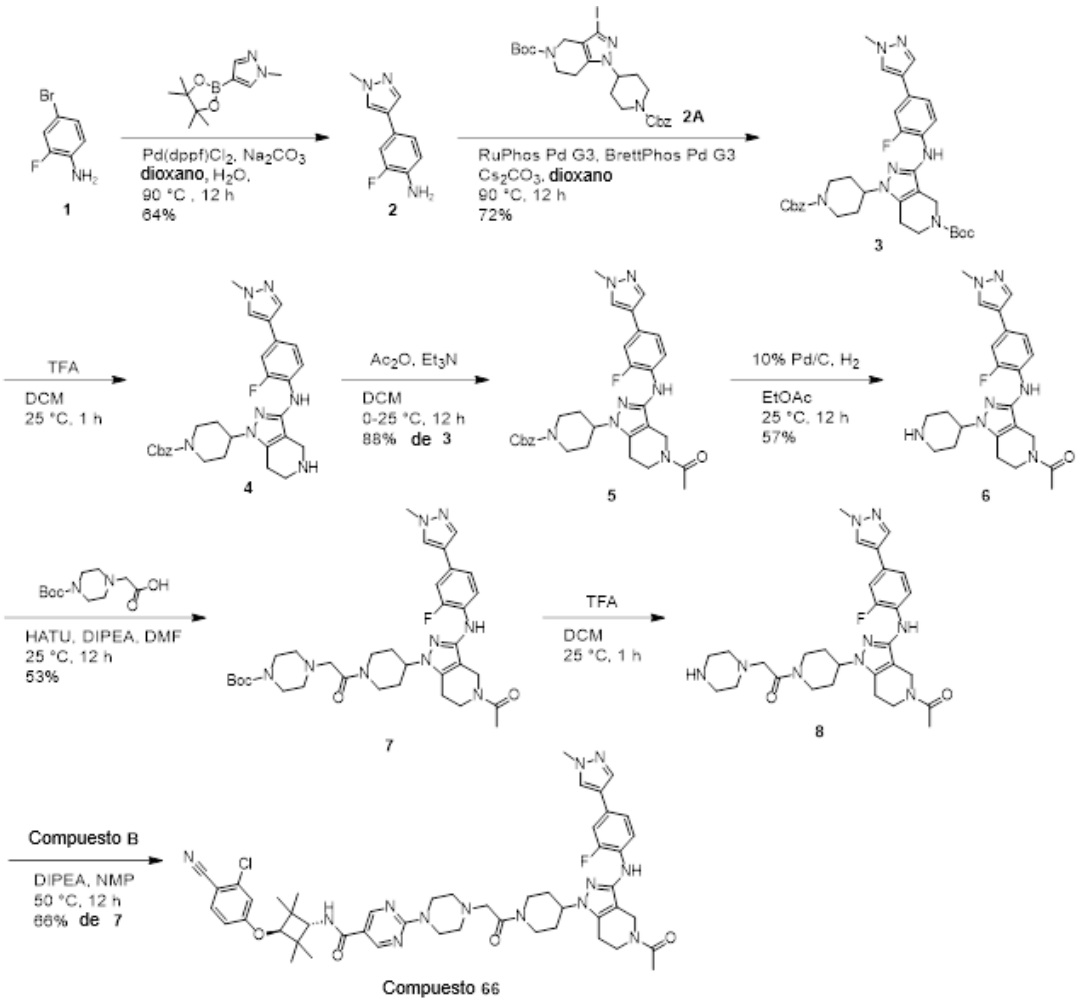
[00472] Las moléculas de TCB se prepararon de acuerdo con los métodos descritos en WO 2018/237370 A1. A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (130 mg, 255 µmol, 1,0 eq) y DIPEA (98,9 mg, 765 µmol, 133 µl, 3,0 eq) en DMF (3 ml) se le agregó 4-clorocarboniloxipiperidina-1-carboxilato de ter-butilo (101 mg, 383 µmol, 1,5 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla se diluyó con EtOAc (100 ml), se lavó con agua (10 ml × 2) y salmuera (10 ml), se secó con sulfato de sodio anhidro, se filtró y se concentró al vacío. El residuo se purificó mediante *prep*-TLC (sílice, DCM/MeOH = 20/1). El compuesto (1-tert-butoxicarbonil-4-piperidilo) 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (130 mg, 162 µmol, 64 % de rendimiento) se obtuvo como un sólido marrón. LC-MS: MS (ESI$^+$): t_R = 0,993 min, m/z = 737,4 [M + H$^+$]

[00473] A una solución de (1-tert-butoxicarbonil-4-piperidilo) 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-

pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (130 mg, 176 µmol, 1,0 eq) en DCM (6 ml) se le agregó TFA (1,54 g, 13,5 mmol, 1 ml, 76,3 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró al vacío. El compuesto 4-piperidil 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (150 mg) se obtuvo como una goma marrón y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,458 min, m/z = 637,4 [M + H^+]

[00474] A una solución de 4-piperidil 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (150 mg) en NMP (3 ml) se le agregó DIPEA (77,5 mg, 599 µmol, 104 µl, 3,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (100 mg, 238 µmol, 1,2 eq). La mezcla se agitó a 50 °C durante 12 h. La mezcla se diluyó con EtOAc (100 ml), se lavó con agua (15 ml × 2), salmuera (15 ml), se secó con sulfato de sodio anhidro, se filtró y se concentró al vacío. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 63 %-93 % B durante 10 min). El compuesto [1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidilo] 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (**Compuesto 70**, 133,17 mg, 128,59 µmol, 64 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8,76 (s, 2 H) 7,89 (d, J=8,8 Hz, 1 H) 7,70 - 7,79 (m, 2 H) 7,49 (s, 1 H) 7,21 (d, J=2,4 Hz, 1 H) 7,10 (s, 1 H) 7,00 (m, 1 H) 6,63 - 6,93 (m, 2 H) 4,89 (m, 1 H) 4,28 - 4,37 (m, 2 H) 4,02 - 4,19 (m, 7 H) 3,86 (s, 3 H) 3,68 - 3,81 (m, 4 H) 3,55 - 3,62 (m, 2 H) 2,94 - 3,09 (m, 2 H) 2,73 - 2,89 (m, 4 H) 2,07 (s, 2 H) 1,93 - 2,01 (m, 4 H) 1,88 (s, 4 H) 1,59 (m, 2 H) 1,19 - 1,24 (m, 6 H) 1,11 (s, 6 H) 1,05 (t, J=7,2 Hz, 1 H). LC-MS: MS (ESI^+): t_R = 2,665 min, m/z = 1019,7 [M + H^+]

[00475] Ejemplo 10: Síntesis de 2-[4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 66**)



[00476] Las moléculas de TCB se prepararon de acuerdo con los métodos descritos en WO 2022/42707 A1.

[00477] A una mezcla de 4-bromo-2-fluoroanilina (5,00 g, 26,3 mmol, 1,0 eq), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazol (8,21 g, 39,5 mmol, 1,5 eq) y ciclopentil(difenil)fosfano; dicloropaladio; hierro (1,93 g, 2,63 mmol, 0,1 eq) en dioxano (50 ml) y H_2O (6 ml) se agregó Na_2CO_3 (8,37 g, 78,9 mmol, 3,0 eq). La mezcla se agitó a 90 °C durante 12 h en N_2. La mezcla de reacción se vertió en agua fría (150 ml). La fase acuosa se extrajo con acetato de etilo (70 ml x 3). La fase orgánica combinada se lavó con salmuera (60 ml x 2), se secó con Na2SO4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto 2-fluoro-4-(1-metilpirazol-4-il)anilina (3,5 g, 16,8 mmol, 64 % de rendimiento) se obtuvo como un sólido blanquecino. LC-MS: MS (ESI^+): t_R = 0,419 min, m/z = 192,0 [M + H^+] ^1H NMR (400 MHz, $CDCl_3$): δ = 7,65 (s, 1 H) 7,49 (s, 1 H) 7,01 - 7,15 (m, 2 H) 6,73 - 6,82 (m, 1 H) 3,92 (s, 3 H)

[00478] A una solución de 1-(1-benciloxicarbonil-4-piperidil)-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato de ter-butilo (0,600 g, 1,06 mmol, 1,0 eq) y 2-fluoro-4-(1-metilpirazol-4-il)anilina (304 mg, 1,59 mmol, 1,5 eq) en dioxano (6 ml) se añadieron RuPhos Pd G3 (88,6 mg, 106 µmol, 0,1 eq), BrettPhos Pd G3 (96,0 mg, 106 µmol, 0,1 eq) y Cs_2CO_3 (1,04 g, 3,18 mmol, 3,0 eq). La mezcla se agitó. a 90 °C durante 12 h bajo N_2. La mezcla se vertió en agua helada (30 ml). La fase acuosa se extrajo con acetato de etilo (20 ml x 3). La capa orgánica combinada se lavó con salmuera (1x100 ml), se secó en sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 1 : El compuesto ter-butil 1-(1-benciloxicarbonil-4-piperidil)-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato (0,60 g, 762 µmol, 72 % de rendimiento) se obtuvo como un sólido marrón. LC-MS: MS (ESI^+): t_R = 0,650 min, m/z = 630,5 [M + H^+]. ^1H NMR (400 MHz, $CDCl_3$): δ = 7,59 - 7,71 (m, 2 H) 7,52 (s, 1 H) 7,31 - 7,41 (m, 5 H) 7,11 - 7,20 (m, 2 H) 5,75 (d, *J*=2,8 Hz, 1 H) 5,16 (s, 2 H) 4,24 - 4,47 (m, 4 H) 4,03 (m, 1 H) 3,94 (s, 3 H) 3,74 (s, 2 H) 2,96 (s, 2 H) 2,68 (t, *J*=5,6 Hz, 2 H) 2,17 (m, 2 H) 1,90 (d, *J*=11,6 Hz, 2 H) 1,67 (s, 3 H) 1,48 (s, 9 H)

[00479] A una solución de 1-(1-benciloxicarbonil-4-piperidil)-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato de ter-butilo (0,450 g, 715 µmol, 1,0 eq) en DCM (5 ml) se le agregó TFA (6,91 g, 60,6 mmol, 4,50 ml, 84,8 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró para obtener un residuo. El compuesto 4-[3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-4,5,6,7-tetrahidropirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de bencilo (0,46 g) se obtuvo como un sólido marrón y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,518 min, m/z = 530,4 [M + H^+]

[00480] A una solución de 4-[3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-4,5,6,7-tetrahidropirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de bencilo (0,46 g) en DCM (8 ml) se añadieron Et_3N (212 mg, 2,10 mmol, 292 µl, 3,0 eq) y Ac_2O (78,5 mg, 769 µmol, 72,2 µl, 1,1 eq) a 0 °C. La mezcla se agitó a 25 °C durante 12 h bajo N_2. La mezcla de reacción se vertió en agua fría (40 ml). La fase acuosa se extrajo con acetato de etilo (30 ml x 3). La fase orgánica combinada se lavó con salmuera (20 ml x 2), se secó con Na2SO4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía en columna de gel de sílice (éter de petróleo/acetato de etilo = 1/1 a 0/1, luego DCM/alcohol metílico = 10/1). El compuesto 4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de bencilo (0,37 g, 615 µmol, 88 % de rendimiento en dos pasos) se obtuvo como un

sólido marrón. LC-MS: MS (ESI^+): t_R = 0,578 min, m/z = 572,4 [M + H^+] ^1H NMR (400 MHz, DMSO-d_6): δ = 8,00 (s, 1 H) 7,73 - 7,86 (m, 2 H) 7,60 - 7,71 (m, 1 H) 7,29 - 7,41 (m, 6 H) 7,23 (t, *J*=10,4 Hz, 1 H) 5,10 (s, 2 H) 4,31 - 4,45 (m, 2 H) 4,17 - 4,27 (m, 1 H) 4,12 (d, *J*=12,4 Hz, 2 H) 3,83 (s, 3 H) 3,64 - 3,76 (m, 2 H) 2,92 - 3,10 (m, 2 H) 2,74 - 2,82 (m, 1 H) 2,66 (m, 1 H) 2,07 (d, *J*=13,2 Hz, 3 H) 1,81 - 1,92 (m, 4 H).

[00481] Pd/C (0,2 g, 10 % Pd sobre carbono, p/p) se agregó a un matraz de fondo redondo de un solo cuello de 30 ml bajo N_2, y luego se agregó EtOAc (10 ml) a 25 °C bajo N_2. Después de la adición, se agregó 4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de bencilo (0,370 g, 647 µmol, 1,0 eq) bajo N_2. La suspensión se desgasificó y se purgó con H_2 3 veces. La mezcla se agitó bajo H_2 (15 psi) a 25 °C durante 1,5 h. La mezcla de reacción se filtró y se lavó con etanol (20 ml × 2). La mezcla de reacción se concentró para proporcionar un residuo. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 8 %-38 % B durante 10 min). El compuesto 1-[3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (0,160 g, 366 µmol, 57 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,732 min, m/z = 438,3 [M + H^+]

[00482] A una solución de ácido 2-(4-tert-butoxicarbonilpiperazin-1-il)acético (67,0 mg, 274 µmol, 1,2 eq) en DMF (1,5 ml) se le agregó HATU (130 mg, 343 µmol, 1,5 eq) y se agitó a 25 °C durante 0,5 h. Se añadieron 1-[3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg, 229 µmol, 1,0 eq) y DIPEA (88,6 mg, 686 µmol, 119 µl, 3,0 eq) en DMF (0,5 ml) a la mezcla de reacción anterior y se agitó a 25 °C durante 11,5 h. La mezcla se diluyó con EtOAc (100 ml), se lavó con agua (15 ml × 2), salmuera (15 ml), se secó con sulfato de sodio anhidro, se filtró y se concentró al vacío. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 18 %-48 % B durante 10 min). El compuesto ter-butil 4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazina-1-carboxilato (80,0 mg, 121 µmol, 53 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,496 min, m/z = 664,5 [M + H^+]

[00483] A una solución de ter-butil 4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazina-1-carboxilato (80,0 mg, 121 µmol, 1,0 eq) en DCM (3 ml) se le agregó TFA (1,54 g, 13,5

mmol, 1 ml, 111,7 eq) y se agitó a 25 °C durante 1 h. La mezcla se concentró para obtener un residuo. El compuesto 1-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-piperazin-1-il-etanona (80 mg) se obtuvo como una goma marrón y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,741 min, m/z = 564,3 [M + H^+]

[00484] A una solución de 1-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-piperazin-1-il-etanona (80 mg) en NMP (3 ml) se le agregó DIPEA (76,3 mg, 590 µmol, 103 µl, 5,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (54,5 mg, 130 µmol, 1,1 eq). La mezcla se agitó a 20 °C durante 12 h. La mezcla de reacción se diluyó con agua (20 ml), se extrajo con EtOAc (20 ml x 15), se secó sobre sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto 2-[4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 66**, 74,3 mg, 78,2 µmol, 66 % de rendimiento en dos pasos) se obtuvo como un sólido blanco. ^{1}H (400 MHz, DMSO-d_6): δ = 8,72 (s, 2 H) 8,29 (s, 1 H) 7,94 (s, 1 H) 7,87 - 7,92 (m, 1 H) 7,68 - 7,78 (m, 3 H) 7,33 (m, 1 H) 7,16 - 7,28 (m, 2 H) 7,00 (m, 1 H) 4,48 (d, *J*=12,4 Hz, 1 H) 4,33 - 4,44 (m, 2 H) 4,24 - 4,33 (m, 2 H) 4,13 - 4,23 (m, 1 H) 4,03 (d, *J*=8,8 Hz, 1 H) 3,82 (s, 2 H) 3,87 (s, 2 H) 3,65 - 3,78 (m, 2 H) 3,42 (m, 7 H) 3,08 - 3,21 (m, 2 H) 2,67 - 2,82 (m, 3 H) 2,07 (br d, *J*=13,6 Hz, 3 H) 1,72 - 1,98 (m, 3 H) 1,21 (s, 6 H) 1,11 (s, 6 H). LC-MS: MS (ESI^+): t_R = 2,195 min, m/z = 946,7 [M + H^+]

[00485] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 10.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
1	2-[4-[2-[2-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]etoxi]etil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (d, J = 1,2 Hz, 2H), 8,33 (s, 1H), 7,72 - 7,39 (m, 4H), 7,20 - 7,10 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,4 Hz, 1H), 6,22 - 5,97 (m, 1H), 5,81 (dd, J = 3,2, 18,0 Hz, 1H), 4,46 (s, 1H), 4,31 (s, 1H), 4,18 - 4,02 (m, 4H), 3,93 (d, J = 1,6 Hz, 3H), 3,88 (quin, J = 4,8 Hz, 5H),	893,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		3,81 (q, J = 5,6 Hz, 2H), 3,71 (br t, J = 6,0 Hz, 1H), 3,59 (br t, J = 4,0 Hz, 2H), 2,84 - 2,71 (m, 2H), 2,59 (t, J = 5,2 Hz, 2H), 2,47 (td, J = 5,2, 10,4 Hz, 4H), 2,16 (d, J = 18,8 Hz, 3H), 1,32 - 1,17 (m, 12H).	
2	2-[4-[2-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]etoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,69 (d, J = 2,8 Hz, 2H), 7,68 (s, 1H), 7,64 - 7,36 (m, 3H), 7,22 - 7,11 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,24 - 5,91 (m, 1H), 5,77 (dd, J = 2,8, 17,2 Hz, 1H), 4,47 - 4,27 (m, 2H), 4,17 - 4,10 (m, 3H), 4,10 - 4,01 (m, 3H), 3,94 (d, J = 2,0 Hz, 3H), 3,90 - 3,81 (m, 3H), 3,69 (t, J = 5,6 Hz, 1H), 3,66 - 3,53 (m, 3H), 2,78 (td, J = 5,6, 18,0 Hz, 2H), 2,12 (d, J = 6,4 Hz, 3H), 1,82 (dt, J = 3,6, 6,4 Hz, 2H), 1,59 - 1,46 (m, 2H), 1,23 (d, J = 14,4 Hz, 12H).	432,9 $[M+H^+]$
3	2-[4-[2-[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,72 - 8,63 (m, 2H), 7,83 - 7,46 (m, 4H), 7,24 - 7,14 (m, 2H), 6,96 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,16 - 5,74 (m, 2H), 5,06 - 4,74 (m, 3H), 4,46 (s, 1H), 4,36 - 4,26 (m, 1H), 4,21 (br t, J = 8,0 Hz, 1H), 4,16 - 4,02 (m, 3H), 3,98 - 3,81 (m, 5H), 3,73 (br t, J = 5,6 Hz, 2H), 3,02 - 2,85 (m, 4H), 2,75 - 2,59 (m, 5H), 2,26 - 2,08 (m, 3H), 1,83 (br d, J = 12,8 Hz, 2H), 1,55 - 1,42 (m, 2H), 1,25 (s, 6H), 1,22 (s, 6H)	903,5
4	2-[4-[[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,4-7,8 (m, 4H), 7,1-7,2 (m, 2H), 6,97 (d, 1H, J=2,0 Hz), 6,81 (dd, 1H, J=2,1, 8,8 Hz), 5,8-6,1 (m, 2H), 5,0-5,2 (m, 1H), 4,8-5,0 (m, 2H), 4,6-4,7 (m, 1H), 4,4-4,6 (m, 2H), 4,28 (s, 1H), 4,1-4,2 (m, 2H), 4,0-4,1	889,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		(m, 2H), 3,8-4,0 (m, 4H), 3,74 (t, 1H, J=5,6 Hz), 3,13 (d, 1H, J=5,5 Hz), 2,97 (t, 3H, J=12,8 Hz), 2,6-2,8 (m, 2H), 2,1-2,3 (m, 4H), 1,8-2,0 (m, 4H), 1,24 (d, 12H, J=15,8 Hz)	
5	2-[4-[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d6) δ 8,30 (d, J = 8,8 Hz, 1H), 7,24 - 7,15 (m, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (d, J = 8,8 Hz, 2H), 5,97 - 7,47 (m, 3H), 5,92 - 5,81 (m, 4H), 5,10 - 4,74 (m, 4H), 4,46 (d, J = 10,2 Hz, 1H) 4,22 - 4,07 (m, 1H), 4,68 - 4,05 (m, 1H), 3,99 (t, J = 8,4 Hz, 1H), 4,28 - 3,95 (m, 1H), 3,93 (br s, 1H), 3,74 (br d, J =5,2 Hz, 1H), 3,21 - 3,07 (m, 2H), 3,05 - 2,85 (m, 1H), 2,79 - 2,67 (m, 1H), 2,20 - 2,13 (m, 1H), 2,02-1,91 (m, 1H), 1,58 (d, J = 6,6 Hz, 3H), 1,24 (d, J = 14,8 Hz, 2H).	875,5
6	2-[4-[2-[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]pirrolidin-1-il]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,69 (s, 2H), 7,68 (s, 1H), 7,63 - 7,35 (m, 2H), 7,38 (br t, J = 8,8 Hz, 1H), 7,23 - 7,08 (m, 2H), 6,96 (d, J = 2,4 Hz, 1H), 6,80 (dd, J = 2,4, 8,8 Hz, 1H), 5,99 (br dd, J = 5,2, 7,6 Hz, 1H), 5,89 - 5,77 (m, 1H), 4,83 (br d, J = 13,2 Hz, 3H), 4,46 (s, 1H), 4,28 (s, 1H), 4,13 (br d, J = 8,4 Hz, 1H), 4,04 (s, 1H), 3,97 - 3,88 (m, 4H), 3,75 - 3,47 (m, 2H), 3,49 (br t, J = 8,8 Hz, 1H), 3,38 - 3,17 (m, 2H), 3,06 - 3,02 (m, 1H), 2,96 - 2,86 (m, 4H), 2,83 - 2,70 (m, 3H), 2,51 - 2,38 (m, 1H), 2,36 - 2,25 (m, 1H), 2,22 - 2,09 (m, 3H), 1,80 (br d, J = 13,2 Hz, 2H), 1,66 - 1,57 (m, 2H), 1,25 (s, 6H), 1,21 (s, 7H)	917,5
7	2-[4-[[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-	δ = 8,70 (s, 2H), 7,70 (d, J = 2,0 Hz, 1H), 7,69 - 7,40 (m,	903,5

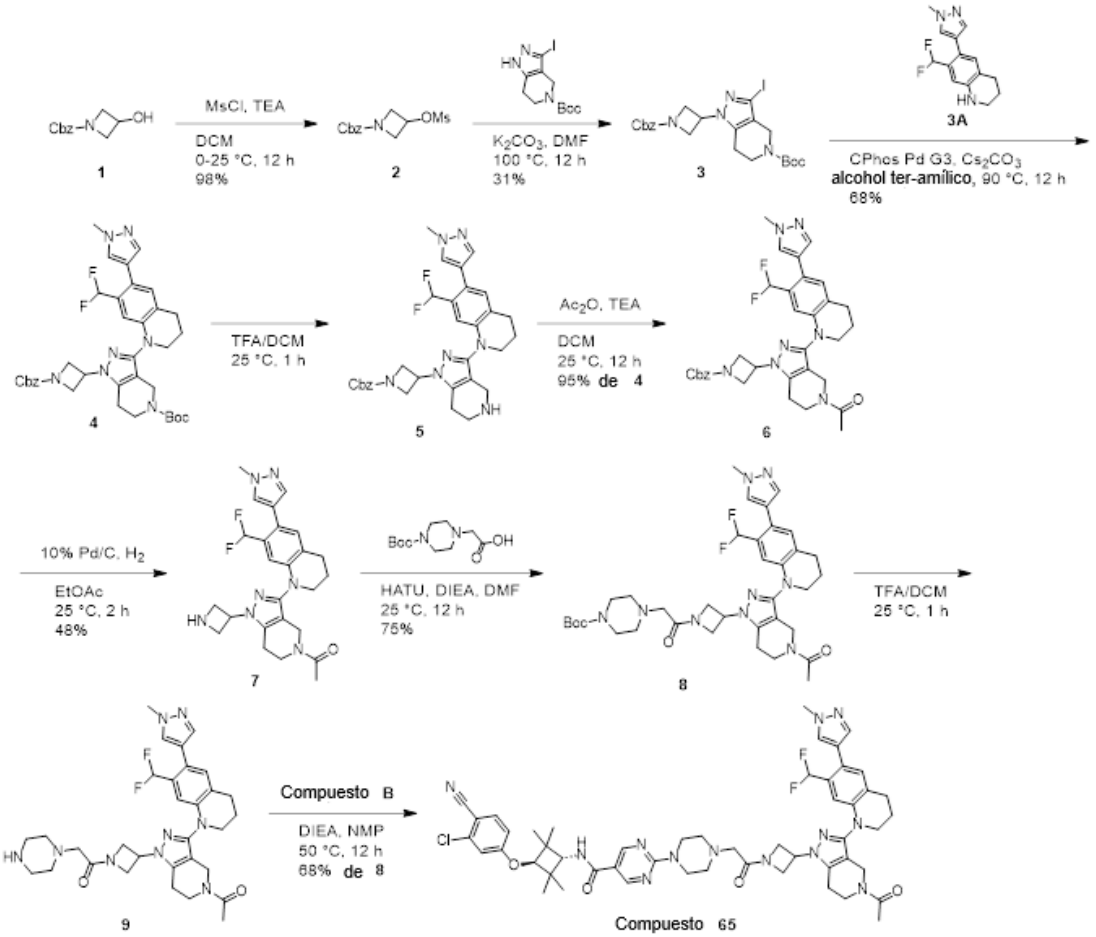
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]pirrolidin-1-il]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	3H), 7,22 - 7,09 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,00 (br d, J = 8,0 Hz, 1H), 5,83 (dd, J = 2,8, 13,6 Hz, 1H), 4,87 (br d, J = 12,0 Hz, 2H), 4,83 - 4,70 (m, 1H), 4,53 - 4,39 (m, 1H), 4,28 (s, 1H), 4,13 (d, J = 8,0 Hz, 1H), 4,05 (s, 1H), 3,94 (s, 3H), 3,93 - 3,83 (m, 1H), 3,75 (br t, J = 5,6 Hz, 1H), 3,48 - 3,26 (m, 1H), 3,20 - 3,01 (m, 1H), 3,01 - 2,88 (m, 4H), 2,81 - 2,71 (m, 2H), 2,63 - 2,51 (m, 4H), 2,44 - 2,25 (m, 2H), 2,22 - 2,10 (m, 3H), 2,01 - 1,81 (m, 3H), 1,24 (d, J = 15,6 Hz, 12H).	
8	2-[4-[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]pirrolidin-1-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 8,35 (s, 1H), 7,69 (s, 1H), 7,68 - 7,38 (m, 3H), 7,21 - 7,11 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 5,99 (dd, J = 5,2, 8,0 Hz, 1H), 5,82 (dd, J = 2,8, 16,8 Hz, 1H), 4,96 - 4,74 (m, 3H), 4,50 - 4,24 (m, 2H), 4,13 (d, J = 8,0 Hz, 1H), 4,05 (s, 1H), 3,94 (s, 3H), 3,93 - 3,84 (m, 1H), 3,75 (br t, J = 6,0 Hz, 1H), 3,73 - 3,51 (m, 1H), 3,39 - 3,18 (m, 1H), 3,16 - 2,99 (m, 4H), 2,96 - 2,70 (m, 3H), 2,44 - 2,30 (m, 2H), 2,20 (br s, 3H), 2,09 - 2,00 (m, 2H), 1,76 - 1,60 (m, 2H), 1,24 (d, J = 15,6 Hz, 12H).	889,5
164	2-[4-[2-[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]etil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,71 (s, 2H), 7,78 - 7,46 (m, 4H), 7,23 - 7,15 (m, 2H), 6,96 (d, J = 2,4 Hz, 1H), 6,80 (dd, J = 2,4, 8,8 Hz, 1H), 5,97 (dd, J = 3,2, 8,4 Hz, 1H), 5,87 (dd, J = 2,0, 17,6 Hz, 1H), 4,96 - 4,79 (m, 1H), 4,45 (s, 1H), 4,27 (s, 1H), 4,13 (br d, J = 8,0 Hz, 2H), 4,05 - 3,82 (m, 10H), 3,74 (br t, J = 5,2 Hz, 2H),	452,9 ± 2

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2,99 (br t, J = 5,2 Hz, 1H), 2,91 (br t, J = 6,0 Hz, 1H), 2,73 (br t, J = 5,2 Hz, 1H), 2,67 (br t, J = 5,6 Hz, 1H), 2,63 - 2,50 (m, 6H), 2,19 - 2,12 (m, 3H), 1,24 (d, J = 14,4 Hz, 12H)	
166	2-[4-[2-[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-oxo-etil]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	δ = 8,67 (s, 2H), 7,96 - 7,64 (m, 2H), 7,61 - 7,53 (m, 2H), 7,24 - 7,14 (m, 2H), 6,96 (d, J = 2,4 Hz, 1H), 6,80 (dd, J = 2,4, 8,8 Hz, 1H), 6,06 - 5,96 (m, 1H), 5,95 - 5,83 (m, 1H), 4,96 - 4,80 (m, 3H), 4,68 (ddd, J = 5,2, 8,4, 14,0 Hz, 1H), 4,58 - 4,36 (m, 4H), 4,31 (s, 1H), 4,13 (d, J = 8,4 Hz, 1H), 4,05 (s, 1H), 3,93 (d, J = 2,4 Hz, 4H), 3,82 - 3,67 (m, 1H), 2,97 (br t, J = 12,4 Hz, 2H), 2,78 - 2,62 (m, 2H), 2,30 - 2,06 (m, 5H), 2,02 - 1,75 (m, 3H), 1,23 (d, J = 16,0 Hz, 14H)	459,4 ± 2
167	2-[4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,78 (s, 2H), 8,01 (s, 1H), 7,92 - 7,69 (m, 5H), 7,36 (ddd, J = 2,0, 8,7, 13,2 Hz, 1H), 7,26 - 7,16 (m, 2H), 7,01 (dd, J = 2,4, 8,8 Hz, 1H), 4,42 (s, 1H), 4,35 (s, 1H), 4,29 (s, 1H), 4,04 (d, J = 9,2 Hz, 1H), 3,86 (br s, 4H), 3,83 (s, 3H), 3,77 - 3,63 (m, 3H), 3,43 - 3,30 (m, 5H), 2,85 - 2,72 (m, 2H), 2,66 (br s, 3H), 2,55 (br s, 4H), 2,28 - 2,12 (m, 2H), 2,07 (d, J = 13,2 Hz, 3H), 2,02 - 1,83 (m, 2H), 1,21 (s, 6H), 1,11 (s, 6H)	932,5
168	2-[4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ=8,70 (s, 2 H) 7,69 (d, *J*=2,40 Hz, 1 H) 7,58 (d, *J*=8,80 Hz, 1 H) 7,55 (d, *J*=3,60 Hz, 1 H) 7,11 - 7,24 (m, 2 H) 6,97 (d, *J*=2,40 Hz, 1 H) 6,81 (dd, *J*=8,80, 2,40 Hz, 1 H) 5,97 (br dd, *J*=7,20, 4,80 Hz, 1 H) 5,70 - 5,83 (m, 1 H) 4,87 (br s, 1 H) 4,84 (br s, 1 H) 4,48 (s, 1 H) 4,30 (s,	931,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2 H) 4,13 (d, *J*=8,00 Hz, 1 H) 4,05 (s, 1 H) 3,95 (s, 3 H) 3,88 - 3,94 (m, 1 H) 3,73 - 3,80 (m, 1 H) 3,57 - 3,73 (m, 2 H) 3,19 - 3,43 (m, 1 H) 3,03 - 3,15 (m, 2 H) 2,92 (br t, *J*=12,40 Hz, 2 H) 2,73 - 2,80 (m, 1 H) 2,69 (br t, *J*=5,20 Hz, 1 H) 2,27 - 2,56 (m, 3 H) 2,21 (s, 2 H) 2,15 (s, 2 H) 1,82 (br s, 3 H) 1,78 (br d, *J*=6,80 Hz, 4 H) 1,26 (s, 6 H)	
177	2-[4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etoxi]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	δ = 8,74 - 8,63 (m, 2H), 7,82 - 7,49 (m, 4H), 7,22 - 7,09 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,11 - 5,98 (m, 1H), 5,79 (dd, J = 3,2, 19,2 Hz, 1H), 4,71 (br d, J = 13,6 Hz, 1H), 4,59 - 4,40 (m, 1H), 4,37 - 4,26 (m, 5H), 4,22 - 4,04 (m, 4H), 3,96 - 3,87 (m, 4H), 3,76 (br d, J = 3,2 Hz, 2H), 3,67 - 3,55 (m, 2H), 3,21 (br t, J = 12,4 Hz, 1H), 2,90 - 2,68 (m, 3H), 2,31 - 2,09 (m, 5H), 1,99 (br s, 4H), 1,75 - 1,69 (m, 2H), 1,26 (s, 6H), 1,22 (s, 6H)	961,7
178	2-[4-[2-[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ=8,69 (s, 2 H) 7,70 (s, 1 H) 7,57 (d, *J*=8,80 Hz, 1 H) 7,53 (d, *J*=4,00 Hz, 1 H) 7,46 (t, *J*=8,80 Hz, 1 H) 7,12 - 7,21 (m, 2 H) 6,97 (d, *J*=2,40 Hz, 1 H) 6,81 (dd, *J*=8,80, 2,40 Hz, 1 H) 5,96 (br d, *J*=8,40 Hz, 1 H) 5,79 (dd, *J*=16,80, 3,20 Hz, 1 H) 4,88 (br d, *J*=12,80 Hz, 2 H) 4,80 (br d, *J*=14,00 Hz, 1 H) 4,40 - 4,55 (m, 1 H) 4,30 (s, 1 H) 4,13 (d, *J*=8,00 Hz, 1 H) 4,05 (s, 1 H) 3,93 (d, *J*=2,80 Hz, 4 H) 3,76 (br d, *J*=5,60 Hz, 1 H) 3,20 (br t, *J*=12,00 Hz, 1 H) 3,00 (br t, *J*=12,40 Hz, 2 H) 2,67 - 2,85 (m, 3 H) 2,30 - 2,38 (m, 2 H) 2,21 (s, 2 H) 2,15 (s, 2 H) 1,90 - 1,99	945,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		(m, 4 H) 1,76 (br d, *J*=1,60 Hz, 6 H) 1,25 (s, 6 H) 1,22 (s, 6 H).	
186	2-[4-[[4-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,4-7,7 (m, 4H), 7,1-7,2 (m, 2H), 6,97 (d, 1H, J=2,4 Hz), 6,81 (dd, 1H, J=2,4, 8,8 Hz), 5,9-6,0 (m, 1H), 5,7-5,8 (m, 1H), 4,87 (d, 2H, J=12,4 Hz), 4,47 (s, 1H), 4,30 (s, 1H), 4,13 (d, 1H, J=8,1 Hz), 4,05 (s, 1H), 3,9-4,0 (m, 5H), 3,75 (t, 1H, J=5,6 Hz), 3,0-3,3 (m, 2H), 2,96 (t, 2H, J=12,4 Hz), 2,7-2,8 (m, 2H), 2,3-2,4 (m, 4H), 2,2-2,2 (m, 2H), 2,14 (s, 2H), 1,94 (d, 5H, J=9,6 Hz), 1,7-1,8 (m, 3H), 1,24 (d, 12H, J=14,8 Hz)	917,5

[00486] Ejemplo 11: Síntesis de 2-[4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 65**)



[00487] Las moléculas de TCB se prepararon de acuerdo con los métodos descritos en WO 2022/42707 A1.

[00488] A una solución de 3-hidroxiazetidina-1-carboxilato de bencilo (5,0 g, 24,13 mmol, 1,0 eq) y Et_3N (3,66 g, 36,19 mmol, 5,04 ml, 1,5 eq) en DCM (80 ml) se le agregó MsCl (3,8 g, 33,17 mmol, 2,57 ml, 1,37 eq) a 0 °C. La mezcla se agitó a 25 °C durante 12 h. La mezcla se vertió en agua helada (100 ml). La capa acuosa se extrajo con DCM (100 ml x 2). La fase orgánica combinada se lavó con salmuera (80 ml x 2), se secó con Na2SO4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : Se obtuvo el compuesto 3 (6,8 g, 23,83 mmol, 98 % de rendimiento) como un aceite amarillo. LC-MS: MS (ES^+): t_R = 0,484 min, m/z = 308,0 [M + Na^+]

[00489] A una solución de 3-metilsulfoniloxiazetidina-1-carboxilato de bencilo (6,8 g, 23,83 mmol, 2,1 eq) en DMF (60 ml) se añadieron K_2CO_3 (4,75 g, 34,37 mmol, 3,0 eq) y 3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridina-5-carboxilato de ter-butilo (4,0 g, 11,46 mmol, 1,0 eq). La mezcla se agitó a 100 °C durante 12 h y luego se vertió en agua (300

ml). La fase acuosa se extrajo con acetato de etilo (300 ml x 2). La capa orgánica combinada se lavó con salmuera (250 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (5–50 % de acetato de etilo en éter de petróleo) y se purificó aún más mediante HPLC preparativa (columna: Kromasil Eternity XT 250*80 mm*10 μm; fase móvil: [agua (NH4HCO3)-ACN]; gradiente: 50 %-80 % B durante 30 min). El compuesto ter-butil 1-(1-benciloxicarbonilazetidin-3-il)-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato (1,93 g, 3,58 mmol, 31 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,627 min, m/z = 539,1 [M + H^+]. ^1H NMR (400 MHz, $CDCl_3$): δ 7,42 - 7,31 (m, 5H), 5,14 (s, 2H), 5,00 (t, J = 7,2 Hz, 2H), 4,42 - 4,35 (m, 2H), 4,23 - 3,71 (m, 2H), 1,51 (s, 9H).

[00490] Una mezcla de 1-(1-benciloxicarbonilazetidin-3-il)-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato de ter-butilo (700 mg, 1,30 mmol, 1,0 eq), 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (479 mg, 1,82 mmol, 1,4 eq), CPHOS PD G3 (105 mg, 130 μmol, 0,1 eq) y Cs_2CO_3 (1,27 g, 3,90 mmol, 3,0 eq) en 2-metilbutan-2-ol (10 ml) se desgasificó y se purgó con N_2 tres veces, y Luego, la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N2. El filtrado se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto ter-butil 1-(1-benciloxicarbonilazetidin-3-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato (600 mg, 890 μmol, 68 % de rendimiento) se obtuvo como un sólido amarillo claro. LC-MS: MS (ESI^+): t_R = 0,611 min, m/z = 674,3 [M + H^+]

[00491] A una solución de 1-(1-benciloxicarbonilazetidin-3-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato de ter-butilo (690 mg, 1,02 mmol, 1,0 eq) en DCM (10 ml) se le agregó TFA (7,67 g, 67,31 mmol, 5,00 ml, 65,7 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró al vacío. El compuesto benzyl 3-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-4,5,6,7-tetrahidropirazolo[4,3-c]piridin-1-il]azetidina-1-carboxilato (585 mg) se obtuvo como una goma amarilla y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,462 min, m/z = 574,3 [M + H^+]

[00492] A una solución de 3-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-4,5,6,7-tetrahidropirazolo[4,3-c]piridin-1-il]azetidina-1-carboxilato de bencilo (585 mg, 1,02 mmol, 1,0 eq) en DCM (15 ml) se añadieron TEA (309 mg, 3,05 mmol, 425 μl, 3,0 eq) y Ac_2O (155 mg, 1,53 mmol, 143 μl, 1,5 eq). La mezcla se agitó a

25 °C durante 12 h. La mezcla se concentró al vacío. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto benzyl 3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidina-1-carboxilato (597 mg, 969 µmol, 95 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo claro. LC-MS: MS (ESI$^+$): t_R = 0,528 min, m/z = 616,3 [M + H$^+$]

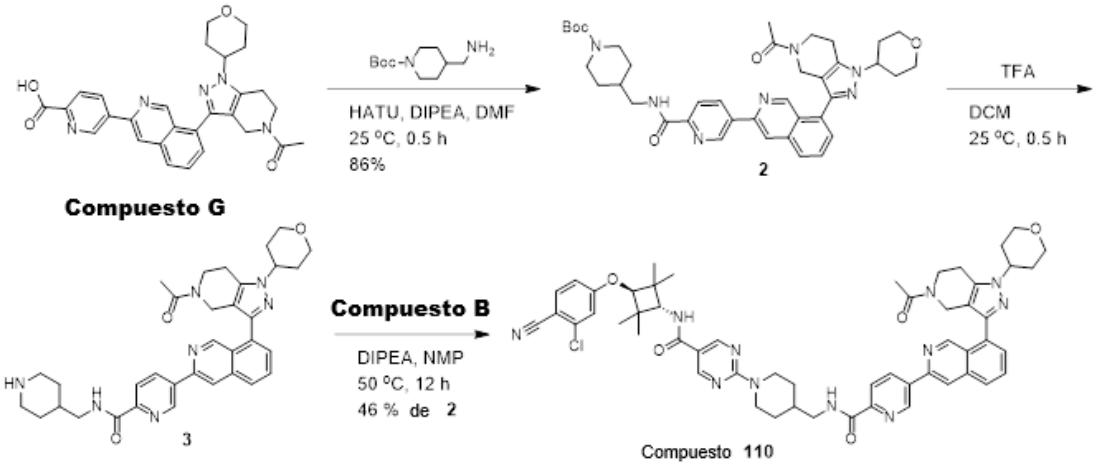
[00493] A una solución de 3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidina-1-carboxilato de bencilo (300 mg, 487 µmol, 1,0 eq) en EtOAc (10 ml) se agregó Pd/C (100 mg, 10 % Pd sobre carbono, p/p) bajo atmósfera de N_2. La suspensión se desgasificó y se purgó con H2 3 veces. La mezcla se agitó bajo H_2 (15 psi) a 25 °C durante 2 h. La mezcla se filtró y se concentró a presión reducida. El residuo se purificó mediante HPLC preparativa (columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua (FA)-ACN]; gradiente: 5 %-35 % B durante 10 min). El compuesto 1-[1-(azetidin-3-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (130 mg, 234 µmol, 48 % de rendimiento, FA) se obtuvo como un sólido amarillo claro. LC-MS: MS (ESI$^+$): t_R = 0,403 min, m/z = 482,2 [M + H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8,53 (s, 1H), 7,55 (d, J = 6,0 Hz, 1H), 7,42 (d, J = 6,4 Hz, 1H), 7,12 - 7,02 (m, 1H), 6,90 (d, J = 8,4 Hz, 1H), 6,71 - 6,38 (m, 1H), 5,31 - 5,12 (m, 1H), 4,59 (t, J = 8,0 Hz, 2H), 4,39 - 4,34 (m, 2H), 4,20 (s, 1H), 4,07 (s, 1H), 3,96 (d, J = 2,4 Hz, 3H), 3,88 (t, J = 5,6 Hz, 1H), 3,81 - 3,69 (m, 3H), 2,88 (td, J = 6,0, 12,4 Hz, 2H), 2,80 - 2,63 (m, 2H), 2,17 - 2,00 (m, 5H).

[00494] A una solución de 1-[1-(azetidin-3-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (130 mg, 246 µmol, 1,0 eq, FA) y ácido 2-(4-tert-butoxicarbonilpiperazin-1-il)acético (66 mg, 271 µmol, 1,1 eq) en DMF (3 ml) se le agregó HATU (140 mg, 369 µmol, 1,5 eq) y DIEA (95 mg, 739 µmol, 128 µl, 3,0 eq). La mezcla se agitó a 25 °C durante 12 h y luego se vertió en agua (40 ml). La fase acuosa se extrajo con acetato de etilo (40 ml x 2). La capa orgánica combinada se lavó con salmuera (40 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía preparativa en capa fina (sílice, diclorometano:metanol = 10:1). El compuesto ter-butil 4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-oxo-etil]piperazina-1-carboxilato (130 mg, 183 µmol, 75 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI$^+$): t_R = 0,446 min, m/z = 708,4 [M + H$^+$]

[00495] A una solución de ter-butil 4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-oxo-etil]piperazina-1-carboxilato (130 mg, 183 µmol, 1,0 eq) en DCM (6 ml) se le agregó TFA (3,07 g, 26,92 mmol, 2,0 ml, 146,6 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró al vacío. El compuesto 1-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-piperazin-1-il-etanona (110 mg) se obtuvo como una goma amarilla y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,405 min, m/z = 608,4 [$M + H^+$]

[00496] A una solución de 1-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-piperazin-1-il-etanona (110 mg) en NMP (2 ml) se le agregó DIEA (93 mg, 720 µmol, 125 µl, 4,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (76 mg, 180 µmol, 1,0 eq). La mezcla se agitó a 50 °C durante 12 h. La mezcla se concentró al vacío. El residuo se purificó mediante HPLC preparativa (columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua (FA)-ACN]; gradiente: 25 %-55 % B durante 15 min). El compuesto 2-[4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 65**, 123 mg, 122 µmol, 68 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino. ^1H (400 MHz, $CDCl_3$): δ = 8,71 (s, 2H), 7,59 (d, J = 8,8 Hz, 1H), 7,57 - 7,50 (m, 1H), 7,46 - 7,38 (m, 1H), 7,11 - 7,03 (m, 1H), 6,98 (d, J = 2,4 Hz, 1H), 6,92 (d, J = 6,0 Hz, 1H), 6,82 (dd, J = 2,4, 8,8 Hz, 1H), 6,71 - 6,38 (m, 1H), 5,98 (d, J = 8,0 Hz, 1H), 5,04 - 4,93 (m, 1H), 4,89 - 4,79 (m, 1H), 4,75 - 4,65 (m, 1H), 4,58 - 4,44 (m, 2H), 4,35 - 4,18 (m, 1H), 4,18 - 4,10 (m, 2H), 4,08 - 4,06 (m, 1H), 4,06 - 3,89 (m, 8H), 3,89 - 3,72 (m, 3H), 3,17 (d, J = 1,2 Hz, 2H), 2,95 - 2,86 (m, 2H), 2,82 - 2,70 (m, 2H), 2,62 (t, J = 4,8 Hz, 4H), 2,20 - 2,03 (m, 5H), 1,25 (d, J = 13,6 Hz, 12H). LC-MS: MS (ESI^+): t_R = 2,276 min, m/z = 990,5 [$M + H^+$]

[00497] **Ejemplo 12**: Síntesis de 2-[4-[[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 110**)



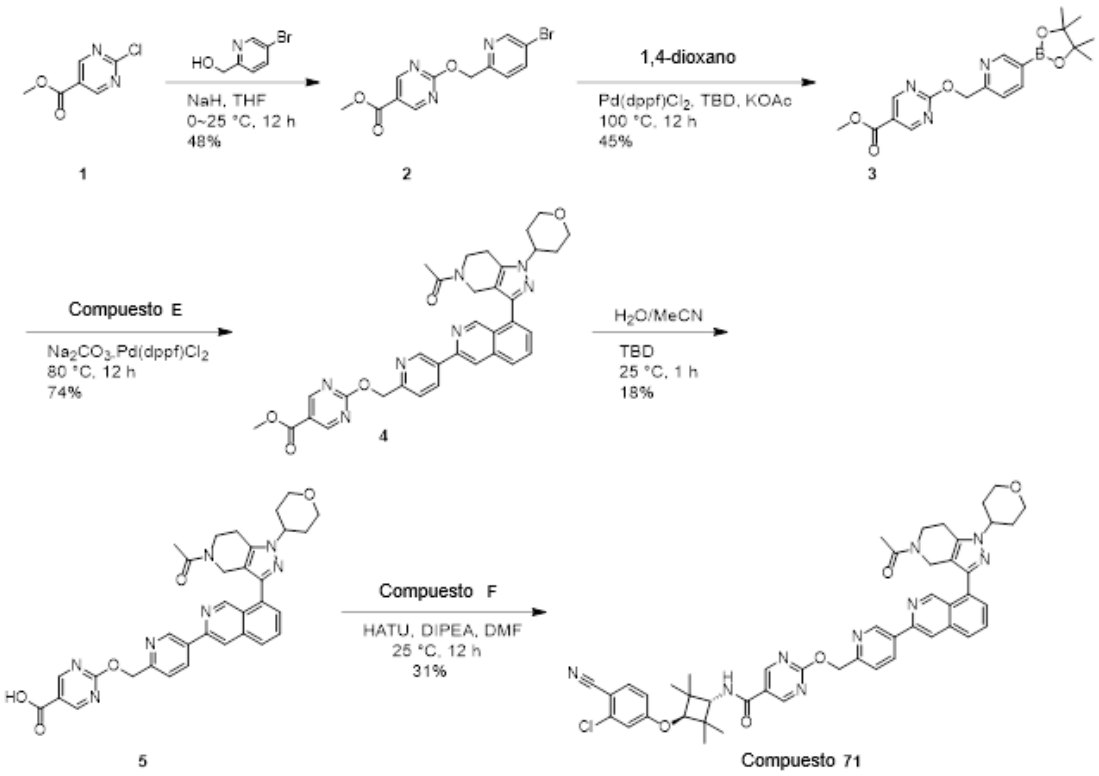
[00498] A una solución de ácido 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carboxílico (16,7 mg, 33,7 µmol, 1,0 eq) 4-(aminometil)piperidina-1-carboxilato de ter-butilo (7,2 mg, 33,7 µmol, 1,0 eq) y DIPEA (13 mg, 101,12 µmol, 17 µl, 3,0 eq) en DMF (1 ml) se le agregó HATU (25 mg, 67,42 µmol, 2,0 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El residuo se purificó mediante TLC preparativa (acetato de etilo: El compuesto ter-butil 4-[[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]metil]piperidina-1-carboxilato (20 mg, 28,8 µmol, 86 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,535 min, m/z = 694,3 [$M + H^+$]

[00499] A una solución de ter-butil 4-[[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]metil]piperidina-1-carboxilato (20 mg, 28,83 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (767 mg, 6,73 mmol, 0,5 ml, 233,5 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-N-(4-piperidilmetil)piridina-2-carboxamida (17 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,352 min, m/z = 233,0 [$M + H^+$]

[00500] A una solución de 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-N-(4-piperidilmetil)piridina-2-carboxamida (17 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (10 mg, 24,02 µmol, 1,0 eq) en NMP (1 ml) se le agregó DIPEA (9 mg, 72,06 µmol, 12 µl, 3,0 eq). A continuación, la mezcla de reacción se agitó a 50 °C durante 12 h y se concentró a presión reducida. El residuo se purificó mediante HPLC preparativa (sílice, columna: YMC-Actus Triart C18 150*30mm*7um; fase móvil:

[agua(FA)-ACN]; gradiente: 65 %-95 % B durante 10 min). El compuesto 2-[4-[[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 110**, 10 mg, 10,9 µmol, 46 % de rendimiento en dos pasos) se obtuvo como un sólido blanco. ^{1}H (400 MHz, $CDCl_3$): δ 9,88 (d, *J*=2,8 Hz, 1 H) 9,27 - 9,34 (m, 1 H) 8,70 (s, 2 H) 8,57 - 8,64 (m, 1 H) 8,33 (dd, *J*=8,4, 3,6 Hz, 1 H) 8,28 (br t, *J*=5,2 Hz, 1 H) 8,19 (d, *J*=10,4 Hz, 1 H) 7,93 (dd, *J*=13,6, 8,4 Hz, 1 H) 7,80 (dt, *J*=12,0, 7,6 Hz, 1 H) 7,63 (dd, *J*=17,2, 6,4 Hz, 1 H) 7,58 (d, *J*=8,8 Hz, 1 H) 6,97 (d, *J*=2,4 Hz, 1 H) 6,81 (dd, *J*=8,8, 2,4 Hz, 1 H) 5,92 (d, *J*=8,0 Hz, 1 H) 4,88 - 4,97 (m, 2 H) 4,68 (s, 1 H) 4,52 (s, 1 H) 4,24 - 4,36 (m, 1 H) 4,16 - 4,23 (m, 2 H) 4,13 (d, *J*=8,0 Hz, 1 H) 4,01 - 4,06 (m, 2 H) 3,87 (t, *J*=5,6 Hz, 1 H) 3,53 - 3,66 (m, 2 H) 3,47 (t, *J*=6,4 Hz, 2 H) 2,92 - 3,06 (m, 3 H) 2,88 (br t, *J*=5,6 Hz, 1 H) 2,39 - 2,55 (m, 2 H) 2,23 (s, 1 H) 2,09 (s, 2 H) 1,93 - 2,01 (m, 4 H) 1,30 - 1,40 (m, 3 H) 1,25 (s, 6 H) 1,22 (s, 6 H). LC-MS: MS (ESI$^+$): t_R = 2,540 min, m/z = 976,5 [M + H$^+$]

[00501] **Ejemplo 13**: Síntesis de 2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metoxi]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 71**)



[00502] A una solución de (5-bromo-2-piridil)metanol (3,27 g, 17 mmol, 1 eq) en THF

(30 ml) se le agregó NaH (834,37 mg, 60 % p/p, 20 mmol, 1,2 eq) a 0 °C y se agitó durante 1 h. Luego, a la mezcla se le agregó 2-cloropirimidina-5-carboxilato de metilo (3 g, 17 mmol, 1 eq) en THF (10 ml) a 0 °C y se agitó a 25 °C durante 12 h. La mezcla se neutralizó con NH_4Cl saturado (20 ml). La mezcla se extrajo con acetato de etilo (20 ml x 3). La fase orgánica combinada se lavó con salmuera (20 ml x 3), se secó en Na_2SO_4 anhidro, se filtró y se concentró a presión reducida. El residuo se purificó mediante cromatografía en columna (sílice, 10-25 % de acetato de etilo en éter de petróleo). El compuesto metil 2-[(5-bromo-2-piridil)metoxi]pirimidina-5-carboxilato (3,0 g, 8 mmol, 48 % de rendimiento, 90 % de pureza) se obtuvo como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,495 min, m/z = 325,9 [M + H^+]. ^1H NMR (400 MHz, DMSO-d_6): δ = 9,23 - 8,99 (m, 2H), 8,69 (s, 1H), 8,09 (dd ancho, J = 1,7, 8,2 Hz, 1H), 7,47 (d ancho, J = 8,4 Hz, 1H), 5,54 (s, 2H), 3,87 (s, 3H)

[00503] A una solución de 2-[(5-bromo-2-piridil)metoxi]pirimidina-5-carboxilato de metilo (1,80 g, 5 mmol, 1 eq) y 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (1,41 g, 5 mmol, 1 eq) en 1,4-dioxano (50 ml) se agregó KOAc (1,64 g, 16 mmol, 3 eq) y $Pd(dppf)Cl_2$ (81,27 mg, 111 µmol, 0,02 eq). La mezcla se agitó a 100 °C durante 12 h. A la mezcla se le adicionó agua (30 ml) y se trató con NaHCO3 acuoso (50 ml). La capa orgánica combinada se lavó con salmuera (20 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna (sílice, 90 % de acetato de etilo en éter de petróleo a 10 % de metanol en diclorometano). El producto metil 2-[[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil]metoxi]pirimidina-5-carboxilato (1 g, 2,51 mmol, 45,12 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,391 min, m/z = 372,1 [M + H^+]. ^1H NMR (400MHz, CLOROFORMO-d) δ = 9,13 - 9,08 (m, 1H), 8,09 (d, J=7,8 Hz, 1H), 7,50 - 7,27 (m, 1H), 5,73 - 5,66 (m, 2H), 3,96 (s, 3H), 1,36 (s, 3H)

[00504] A una solución de [8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil] trifluorometanosulfonato (100 mg, 190 µmol, 1 eq) y 2-[[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil]metoxi]pirimidina-5-carboxilato de metilo (84,92 mg, 228 µmol, 1,2 eq) en 1,4-dioxano (5 ml) y H_2O (0,5 ml) se agregó Na_2CO_3 (60,62 mg, 571 µmol, 3 eq) y $Pd(dppf)Cl_2$ (7,78 mg, 9 µmol, 0,05 eq). La mezcla se agitó a 80 °C durante 12 h en N_2. A la mezcla se agregó agua (20 ml) y se extrajo con acetato de etilo (20 ml x 3). La capa orgánica combinada se lavó con salmuera (20 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía rápida en gel de sílice (10 % de metanol en diclorometano). El producto metil 2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-

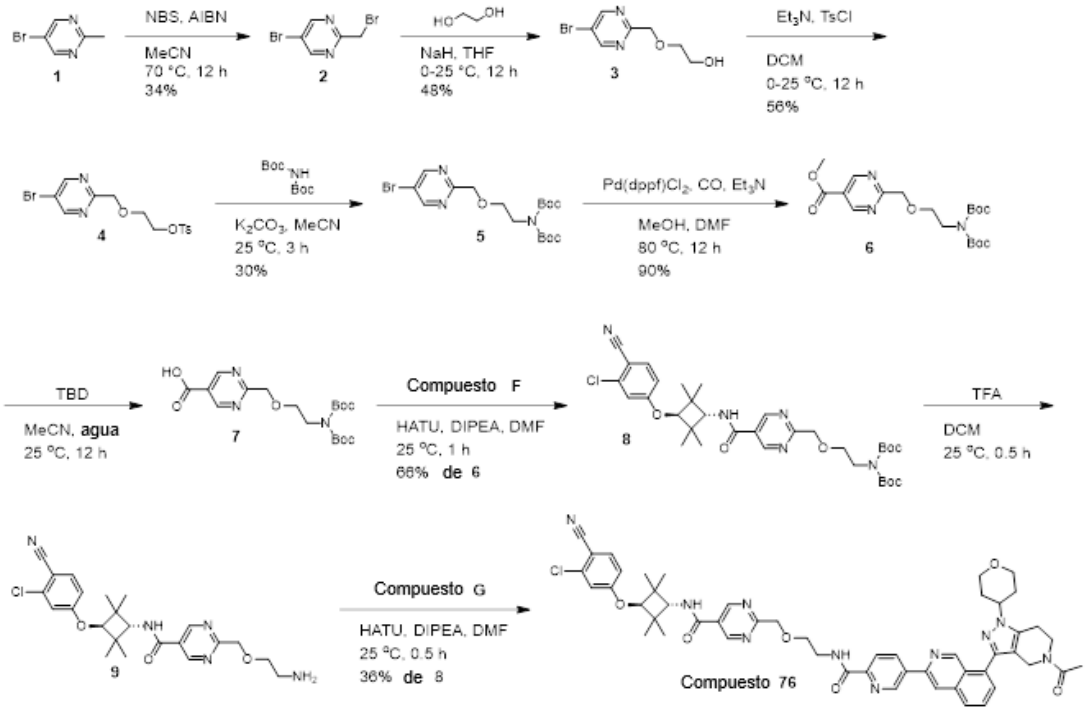
pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metoxi]pirimidina-5-carboxilato (120 mg, 141,37 µmol, 74,15 % de rendimiento, 73 % de pureza) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,498 min, m/z = 620,3 [M + H^+]

[00505] A una solución de 2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metoxi]pirimidina-5-carboxilato de metilo (120 mg, 141 µmol, 1 eq) en MeCN (12 ml) y H_2O (4 ml) se agregó 3,4,6,7,8,9-hexahidro-2H-pirimido[1,2-a]pirimidina (59,03 mg, 424 µmol, 3 eq). La mezcla se agitó a 25 °C durante 1 h. Se agregó H_2O (20 ml) y se extrajo con acetato de etilo (20 ml × 3). Las fases orgánicas combinadas se lavaron con salmuera (20 ml), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 20 %-50 % B durante 1 min). El producto ácido 2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metoxi]pirimidina-5-carboxílico (15 mg, 24 µmol, 17,52 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,462 min, m/z = 606,3 [M + H^+]

[00506] A una solución de ácido 2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metoxi]pirimidina-5-carboxílico (30 mg, 49 µmol, 1 eq) y 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (13,81 mg, 49 µmol, 1 eq) en DMF (2 ml) se le agregó DIPEA (32,01 mg, 247 µmol, 43,14 µl, 5 eq) y HATU (94,17 mg, 247 µmol, 5 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se concentró al vacío para obtener el producto crudo. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua(FA)-ACN]; gradiente: 50 %-80 % B durante 15 min). El producto 2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metoxi]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 71**, 13,62 mg, 15 µmol, 31,13 % de rendimiento) se obtuvo como un sólido amarillo. ^1H NMR (400 MHz, DMSO-d_6) δ = 9,97 (dd, J = 1,2, 5,3 Hz, 1H), 8,67 - 8,57 (m, 2H), 8,14 - 8,02 (m, 2H), 7,94 - 7,84 (m, 1H), 7,74 - 7,59 (m, 1H), 7,22 (t, J = 2,4 Hz, 1H), 7,01 (dd, J = 2,5, 8,8 Hz, 1H), 5,65 - 4,57 (m, 1H), 4,48 - 4,29 (m, 3H), 4,10 - 3,96 (m, 2H), 3,90 - 3,77 (m, 2H), 3,53 (s, 3H), 3,00 - 2,82 (m, 2H), 2,11 - 2,02 (m, 1H), 2,00 - 1,92 (m, 1H), 1,23 - 1,12 (m, 3H). LC-MS: MS (ESI^+): t_R = 2,232 min, m/z = 866,6 [M + H^+]

[00507] Ejemplo 14: Síntesis de 2-[2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]etoximetil]-N-[3-(3-

cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 76**)



[00508] A una solución de 5-bromo-2-metilpirimidina (10 g, 57,80 mmol, 1 eq) y NBS (30,86 g, 173,40 mmol, 3 eq) en MeCN (100 ml) se le agregó AIBN (3,32 g, 20,23 mmol, 0,35 eq). La mezcla se agitó a 80 °C durante 12 horas, luego se concentró a presión reducida. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 10/1). Se obtuvo el compuesto 5 (5,0 g, 19,85 mmol, 34 % de rendimiento) como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,443 min, m/z = 252,7 [M + H^+]

[00509] A una solución de 5-bromo-2-(bromometil)pirimidina (1 g, 3,97 mmol, 1,0 eq) y NaH (220 mg, 60 % p/p, 5,9 mmol, 1,5 eq) en THF (10 ml) se le agregó etilenglicol (493 mg, 7,94 mmol, 442,75 µl, 2,0 eq) a 0 °C. La mezcla se agitó a 0-25 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se neutralizó con NH_4Cl acuoso saturado (100 ml) a 0 °C gota a gota. La mezcla se extrajo con acetato de etilo (100 ml x 3). Los orgánicos combinados se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 10/1). El compuesto 2-[(5-bromopirimidin-2-il)metoxi]etanol (0,45 g, 1,93 mmol, 48 % de rendimiento) se obtuvo como un aceite incoloro. LC-MS: MS (ESI^+): t_R = 0,352 min, m/z = 233,0 [M + H^+]

[00510] A una solución de 2-[(5-bromopirimidin-2-il)metoxi]etanol (0,45 g, 1,93 mmol,

1 eq) y Et_3N (586,13 mg, 5,79 mmol, 806,23 µl, 3 eq) en DCM (5 ml) se agregó TosCl (375,47 mg, 1,97 mmol, 1,02 eq) a 0 °C. La mezcla se agitó a 0-25 °C durante 12 h. La mezcla se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 10/1). El compuesto 2-[(5-bromopirimidin-2-il)metoxi]etil 4-metilbencenosulfonato (0,42 g, 1,08 mmol, 56 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,527 min, m/z = 409,0 [M + Na^+]

[00511] A una solución de 2-[(5-bromopirimidin-2-il)metoxi]etil 4-metilbencenosulfonato (0,42 g, 1,08 mmol, 1,0 eq) y Cs_2CO_3 (530,06 mg, 1,63 mmol, 1,5 eq) en DMF (5 ml) se agregó N-terc-butoxicarbonilcarbamato de ter-butilo (235,64 mg, 1,08 mmol, 1,0 eq). La mezcla se agitó a 25 °C durante 30 min. La reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (100 ml x 2). La capa orgánica combinada se lavó con salmuera (100 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 10/1). Se obtuvo el compuesto ter-butil N-[2-[(5-bromopirimidin-2-il)metoxi]etil]-N-tert-butoxicarbonil-carbamato (0,14 g, 323,84 µmol, 30 % de rendimiento) como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,643 min, m/z = 887,3 [2M + Na^+]

[00512] A una solución de N-[2-[(5-bromopirimidin-2-il)metoxi]etil]-N-tert-butoxicarbonil-carbamato de ter-butilo (0,14 g, 323,8 µmol, 1,0 eq), Et_3N (98,3 mg, 971,5 µmol, 135,2 µl, 3,0 eq) en MeOH (2 ml) y DMF (2 ml) se agregó $Pd(dppf)Cl_2$ (23,70 mg, 32,38 µmol, 0,1 eq). La mezcla se agitó a 80 °C durante 12 h en atmósfera de N2. La mezcla de reacción se vertió en agua helada (100 ml) y se extrajo con acetato de etilo (100 ml x 2). La fase orgánica combinada se lavó con salmuera (100 ml x 2), se secó en Na_2SO_4 anhidro, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 5/1). Se obtuvo el compuesto metil 2-[2-[bis(tert-butoxicarbonil)amino]etoximetil]pirimidina-5-carboxilato (0,12 g, 291,65 µmol, 90 % de rendimiento) como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,552 min, m/z = 845,4 [2M + Na^+]

[00513] A una solución de 2-[2-[bis(tert-butoxicarbonil)amino]etoximetil]pirimidina-5-carboxilato de metilo (0,12 g, 292 µmol, 1,0 eq) en MeCN (3 ml) y H_2O (1 ml) se agregó TBD (81,2 mg, 583 µmol, 2,0 eq). La mezcla se agitó a 18 °C durante 12 h. La mezcla se diluyó con agua (15 ml), y se extrajo con EtOAc (15 ml x 2). La fase orgánica combinada se lavó con salmuera (100 ml x 2), se secó en Na_2SO_4 anhidro, se filtró y se concentró a presión reducida. El compuesto ácido 2-[2-[bis(tert-

butoxicarbonil)amino]etoximetil]pirimidina-5-carboxílico (0,11 g) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI^+): t_R = 0,518 min, m/z = 817,4 [2M + Na^+]

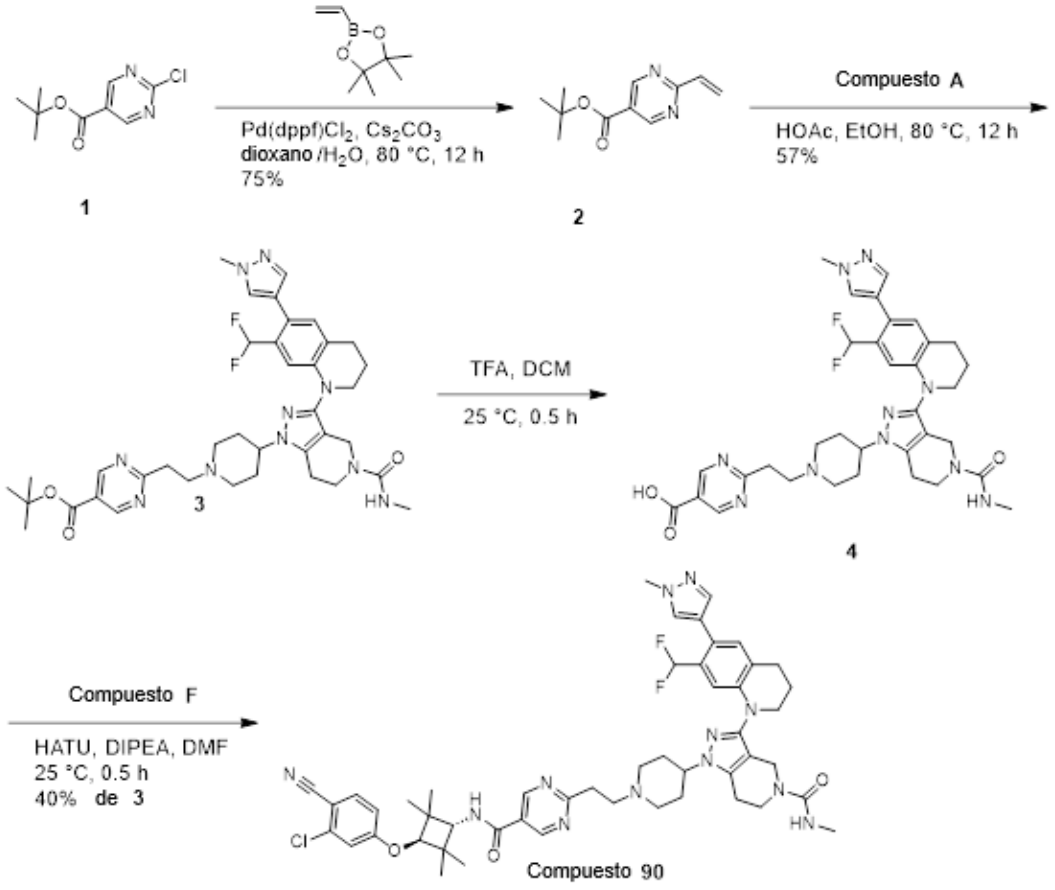
[00514] A una solución de ácido 2-[2-[bis(tert-butoxicarbonil)amino]etoximetil]pirimidina-5-carboxílico (0,11 g), 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (70 mg, 252 µmol, 1,0 eq) y DIPEA (98 mg, 752 µmol, 131 µl, 3,0 eq) en DMF (2 ml) se le agregó HATU (191 mg, 503 µmol, 2,0 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla se vertió en agua helada (100 l) y se extrajo con EtOAc (100 l dos veces). La fase orgánica combinada se lavó con salmuera (100 ml x 2), se secó en Na_2SO_4 anhidro, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 2/1). El compuesto ter-butil N-tert-butoxicarbonil-N-[2-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metoxi]etil]carbamato (0,11 g, 167,1 µmol, 66 % de rendimiento en dos pasos) se obtuvo como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,668 min, m/z = 680,3 [M + Na^+]

[00515] A una solución de N-tert-butoxicarbonil-N-[2-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metoxi]etil]carbamato de ter-butilo (55 mg, 83,56 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (844 mg, 7,40 mmol, 550 µl, 88,6 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto 2-(2-aminoetoximetil)-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (36 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00516] A una solución de 2-(2-aminoetoximetil)-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (36 mg), ácido 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carboxílico (33,6 mg, 67,5 µmol, 1,1 eq) y DIPEA (24,4 mg, 189 µmol, 32,9 µl, 3,0 eq) en DMF (1 ml) se le agregó HATU (47,9 mg, 126 µmol, 2,0 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El residuo se purificó mediante HPLC preparativa (columna: YMC-Actus Triart C18 150*30mm*7um; fase móvil: [agua(FA)-ACN]; gradiente: 53 %-83 % B durante 10 min). El compuesto 2-[2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]etoximetil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 76**, 21,82 mg, 22,81 µmol, 36 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9,90 (d, *J*=13,2 Hz, 1 H) 9,31 - 9,39 (m, 1 H) 9,16 (s, 2 H) 8,85 - 9,01 (m,

1 H) 8,61 (dd, *J*=8,0, 2,0 Hz, 1 H) 8,34 (d, *J*=8,0 Hz, 1 H) 8,21 (d, *J*=9,6 Hz, 1 H) 7,93 (dd, *J*=14,8, 7,6 Hz, 1 H) 7,80 (dt, *J*=11,6, 7,6 Hz, 1 H) 7,62 (dd, *J*=15,6, 7,2 Hz, 1 H) 7,45 - 7,56 (m, 1 H) 6,93 (dd, *J*=8,0, 2,4 Hz, 1 H) 6,73 (td, *J*=8,8, 2,0 Hz, 1 H) 6,17 - 6,25 (m, 1 H) 4,94 (s, 2 H) 4,67 (s, 1 H) 4,51 (s, 1 H) 4,23 - 4,37 (m, 1 H) 4,10 - 4,22 (m, 3 H) 3,98 - 4,07 (m, 2 H) 3,90 - 3,96 (m, 2 H) 3,80 - 3,89 (m, 3 H) 3,54 - 3,63 (m, 2 H) 2,79 - 3,02 (m, 2 H) 2,32 - 2,53 (m, 2 H) 2,05 - 2,30 (m, 3 H) 1,97 (br d, *J*=11,6 Hz, 2 H) 1,25 (s, 3 H) 1,23 (s, 3 H) 1,22 (s, 3 H) 1,20 (s, 3 H). LC-MS: MS (ESI^+): t_R = 2,273 min, m/z = 937,6 [$M + H^+$]

[00517] Ejemplo 15: Síntesis de 1-[1-[2-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]etil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 90**)



[00518] **1** se preparó de acuerdo con el procedimiento descrito en US2021/87171 A1.A una mezcla de 2-cloropirimidina-5-carboxilato de ter-butilo (5,00 g, 23,3 mmol, 1,0 eq), 4,4,5,5-tetrametil-2-vinil-1,3,2-dioxaborolano (5,67 g, 36,9 mmol, 6,25 ml, 1,6 eq), $Pd(dppf)Cl_2$ (1,75 g, 2,39 mmol, 0,1 eq) en dioxano (75 ml) se desgasificó y se purgó

con N_2 durante 3 veces, y luego una solución de Cs_2CO_3 (15,2 g, Se añadieron 46,6 mmol, 2,0 eq) en H_2O (15 ml) y se purgó con N_2 3 veces. La mezcla se agitó a 80 °C durante 12 h en atmósfera de N_2. La reacción se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 10/1 a 3/1). Se obtuvo el compuesto 2 (3,60 g, 17,5 mmol, 75 % de rendimiento) como un sólido amarillo. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9,17 (s, 1H), 6,99 - 6,89 (m, 1H), 6,79 - 6,71 (m, 1H), 5,91 - 5,82 (m, 1H).

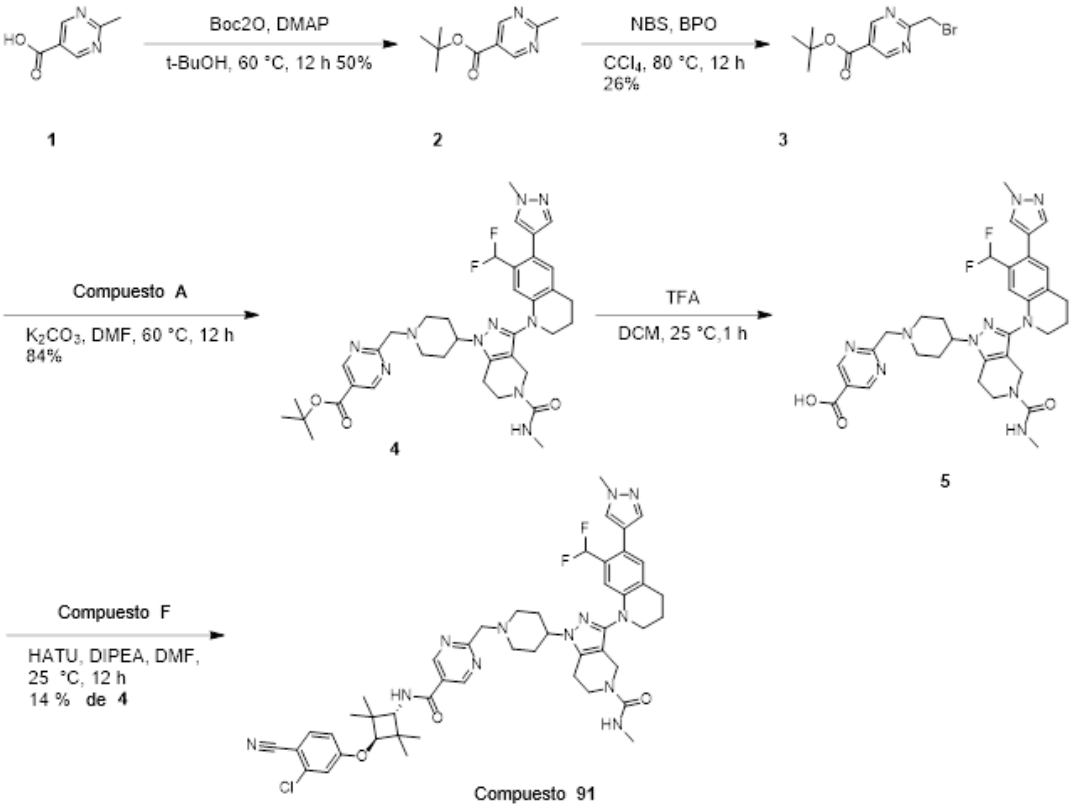
[00519] A una mezcla de 2-vinilpirimidina-5-carboxilato de ter-butilo (100 mg, 485 µmol, 3,2 eq) en EtOH (3 ml) se añadieron 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (100 mg, 153 µmol, 1,0 eq) y HOAc (31,5 mg, 524 µmol, 30 µl, 3,4 eq). La mezcla se calentó a 80 °C bajo atmósfera de N_2 durante 12 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía preparativa en capa fina (sílice, DCM/MeOH = 10:1). El compuesto ter-butil 2-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]pirimidina-5-carboxilato (63,0 mg, 86,2 µmol, 57 % de rendimiento) se obtuvo como un sólido blanco. LC-MS: MS (ESI$^+$): t_R = 0,536 min, m/z = 731,5 [M + H$^+$]

[00520] A una mezcla de 2-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]pirimidina-5-carboxilato de ter-butilo (63,0 mg, 86,2 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (1,54 g, 13,5 mmol, 1 ml, 156 eq). La mezcla se calentó a 25 °C bajo atmósfera de nitrógeno durante 0,5 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El producto crudo ácido 2-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]pirimidina-5-carboxílico (58,0 mg) se utilizó directamente en el siguiente paso sin purificación adicional. LC-MS: MS (ESI$^+$): t_R = 0,495 min, m/z = 675,5 [M + H$^+$]

[00521] A una solución de ácido 2-[2-[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]pirimidina-5-carboxílico (58,0 mg, 85,96 µmol, 1,0 eq) y 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (25,0 mg, 89,68 µmol, 1,1 eq) en DMF (0,5 ml) se agregó HATU (40,0 mg, 105,2 µmol, Se añadieron 1,2 eq) y DIPEA (37,1 mg, 287,1 µmol, 50 µl, 3,3 eq) y la mezcla se agitó a 25 °C durante 0,5 h. La reacción se detuvo añadiendo H_2O (10 ml) y se extrajo con DCM (20 ml × 3). Las capas orgánicas

combinadas se lavaron con salmuera (20 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (condición FA; columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 25 %-55 % B durante 10 min). El compuesto 1-[1-[2-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]etil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 90**, 32,28 mg, 34,22 µmol, 40 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 1,877 min, m/z = 935,6 [M + H^+]. ^1H (400 MHz, DMSO-d_6): δ = 9,04 (s, 2H), 8,22 (t, J = 4,4 Hz, 1H), 7,90 (d, J = 8,8 Hz, 1H), 7,74 (s, 1H), 7,49 (s, 1H), 7,22 (d, J = 2,4 Hz, 1H), 7,08 (s, 1H), 7,04 - 6,98 (m, 1H), 6,93 - 6,59 (m, 2H), 6,52 (br d, J = 4,4 Hz, 1H), 4,30 (s, 1H), 4,06 (d, J = 8,8 Hz, 1H), 4,04 - 3,96 (m, 3H), 3,86 (s, 3H), 3,61 - 3,54 (m, 4H), 3,12 (br t, J = 7,2 Hz, 2H), 3,02 (br d, J = 10,8 Hz, 2H), 2,90 - 2,80 (m, 4H), 2,71 (br s, 2H), 2,53 (d, J = 4,4 Hz, 3H), 2,13 (br t, J = 11,2 Hz, 2H), 2,00 - 1,87 (m, 4H), 1,85 - 1,77 (m, 2H), 1,23 (s, 6H), 1,12 (s, 6H).

[00522] Ejemplo 16: Síntesis de 1-[1-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 91**)



[00523] A una solución de ácido 2-metilpirimidina-5-carboxílico (3,00 g, 21,7 mmol, 1,0 eq) en *t*-BuOH (80 ml) se añadieron Boc_2O (5,69 g, 26,1 mmol, 5,99 ml, 1,2 eq) y DMAP (7,96 g, 65,2 mmol, 3,0 eq). La mezcla de reacción se agitó a 60 °C durante 12 h. La mezcla se concentró hasta secarse. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 20/1 a 5/1). Se obtuvo el compuesto 2 (2,10 g, 10,8 mmol, 50 % de rendimiento) como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,558 min, m/z = 139,2 $[M - 55]^+$

[00524] A una solución de 2-metilpirimidina-5-carboxilato de ter-butilo (0,50 g, 2,57 mmol, 1,0 eq) en CCl_4 (5 ml) se añadieron NBS (549 mg, 3,09 mmol, 1,2 eq) y BPO (62,4 mg, 257 µmol, 0,1 eq). La mezcla se agitó a 80 °C durante 12 h. La mezcla de reacción se detuvo mediante la adición de Na_2SO_3 (30 ml) a 0 °C, y luego se extrajo con $CHCl_3$ (50 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 20/1 a 10/1). Se obtuvo el compuesto 2-(bromometil)pirimidina-5-carboxilato de ter-butilo (183 mg, 670 µmol, 26 % de rendimiento) como un sólido blanco. LC-MS: MS (ESI^+): t_R = 0,827 min, m/z = 273,2 $[M + H^+]$

[00525] A una solución de 2-(bromometil)pirimidina-5-carboxilato de ter-butilo (50,0 mg, 183 µmol, 1,0 eq), 3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (83,3 mg, 159 µmol, 0,8 eq) en DMF (2 ml) se agregó K_2CO_3 (75,9 mg, 549 µmol, 3,0 eq).La mezcla se agitó a 60 °C durante 12 h. El residuo se diluyó con H_2O (100 ml) y se extrajo con acetato de etilo (100 ml × 3). El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 5 : El compuesto ter-butil 2-[[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]pirimidina-5-carboxilato (110 mg, 153 µmol, 84 % de rendimiento) se obtuvo como un sólido amarillo. LC-MS: MS (ESI^+): t_R = 0,528 min, m/z = 717,5 [M + H^+]

[00526] A una solución de 2-[[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]pirimidina-5-carboxilato de ter-butilo (130 mg, 181 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (1,54 g, 13,46 mmol, 1 ml, 74 eq). La mezcla se agitó a 25 °C durante 1 h y, luego, se concentró para obtener el compuesto 295e (0,5 g). El compuesto 2-[[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]pirimidina-5-ácido carboxílico (110 mg) se obtuvo como un sólido blanco y se utilizó directamente para el siguiente paso sin purificación. LC-MS (ESI): m/z = 661,3 [M+H]+.

[00527] A una solución de ácido 2-[[4-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-5-(metilcarbamoil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]pirimidina-5-carboxílico (90 mg del material anterior), 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (41,8 mg, 150 µmol, 1,1 eq), DIPEA (52,8 mg, 409 µmol, 71,2 µl, 3,0 eq) en DMF (2 ml) se agregó HATU (62,2 mg, 163 µmol, 1,2 eq) y se agitó a 25 °C durante 12 h. El residuo se diluyó con $_{H_2}O$ 10 ml y se extrajo con acetato de etilo (10 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (10 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex luna C18 150*25mm*10um; fase móvil: [agua (FA)-ACN]; gradiente: 24 %-54 % B durante 10 min). El compuesto 1-[1-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida (**Compuesto 91**, 19,0 mg, 20,2 µmol, 14 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo. LC-MS (ESI): m/z = 921,7

[M+H]+. ^{1}H (400 MHz, DMSO-d_6) δ = 9,11 (s, 2H), 8,22 (d, *J* = 8,8 Hz, 1H), 8,13 (s, 1H), 7,89 (d, *J* = 8,8 Hz, 1H), 7,74 (s, 1H), 7,49 (s, 1H), 7,22 (d, *J* = 2,4 Hz, 1H), 7,09 (s, 1H), 7,05 - 6,98 (m, 1H), 6,94 - 6,61 (m, 2H), 6,49 (br d, *J* = 4,4 Hz, 1H), 4,31 (s, 1H), 4,08 (d, *J* = 9,2 Hz, 1H), 4,01 (s, 3H), 3,86 (s, 5H), 3,64 - 3,53 (m, 4H), 3,10 - 2,95 (m, 2H), 2,84 (br t, *J* = 5,6 Hz, 2H), 2,71 (br t, *J* = 4,8 Hz, 2H), 2,54 (d, *J* = 4,4 Hz, 3H), 2,44 - 2,27 (m, 2H), 2,10 - 1,93 (m, 4H), 1,91 - 1,78 (m, 2H), 1,25 (s, 6H), 1,13 (s, 6H).

[00528] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en los ejemplos 1, 2, 3, 4, 8, 15 y 16.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
41	1-[1-[2-[4-[4-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]piperazin-1-il]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	7,68H NMR (8,8 Hz, DMSO-d6) δ = 7,53 (s, 1H), 7,40 - 7,05 (m, 2H), 6,97 - 7,91 (m, 1H), 6,93 - 6,85 (m, 3H), 6,84 - 6,78 (m, 1H), 6,68 - 6,36 (m, 2H), 6,12 - 4,72 (m, 1H), 4,43 - 4,29 (m, 1H), 4,20 - 4,09 (m, 2H), 4,00 - 3,91 (m, 1H), 3,87 - 3,74 (m, 1H), 3,72 - 3,62 (m, 1H), 3,41 - 3,28 (m, 1H), 3,26 - 3,13 (m, 2H), 3,05 - 2,87 (m, 3H), 2,82 - 2,65 (m, 1H), 2,35 - 2,17 (m, 1H), 2,15 - 1,91 (m, 1H), 1,27 - 1,23 (m, 2H).	1031,7
42	1-[1-[2-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]-2-piridil]piperazin-1-il]acetil]-4-piperidil]-3-[7-	(DMSO-d_6) δ = 8,61 (d, *J* = 2,0 Hz, 1H),	1032,9

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	8,37 (s, 1H), 7,97 - 7,87 (m, 2H), 7,71 (s, 1H), 7,61 (d, *J* = 8,8 Hz, 1H), 7,47 (s, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,08 (s, 1H), 7,03 - 6,98 (m, 1H), 6,90 - 6,58 (m, 3H), 6,54 (br d, *J* = 4,8 Hz, 1H), 4,49 - 4,40 (m, 1H), 4,38 - 4,33 (m, 1H), 4,32 - 4,29 (m, 1H), 4,20 - 4,13 (m, 1H), 4,05 (br d, *J* = 9,2 Hz, 1H), 4,01 (s, 2H), 3,85 (s, 3H), 3,71 - 3,52 (m, 10H), 3,24 - 3,06 (m, 3H), 2,92 - 2,68 (m, 6H), 2,21 - 1,79 (m, 6H), 1,75 (br d, *J* = 2,4 Hz, 1H), 1,30 - 1,15 (m, 8H), 1,12 (s, 6H).	
86	1-[1-[2-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metoxi]etil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	(DMSO-d6) δ = 9,11 (s, 2H), 8,35 - 8,32 (m, 1H), 8,24 (d, *J* = 8,8 Hz, 1H), 7,90 (d, *J* = 8,4 Hz, 1H), 7,74 (s, 1H), 7,49 (s, 1H), 7,24 - 7,21 (m, 1H), 7,09 (s, 1H), 7,04 -	965,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		6,99 (m, 1H), 6,93 - 6,49 (m, 3H), 4,73 (s, 2H), 4,31 (s, 1H), 4,07 (d, *J* = 9,2 Hz, 1H), 4,01 (s, 3H), 3,86 (s, 3H), 3,69 (t, *J* = 6,0 Hz, 2H), 3,61 - 3,55 (m, 4H), 3,03 - 2,96 (m, 2H), 2,87 - 2,81 (m, 2H), 2,75 - 2,68 (m, 2H), 2,57 (br d, *J* = 6,4 Hz, 2H), 2,53 (d, *J* = 4,4 Hz, 3H), 2,18 - 2,09 (m, 2H), 2,02 - 1,94 (m, 4H), 1,84 - 1,77 (m, 2H), 1,23 (s, 6H), 1,12 (s, 6H)	
87	1-[1-[2-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]oxietil]-4-piperidilo]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	(400 MHz, DMSO-d7,64, ppm) δ 7,41 (s, 1H), 7,04 (s, 1H), 6,97-6,71 (m, 3H), 6,86 (s, 1H), 6,84-6,78 (m, 1H), 6,73-4,30 (m, 3H), 4,30-4,63 (m, 3H), 4,45-4,36 (m, 1H), 4,16-4,07 (m, 1H), 3,99-3,93 (m, 1H), 3,82-3,68 (m, 1H), 3,82-3,65 (m, 1H), 3,26-3,15 (m, 2H), 2,94-2,87 (m, 1H),	951,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2,80-2,73 (m, 1H), 2,45-2,21 (m, 3H), 2,10-1,92 (m, 3H).	
93	1-[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	$_1$H NMR (400 MHz, METANOL-d4) δ = 8,80 - 8,74 (m, 1H), 7,82 - 7,76 (m, 1H), 7,75 (s, 1H), 7,94 - 7,69 (m, 2H), 7,65 - 7,60 (m, 2H), 7,51 - 7,47 (m, 1H), 7,15 - 7,11 (m, 1H), 7,09 - 7,05 (m, 1H), 7,01 - 6,94 (m, 1H), 6,65 - 6,84 (m, 1H), 5,08 - 4,99 (m, 1H), 4,30 – 4,24 (m, 2H), 4,17 - 4,11 (m, 2H), 4,10 - 4,05 (m, 2H), 3,96 - 3,89 (m, 2H), 3,78 - 3,71 (m, 2H), 3,67 - 3,60 (m, 2H), 3,23 - 3,22 (m, 2H), 3,23 - 3,14 (m, 3H), 2,93 - 2,83 (m, 2H), 2,72 - 2,66 (m, 2H), 2,10 - 2,01 (m, 1H), 1,32 - 1,25 (m, 1H), 1,22 - 1,20 (m, 1H).	907,5
97	1-[1-[2-[3-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-	8,75H NMR (400 MHz,	1120,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]metoxi]propoxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	DMSO-d7,35) δ = 7,02 (s, 1H), 6,99 - 6,94 (m, 1H), 6,88 - 6,83 (m, 2H), 6,83 - 6,78 (m, 2H), 6,72 - 7,28 (m, 1H), 7,28 - 5,94 (m, 2H), 4,91 - 4,80 (m, 1H), 4,73 - 4,60 (m, 1H), 4,46 - 4,37 (m, 2H), 4,23 - 4,08 (m, 1H), 4,07 - 4,02 (m, 1H), 3,99 - 3,92 (m, 1H), 3,86 - 3,76 (m, 1H), 3,75 - 3,66 (m, 1H), 3,64 - 3,57 (m, 2H), 3,56 - 3,47 (m, 2H), 3,33 - 3,26 (m, 2H), 3,24 - 3,12 (m, 1H), 3,00 - 2,82 (m, 1H), 2,79 - 2,75 (m, 1H), 2,26 - 1,94 (m, 1H), 1,93 - 1,81 (m, 1H).	
98	1-[1-[2-[2-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]oxi]etoxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	0001H NMR (DMSO-d6) δ = 7,61-7,52 (m, 1H), 8,37-7,42 (m, 2H), 8,15-7,04 (m, 1H), 6,97 (d, J=2,4 Hz, 1H), 6,89-6,77 (m, 2H), 6,55 (dd, J=11,3, 2,8	1092,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		Hz, 1H), 4,65-4,42 (m, 1H), 4,33-4,22 (m, 1H), 4,20-4,09 (m, 1H), 5,36-4,05 (m, 1H), 3,96-3,81 (m, 1H), 3,78-3,68 (m, 1H), 3,68-3,63 (m, 3H), 3,62-3,51 (m, 1H), 3,20 (s, 3H), 2,92-2,82 (m, 3H), 2,79-2,73 (m, 1H), 2,28-2,10 (m, 1H), 2,09-2,03 (m, 1H), 2,03-1,85 (m, 1H), 1,64 (br s, 1H).	
102	1-[1-[2-[2-[3-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazin-1-il]propoxi]etoxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	δ = 8,71 (s, 2H), 7,57 (d, *J* = 8,8 Hz, 1H), 7,53 (s, 1H), 7,41 (s, 1H), 7,04 (s, 1H), 6,97 (d, *J* = 2,4 Hz, 1H), 6,86 (s, 1H), 6,84 - 6,78 (m, 1H), 6,71 - 6,38 (m, 1H), 6,09 (d, *J* = 7,6 Hz, 1H), 4,66 (br d, *J* = 12,4 Hz, 1H), 4,43 (br d, *J* = 4,4 Hz, 1H), 4,24 (s, 2H), 4,18 - 4,09 (m, 3H), 4,06 (s, 1H), 4,05 – 3,98 (m, 3H), 3,98 - 3,95 (m, 5H), 3,83 - 3,74 (m, 2H),	1135,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		3,73 - 3,68 (m, 4H), 3,67 - 3,61 (m, 2H), 3,57 (t, *J* = 6,4 Hz, 2H), 3,19 (br s, 1H), 2,90 - 2,81 (m, 3H), 2,78 (d, *J* = 4,4 Hz, 3H), 2,74 (br t, *J* = 5,6 Hz, 2H), 2,71 - 2,59 (m, 5H), 2,24 - 2,12 (m, 2H), 2,11 - 2,01 (m, 4H), 2,00 - 1,95 (m, 2H), 1,95 - 1,92 (m, 1H), 1,26 (s, 6H), 1,22 (s, 6H)	
103	1-[1-[2-[2-[2-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazin-1-il]etoxi]etoxi]acetil]-4-piperidilo]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	δ = 8,70 (s, 2 H) 7,57 (d, *J*=8,8 Hz, 1 H) 7,53 (s, 1 H) 7,41 (s, 1 H) 7,27 (s, 2 H) 7,04 (s, 1 H) 6,97 (d, *J*=2,4 Hz, 1 H) 6,85 (s, 1 H) 6,81 (m, 1 H) 6,39 - 6,69 (m, 1 H) 6,12 (d, *J*=8,0 Hz, 1 H) 4,67 (d, *J*=12,8 Hz, 1 H) 4,44 (q, *J*=4,4 Hz, 1 H) 4,24 (s, 2 H) 4,09 - 4,19 (m, 3 H) 4,05 (s, 1 H) 3,91 - 4,00 (m, 8 H) 3,78 - 3,86 (m, 1 H) 3,66 - 3,76 (m, 9 H) 3,19 (m, 1	1121,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		H) 2,82 - 2,90 (m, 3 H) 2,63 - 2,79 (m, 10 H) 2,11 - 2,22 (m, 2 H) 2,04 - 2,08 (m, 2 H) 1,99 (m, 3 H) 1,24 (d, *J*=16,4 Hz, 12 H)	
104	1-[1-[2-[2-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidil]metoxi]etoxi]acetil]-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	δ =8,69 (s, 2H), 7,57 (d, J = 8,8 Hz, 1H), 7,54 (s, 1H), 7,41 (s, 1H), 7,04 (s, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,86 (s, 1H), 6,83 - 6,78 (m, 1H), 6,69 - 6,38 (m, 1H), 6,05 (br d, J = 7,8 Hz, 1H), 4,89 - 4,79 (m, 2H), 4,72 - 4,62 (m, 1H), 4,48 - 4,39 (m, 1H), 4,24 (s, 2H), 4,19 - 4,09 (m, 3H), 4,05 (s, 1H), 4,01 - 3,92 (m, 5H), 3,90 - 3,80 (m, 1H), 3,77 - 3,67 (m, 5H), 3,66 - 3,61 (m, 2H), 3,35 (d, J = 6,5 Hz, 2H), 3,26 - 3,13 (m, 1H), 2,98 - 2,82 (m, 5H), 2,81 - 2,72 (m, 6H), 2,25 - 2,13 (m, 2H), 2,11 - 2,04 (m, 2H), 2,03	1106,6

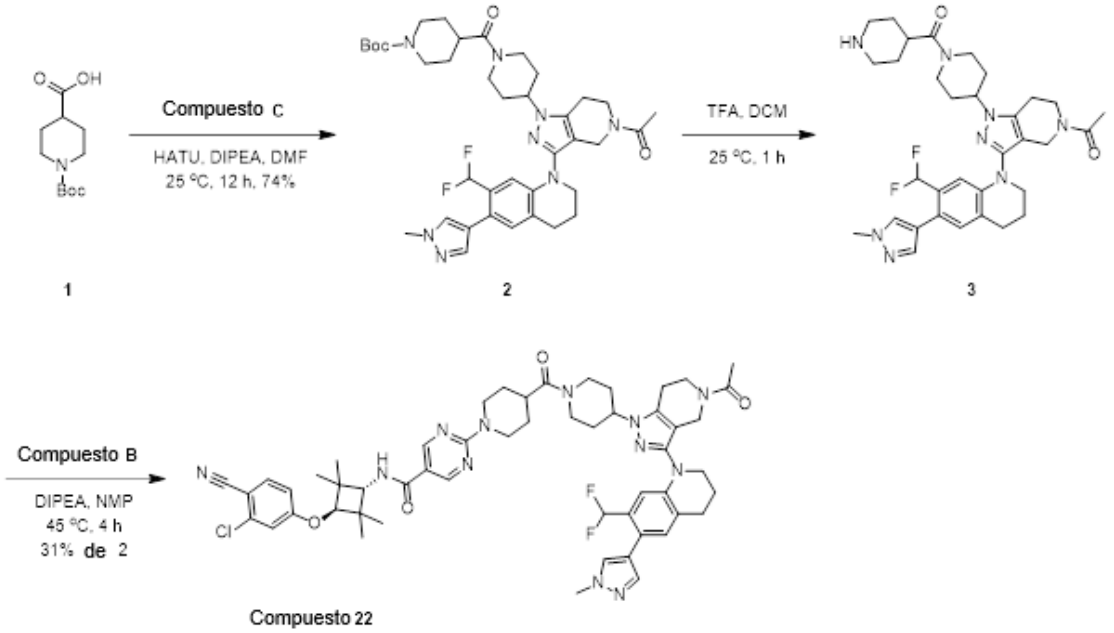
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		- 1,89 (m, 4H), 1,88 - 1,80 (m, 2H), 1,25 (s, 6H), 1,22 (s, 6H)	
105	1-[1-[2-[3-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazin-1-il]propoxi]acetil]-4-piperidilo]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	*1*H NMR (500 MHz, DMSO-d6) δ = 7,51 - 7,42 (m, 1H), 7,06 - 7,02 (m, 1H), 7,00 - 6,84 (m, 1H), 6,83 - 6,79 (m, 1H), 6,71 - 6,38 (m, 1H), 6,10 - 5,97 (m, 1H), 4,73 - 4,60 (m, 2H), 4,46 - 4,39 (m, 1H), 4,21 - 4,09 (m, 1H), 4,09 - 3,99 (m, 3H), 3,98 - 3,96 (m, 1H), 3,85 - 3,75 (m, 1H), 3,74 - 3,68 (m, 2H), 3,65 - 3,39 (m, 1H), 3,27 (br s, 1H), 2,94 - 2,83 (m, 1H), 2,83 - 2,77 (m, 3H), 2,75 (br s, 1H), 2,27 - 2,12 (m, 1H), 2,11 - 2,03 (m, 1H), 2,00 (d, *J* = 8,4 Hz, 3H), 1,26 - 1,23 (m, 3H).	1091,6
106	1-[1-[2-[2-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazin-1-il]etoxi]acetil]-4-piperidilo]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	δ = 8,69 (s, 2 H) 7,57 (d, J=8,8 Hz, 1 H) 7,53 (s, 1 H) 7,41 (s, 1 H) 7,03 (s, 1 H) 6,97 (d,	1077,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		J=2,4 Hz, 1 H) 6,85 (s, 1 H) 6,81 (m, 1 H) 6,34 - 6,71 (m, 1 H) 5,97 (d, J=8,00 Hz, 1 H) 4,68 (d, J=12,4 Hz, 1 H) 4,42 (q, J=4,4 Hz, 1 H) 4,23 (d, J=1,6 Hz, 2 H) 4,06 - 4,19 (m, 3 H) 4,05 (s, 1 hora) 3,90 - 4,00 (m, 9 H) 3,75 - 3,86 (m, 2 H) 3,67 - 3,74 (m, 4 H) 3,12 - 3,25 (m, 1 H) 2,81 - 2,92 (m, 3 H) 2,78 (d, J=4,4 Hz, 3 H) 2,73 (m, 4 H) 2,61 (m, 4 H) 2,10 - 2,27 (m, 2 H) 1,93 - 2,07 (m, 4 H) 1,25 (s, 6 H) 1,22 (s, 6 H).	
107	1-[1-[2-[[1-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]-4-piperidilo]metoxi]acetil]-4-piperidilo]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	δ = 8,69 (s, 2H), 7,61 - 7,51 (m, 2H), 7,41 (s, 1H), 7,04 (s, 1H), 6,97 (d, *J* = 2,4 Hz, 1H), 6,86 (s, 1H), 6,84 - 6,77 (m, 1H), 6,72 - 6,39 (m, 1H), 5,97 (d, *J* = 8,2 Hz, 1H), 4,86 (br d, *J* = 12,8 Hz, 2H), 4,67 (br d, *J* = 11,8 Hz, 1H), 4,49	1062,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		- 4,38 (m, 1H), 4,18 (s, 2H), 4,13 (br d, *J* = 8,0 Hz, 2H), 4,05 (s, 1H), 3,97 (s, 2H), 3,96 - 3,93 (m, 3H), 3,87 - 3,75 (m, 2H), 3,74 - 3,64 (m, 2H), 3,47 - 3,35 (m, 2H), 3,19 (br t, *J* = 12,4 Hz, 1H), 2,95 (br t, *J* = 11,6 Hz, 2H), 2,91 - 2,81 (m, 3H), 2,79 (d, *J* = 4,6 Hz, 3H), 2,75 (br t, *J* = 5,4 Hz, 2H), 2,27 - 2,09 (m, 2H), 2,09 - 2,04 (m, 2H), 2,04 - 1,95 (m, 3H), 1,93 - 1,84 (m, 2H), 1,66 (br s, 3H), 1,25 (s, 6H), 1,22 (s, 6H)	
108	1-[1-[3-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazin-1-il]propanoil]-4-piperidilo]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-N-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxamida	δ 8,71 (br s, 2 H), 7,50 (s, 2 H), 1 - 6,93 (m, 2 H), 6,75 (s, 2 H), 6,74 - 6,35 (m, 1 H), 5,90 (s, 2 H), 4,82 (br s, 2 H), 4,50 (br s, 2 H), 4,30 (d, J=5,88 Hz, 2 H), 3,65 (s, 3 H), 3,13 (s, 3 H), 2,98 - 2,53 (m, 2 H), 2,22 - 1,96 (m, 2 H), 1,27	1047,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		- 1,17 (m, 2 H)	

[00529] **Ejemplo 17**: Síntesis de 2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 22**)



[00530] A una solución de ácido 1-tert-butoxicarbonilpiperidina-4-carboxílico (23 mg, 100,08 µmol, 1 eq), DIPEA (39 mg, 300,24 µmol, 0,05 ml, 3 eq) en DMF (0,5 ml) se le añadieron 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (60 mg, 100,08 µmol, 1 eq) y HATU (42 mg, 110,09 µmol, 1,1 eq). La mezcla se agitó a 25 °C durante 30 min. La reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (100 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó mediante cromatografía preparativa en capa fina (sílice, diclorometano/metanol = 10:1). El compuesto ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]piperidina-1-carboxilato (56 mg, 74,56 µmol, 74 % de rendimiento) se obtuvo como un sólido blanco.

[00531] **LC-MS:** MS (ES^+): t_R = 0,586 min, m/z = 721,6 [M + H^+]

[00532] A una solución de ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]piperidina-1-carboxilato (56 mg, 74,56 µmol, 1 eq) en DCM (1 ml) se le agregó TFA (737 mg, 6,46 mmol, 0,5 ml, 86,64 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró para obtener un residuo. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(piperidina-4-carbonil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (54 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

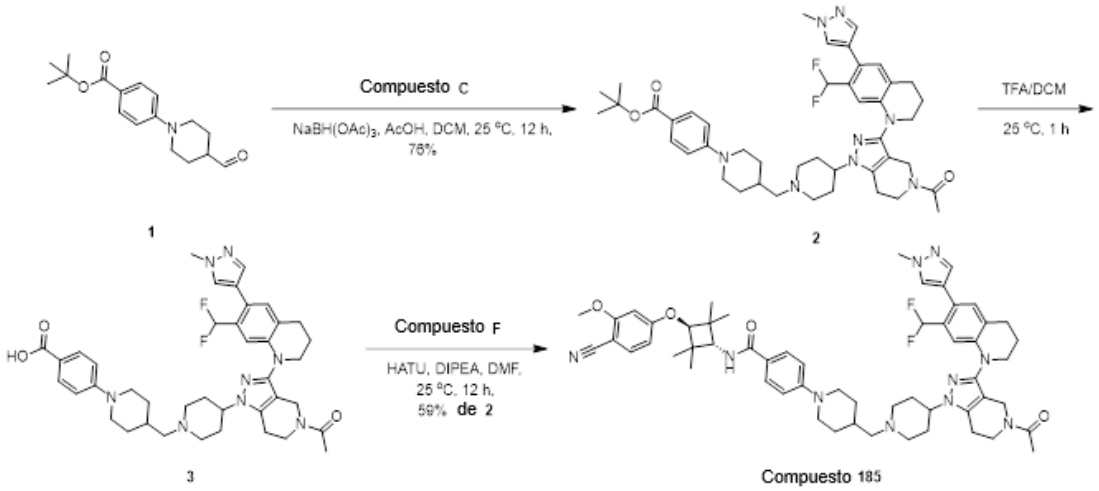
[00533] **LC-MS:** MS (ES^+): t_R = 0,489 min, m/z = 621,6 [M + H^+]

[00534] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(piperidina-4-carbonil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (54 mg) en NMP (0,5 ml) se le agregó DIPEA (28,50 mg, 220,48 µmol, 0,04 ml, 3 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (31 mg, 73,49 µmol, 1 eq). La mezcla de reacción se agitó a 45 °C durante 4 h. La mezcla se concentró hasta secarse. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex Luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 53 %-83 % B durante 10 min) para obtener 2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (23 mg, 22,85 µmol, 31 % de rendimiento) (en dos pasos) se obtuvo como un sólido blanquecino

[00535] ^{1}H NMR (400 MHz, DMSO-d6) δ = 8,63 (s, 1H), 7,48 - 7,45 (m, 1H), 7,35 - 7,32 (m, 2H), 6,96 - 6,89 (m, 2H), 6,83 - 7,28 (m, 1H), 7,28 - 7,13 (m, 2H), 6,63 - 6,30 (m, 1H), 5,86 - 4,81 (m, 1H), 4,72 - 4,62 (m, 2H), 4,28 - 4,12 (m, 1H), 4,11 - 4,01 (m, 1H), 3,97 - 3,88 (m, 1H), 3,87 - 3,74 (m, 1H), 3,73 - 3,66 (m, 1H), 3,66 - 3,57 (m, 2H), 3,27 - 3,11 (m, 1H), 3,07 - 2,94 (m, 2H), 2,84 - 2,66 (m, 1H), 2,25 - 2,12 (m, 1H), 2,10 - 1,95 (m, 1H), 1,94 - 1,87 (m, 1H), 1,76 - 1,18 (m, 1H).

[00536] **LC-MS:** MS (ES^+): t_R = 2,781 min, m/z = 1003,4 [M + H^+]

[00537] **Ejemplo 18**: Síntesis de 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 185**)



[00538] La síntesis de **1** fue reportada en US2018/215731 A1.

[00539] A una solución de 4-(4-formil-1-piperidil)benzoato de ter-butilo (80 mg, 276 µmol, 1,4 eq) y 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg, 196 µmol, 1,0 eq) en DCM (8 ml) se agregó AcOH (20 mg, 333 µmol, 1,7 eq) y se agitó a 25 °C durante 0,5 h, NaBH(OAc) (200 mg, 944 µmol, 4,8 eq.) se agregó a la mezcla y se agitó a 25 °C durante 12 h. La mezcla se vertió lentamente en una solución de NaHCO (80 ml). La capa acuosa se extrajo con DCM (40 ml x 3). La fase orgánica combinada se lavó con salmuera (30 ml x 2), se secó con Na2SO4 anhidro, se filtró y se concentró a vacío. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 3/1 a 10/1). El compuesto ter-butil 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]benzoato (117 mg, 149 µmol, 76 % de rendimiento) se obtuvo como un aceite incoloro.

[00540] **LC-MS:** MS (ESI^+): t_R = 0,559 min, m/z = 783,5 [M + H^+]

[00541] A una solución de 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]benzoato de ter-butilo (100 mg, 128 µmol, 1,0 eq) en DCM (5 ml) se agregó TFA (4,60 g, 40,4 mmol, 316,2 eq) y se agitó a 25 °C durante 1 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El compuesto ácido 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]benzoico (103 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00542] **LC-MS:** MS (ESI$^+$): t_R = 0,470 min, m/z = 727,5 [M + H$^+$]

[00543] A una solución de ácido 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]benzoico (60 mg, 71,4 µmol, 1,0 eq), 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (40 mg, 103 µmol, 1,4 eq) en DMF (3 ml) se agregó DIPEA (74 mg, 574 µmol, 8,1 eq) y HATU (41 mg, 107 µmol, 1,5 eq) y se agitó a 25 °C durante 1 h. La mezcla se diluyó con acetato de etilo (100 ml), se lavó con agua (15 ml × 2), salmuera (15 ml), se secó con sulfato de sodio anhidro, se filtró y se concentró al vacío. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (41,75 mg, 41,8 µmol, 59 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino.

[00544] **^{1}H NMR** (400 MHz, CLOROFORMO-*d*) δ ppm 7,68 (d, *J*=8,8 Hz, 2 H) 7,54 (d, *J*=6,0 Hz, 1 H) 7,46 (d, *J*=8,8 Hz, 1 H) 7,41 (d, *J*=6,8 Hz, 1 H) 7,04 (d, *J*=19,2 Hz, 1 H) 6,91 (m, 3 H) 6,36 - 6,72 (m, 3 H) 6,12 (m, 1 H) 4,30 (s, 1 H) 4,12 - 4,19 (m, 2 H) 4,05 (s, 1 H) 3,96 (s, 3 H) 3,88 - 3,94 (m, 4 H) 3,84 (m, 2 H) 3,64 - 3,79 (m, 3 H) 3,15 (s, 2 H) 2,73 - 2,92 (m, 6 H) 2,34 - 2,56 (m, 3 H) 2,23 - 2,32 (m, 2 H) 2,18 (s, 2 H) 2,02 - 2,13 (m, 5 H) 1,87 - 1,99 (m, 4 H) 1,31 - 1,39 (m, 2 H) 1,25 (d, *J*=10,4 Hz, 12 H).

[00545] **LC-MS:** MS (ESI$^+$): t_R =1,992 min, m/z = 983,8 [M + H$^+$]

[00546] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en los ejemplos 5, 6, 7, 9, 11, 17 y 18.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS (M+H)$^+$:**
10	2-[4-[[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	*δ* = 8,69 (s, 2H), 7,57 (d, J = 8,8 Hz, 1H), 7,54 (d, J = 5,6 Hz, 1H), 7,42 (d, J = 5,6 Hz, 1H), 7,12 (d, J = 16,0 Hz, 1H), 7,04 (d, J = 8,8 Hz, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,71 - 6,39 (m, 1H), 5,98 (br d, J = 8,0 Hz, 1H), 5,22 - 5,04 (m, 1H), 4,90 (br d, J = 12,8 Hz, 2H), 4,70 - 4,43 (m, 2H), 4,29 (s, 1H), 4,21 - 4,03 (m, 5H), 3,97 (s, 3H), 3,88 (br t, J =	961,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		5,6 Hz, 1H), 3,78 - 3,69 (m, 3H), 3,06 (br d, J = 6,4 Hz, 1H), 3,00 - 2,85 (m, 5H), 2,79 - 2,68 (m, 2H), 2,19 - 1,97 (m, 7H), 1,90 (br d, J = 12,0 Hz, 2H), 1,32 - 1,28 (m, 1H), 1,23 (d, J = 15,2 Hz, 12H).	
11	2-[4-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,58 (d, J = 8,8 Hz, 1H), 7,55 (d, J = 4,4 Hz, 1H), 7,42 (d, J = 4,8 Hz, 1H), 7,12 (br d, J = 5,6 Hz, 1H), 7,07 (s, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,73 - 6,42 (m, 1H), 5,99 (d, J = 8,0 Hz, 1H), 5,36 - 5,12 (m, 1H), 5,02 - 4,84 (m, 2H), 4,68 - 4,41 (m, 2H), 4,33 (s, 1H), 4,32 - 4,25 (m, 1H), 4,17 - 4,11 (m, 2H), 4,06 (s, 1H), 3,97 (d, J = 1,6 Hz, 3H), 3,89 (br t, J = 6,0 Hz, 1H), 3,74 (q, J = 6,0 Hz, 3H), 3,35 - 3,16 (m, 1H), 3,10 - 2,98 (m, 2H), 2,95 - 2,87 (m, 2H), 2,82 - 2,69 (m, 2H), 2,17 (s, 2H), 2,14 - 2,08 (m, 2H), 2,07 - 1,96 (m, 4H), 1,68 - 1,60 (m, 2H), 1,25 (d, J = 17,6 Hz, 12H).	947,5
12	2-[4-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]pirrolidin-1-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	*δ* = 8,70 (s, 2 H) 7,49 - 7,61 (m, 2 H) 7,41 (d, *J*=6,0 Hz, 1 H) 6,90 - 7,08 (m, 3 H) 6,81 (m, 1 H) 6,38 - 6,71 (m, 1 H) 5,94 (d, *J*=8,4 Hz, 1 H) 4,69 - 4,86 (m, 3 H) 4,09 - 4,32 (m, 3 H) 4,05 (s, 1 H) 3,96 (d, *J*=1,6 Hz, 3 H) 3,84 - 3,94 (m, 1 H) 3,63 - 3,78 (m, 3 H) 3,32 - 3,52 (m, 1 H) 3,01 - 3,21 (m, 3 H) 2,84 - 2,99 (m, 4 H) 2,73 - 2,83 (m, 2 H) 2,53 - 2,71 (m, 1 H) 2,30 - 2,44 (m, 2 H) 2,17 (s, 1 H) 1,97 - 2,12 (m, 6 H) 1,54 - 1,62 (m, 2 H) 1,26 (s, 6 H) 1,22 (s, 6 H)	961,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
13	2-[4-[[4-[5-acetil-3-[6-(difluorometil)-5-(1-metilpirazol-4-il)indolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6) δ = 8,75 (s, 2 H) 7,90 (d, *J*=8,8 Hz, 1 H) 7,68 - 7,79 (m, 3 H) 7,52 (s, 1 H) 7,17 - 7,23 (m, 2 H) 6,68 - 7,03 (m, 2 H) 4,74 (m, 2 H) 4,55 (m, 2 H) 4,29 (s, 1 H) 3,94 - 4,13 (m, 4 H) 3,88 (s, 3 H) 3,66 - 3,79 (m, 2 H) 3,13 - 3,23 (m, 3 H) 2,89 - 3,06 (m, 5 H) 2,81 (m, 1 H) 2,67 (m, 1 H) 2,19 (m, 2 H) 2,10 (m, 3 H) 2,03 - 2,07 (m, 3 H) 1,82 (m, 4 H) 1,21 (s, 6 H) 1,11 (s, 6 H) 0,99 - 1,08 (m, 2 H)	975,7
15	2-[2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]triazol-1-il]etil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6) δ = 9,05 (s, 2H), 8,23 (d, *J* = 8,8 Hz, 1H), 8,02 - 7,93 (m, 1H), 7,74 (s, 1H), 7,54 - 7,44 (m, 1H), 7,21 (d, *J* = 2,0 Hz, 1H), 7,09 (s, 1H), 7,04 - 6,97 (m, 1H), 6,95 - 6,59 (m, 2H), 4,87 (br t, *J* = 6,8 Hz, 2H), 4,35 - 4,25 (m, 1H), 4,16 - 4,08 (m, 2H), 4,05 (d, *J* = 9,2 Hz, 1H), 4,01 - 3,91 (m, 1H), 3,86 (s, 3H), 3,76 - 3,65 (m, 2H), 3,56 (br d, *J* = 10,8 Hz, 6H), 2,91 - 2,70 (m, 6H), 2,09 - 1,90 (m, 9H), 1,86 - 1,74 (m, 2H), 1,21 (s, 6H), 1,09 (s, 6H).	1001,4
18	2-[5-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]pent-3-inil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(400 MHz, DMSO-*d6*, *ppm*) δ 7,52 (s, 1H), 7,39 (s, 1H), 7,08-7,00 (m, 3H), 6,98 (s, 1H), 6,94-6,86 (m, 1H), 6,84-4,30 (m, 3H), 4,30-6,34 (m, 3H), 4,29-4,18 (m, 1H), 4,15-4,03 (m, 3H), 3,95-3,87 (m, 1H), 3,79-3,65 (m, 1H), 3,54-3,38 (m, 1H), 3,32-3,13 (m, 4H), 2,93-2,72 (m, 1H), 2,36-2,23 (m, 1H), 2,19-2,04 (m, 3H), 1,30-1,25 (m, 3H).	968,7
19	2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-	1H NMR (400 MHz, DMSO-d6) δ = 9,08 (s, 1H), 7,63 - 7,50 (m, 2H), 7,44 - 7,37 (m, 1H), 7,08 - 6,95 (m,	930,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]prop-1-inil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H), 6,90 - 6,78 (m, 1H), 6,72 - 6,33 (m, 1H), 6,24 - 6,11 (m, 2H), 4,28 - 4,07 (m, 1H), 4,02 - 3,86 (m, 1H), 3,81 - 3,65 (m, 2H), 3,17 - 3,01 (m, 2H), 2,92 - 2,71 (m, 4H), 2,70 - 2,53 (m, 1H), 2,26 (s, 1H), 2,17 (s, 2H), 2,11 - 1,92 (m, 1H), 1,30 (s, 2H), 1,25 (s, 1H), 2,66 - 2,56 (m, 1H).	
20	2-[3-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d8,74) δ = 8,66 (s, 1H), 7,61 - 7,50 (m, 1H), 7,43 - 7,37 (m, 2H), 7,08 - 6,94 (m, 2H), 6,91 - 7,28 (m, 1H), 7,28 - 6,77 (m, 2H), 6,72 - 6,35 (m, 1H), 5,93 - 4,75 (m, 1H), 4,38 - 4,28 (m, 2H), 4,28 - 4,20 (m, 1H), 4,16 - 4,10 (m, 1H), 4,73 - 4,05 (m, 1H), 4,01 - 3,94 (m, 1H), 3,93 - 3,86 (m, 1H), 3,80 - 3,66 (m, 3H), 3,15 - 2,94 (m, 3H), 2,93 - 2,72 (m, 2H), 2,39 - 2,21 (m, 1H), 2,63 - 2,17 (m, 1H), 2,11 - 2,02 (m, 1H), 2,00 - 1,86 (m, 1H), 1,25 - 1,22 (m, 1H).	961,6
21	2-[4-[[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]pirrolidin-1-il]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d6) δ = 7,51 (s, 1H), 7,41 - 8,11 (m, 1H), 7,09 - 6,96 (m, 2H), 6,94 - 6,88 (m, 2H), 6,85 - 7,28 (m, 1H), 7,28 - 6,36 (m, 2H), 5,96 - 5,87 (m, 1H), 4,92 - 4,80 (m, 1H), 4,79 - 4,67 (m, 2H), 5,21 - 4,26 (m, 1H), 4,16 - 4,09 (m, 1H), 3,99 - 3,91 (m, 1H), 4,56 - 3,85 (m, 1H), 3,79 - 3,67 (m, 1H), 3,21 - 3,08 (m, 1H), 3,03 - 2,66 (m, 9H), 2,53 - 2,28 (m, 2H), 2,89 - 2,17 (m, 1H), 2,12 - 2,00 (m, 1H), 1,98 - 1,87 (m, 1H), 1,86 - 1,72 (m, 1H), 1,25 - 1,22 (m, 1H).	975,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
24	2-[4-[[4-[5-acetil-3-[6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	620, *1*H NMR (400 MHz, DMSO-*d6*) δ = 7,94 - 7,86 (m, 1H), 7,73 - 7,64 (m, 1H), 7,24 - 7,16 (m, 1H), 7,14 - 7,06 (m, 1H), 7,03 - 6,98 (m, 3H), 6,46 - 6,38 (m, 2H), 4,73 (br d, *J* =12,8 Hz, 1H), 4,15 - 4,07 (m, 1H), 4,05 - 3,94 (m, 1H), 3,86 - 3,79 (m, 1H), 3,74 – 4,83 (m, 1H), 3,69 - 4,61 (m, 1H), 3,57 - 3,51 (m, 1H), 3,01 - 2,91 (m, 3H), 2,84 - 2,77 (m, 1H), 2,73 - 2,66 (m, 3H), 2,18 (s, 1H), 2,08 (s, 2H), 1,89 - 1,77 (m, 1H), 1,21 - 1,11 (m, 1H), 1,06 - 0,94 (m, 1H).	939,7
25	2-[4-[[4-[5-acetil-3-[7-cloro-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,6-7,7 (m, 2H), 7,57 (d, 1H, J=8,8 Hz), 7,0-7,1 (m, 1H), 6,97 (d, 1H, J=2,4 Hz), 6,81 (dd, 1H, J=2,4, 8,8 Hz), 6,56 (s, 1H), 5,93 (d, 1H, J=8,4 Hz), 4,85 (br d, 2H, J=13,2 Hz), 4,31 (s, 1H), 4,1-4,2 (m, 2H), 4,04 (s, 1H), 3,9-4,0 (m, 5H), 3,76 (t, 1H, J=5,6 Hz), 3,6-3,7 (m, 2H), 2,9-3,1 (m, 4H), 2,7-2,9 (m, 4H), 2,2-2,3 (m, 4H), 2,1-2,2 (m, 2H), 2,0-2,1 (m, 4H), 1,8-2,0 (m, 6H), 1,24 (d, 12H, J=13,0 Hz), 1,1-1,2 (m, 2H)	973,7
26	2-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,62 - 7,51 (m, 2H), 7,41 - 7,33 (m, 1H), 7,03 - 6,91 (m, 2H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,38 (s, 1H), 5,92 (d, J = 8,0 Hz, 1H), 4,85 (br d, J = 12,8 Hz, 2H), 4,32 - 4,02 (m, 4H), 3,98 - 3,88 (m, 5H), 3,78 - 3,60 (m, 3H), 3,08 - 2,90 (m, 4H), 2,86 - 2,71 (m, 4H), 2,38 - 2,23 (m, 6H), 2,22 - 2,10 (m, 4H), 2,08 - 2,00 (m, 4H), 1,90 (br d, J = 12,0 Hz, 5H), 1,24 (d, J = 12,8 Hz, 12H), 1,20 - 1,09 (m, 2H).	953,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
27	2-[4-[[4-[5-acetil-3-[6-(1-metilpirazol-4-il)-7-(trifluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	7,57 (d, J = 8,8 Hz, 1H), 7,53 (br d, J = 8,4 Hz, 1H), 7,41 (s, 1H), 7,05 (d, J = 8,1 Hz, 1H), 6,98 - 6,87 (m, 1H), 6,81 (d, J = 8,8 Hz, 1H), 5,94 (dd, J = 4,6, 8,4 Hz, 1H), 4,86 (d, J = 8,1 Hz, 1H), 4,32 - 4,24 (m, 1H), 4,18 - 4,09 (m, 3H), 4,05 - 3,90 (m, 4H), 3,79 - 3,63 (m, 3H), 3,03 - 2,68 (m, 1H), 2,43 - 2,03 (m, 1H), 1,91 (d, J = 12,8 Hz, 3H), 1,24 (d, J = 14,4 Hz, 3H).	1007,5
28	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]sulfonil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d6) δ = 7,53 - 8,26 (m, 1H), 7,41 - 7,78 (m, 1H), 7,09 - 6,95 (m, 3H), 6,90 - 7,40 (m, 1H), 6,84 - 6,78 (m, 1H), 6,71 - 6,36 (m, 1H), 6,02 - 5,93 (m, 1H), 5,09 - 4,96 (m, 1H), 5,57 - 4,28 (m, 1H), 4,17 - 4,03 (m, 1H), 4,00 - 3,86 (m, 1H), 3,80 - 3,64 (m, 2H), 3,29 - 3,09 (m, 6H), 2,97 (s, 3H), 2,91 - 2,83 (m, 2H), 2,83 - 2,73 (m, 3H), 2,33 - 2,14 (m, 5H), 2,12 - 1,97 (m, 2H), 1,88 - 1,35 (m, 2H), 1,35 - 1,23 (m, 6H).	1039,6
64	2-[4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]pirrolidin-1-il]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	(400 MHz, DMSO-d6, ppm) δ 7,6 (s, 1H), 7,5 (s, 1H), 7,40-6,71 (m, 3H), 7,1 (s, 1H), 6,81-4,75 (m, 1H), 6,3-4,30 (m, 3H), 4,30-6,2 (m, 3H), 4,6-4,9 (m, 1H), 4,3-4,5 (m, 1H), 4,1-4,2 (m, 1H), 3,9-4,1 (m, 1H), 3,6-3,7 (m, 1H), 3,3-3,6 (m, 2H), 2,7-3,1 (m, 1H), 2,3-2,6 (m, 1H), 2,06-1,62 (m, 3H), 1,2-1,3 (m, 3H).	1004,5
69	2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etoxi]-1-piperidil]-N-[3-(3-cloro-4-	1H NMR (400 MHz, DMSO-d6) δ = 7,52 (s, 1H), 7,46 - 7,40 (m, 1H), 7,11 - 6,96 (m, 2H), 6,92 - 6,86 (m, 2H), 6,85 - 7,28 (m, 1H), 7,28 - 6,37 (m, 2H), 6,06 - 5,93 (m, 1H), 4,77 - 4,62	1033,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	(m, 1H), 4,36 - 4,26 (m, 2H), 4,39 - 4,24 (m, 1H), 4,23 - 4,13 (m, 1H), 4,01 - 3,84 (m, 1H), 3,82 - 3,66 (m, 1H), 3,65 - 3,24 (m, 1H), 2,95 - 2,80 (m, 4H), 3,08 - 2,76 (m, 1H), 2,31 - 2,11 (m, 2H), 2,11 - 2,04 (m, 1H), 2,04 - 1,96 (m, 1H), 2,04 - 1,95 (m, 1H), 1,74 - 1,68 (m, 1H), 1,27 - 1,24 (m, 1H).	
88	2-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etoximetil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d6) δ = 9,12 (s, 2H), 8,24 (d, *J* = 8,8 Hz, 1H), 8,20 (s, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,75 (s, 1H), 7,49 (s, 1H), 7,22 (d, *J* = 2,0 Hz, 1H), 7,10 (s, 1H), 7,04 - 6,99 (m, 1H), 6,96 - 6,62 (m, 2H), 4,73 (s, 2H), 4,30 (s, 1H), 4,19 - 4,05 (m, 3H), 4,04 - 3,95 (m, 1H), 3,86 (s, 3H), 3,74 - 3,65 (m, 4H), 3,61 - 3,55 (m, 2H), 3,05 - 2,96 (m, 2H), 2,84 (br d, *J* = 6,0 Hz, 3H), 2,76 - 2,69 (m, 1H), 2,58 (br t, *J* = 6,0 Hz, 2H), 2,19 - 2,10 (m, 2H), 2,07 (s, 2H), 2,01 - 1,92 (m, 5H), 1,82 (br d, *J* = 11,2 Hz, 2H), 1,23 (s, 6H), 1,12 (s, 6H)	950,4
89	2-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etoxi]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d6) δ = 8,97 (s, 2H), 8,14 (s, 1H), 8,05 (d, *J* = 9,2 Hz, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,75 (s, 1H), 7,49 (s, 1H), 7,22 (d, *J* = 2,0 Hz, 1H), 7,10 (s, 1H), 7,04 - 6,98 (m, 1H), 6,95 - 6,62 (m, 2H), 4,51 (br t, *J* = 5,2 Hz, 2H), 4,30 (s, 1H), 4,19 - 4,09 (m, 2H), 4,08 - 3,97 (m, 2H), 3,86 (s, 3H), 3,77 - 3,65 (m, 2H), 3,62 - 3,55 (m, 2H), 3,05 (br d, *J* = 9,6 Hz, 2H), 2,84 (br d, *J* = 6,4 Hz, 3H), 2,80 - 2,65 (m, 3H), 2,23 (br t, *J* = 11,2 Hz, 2H), 2,07 (s, 2H), 2,02 - 1,93 (m, 5H), 1,88 - 1,80	936,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		(m, 2H), 1,23 (s, 6H), 1,11 (s, 6H)	
92	2-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6) δ = 9,04 (s, 2H), 8,22 (d, *J* = 9,6 Hz, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,74 (s, 1H), 7,49 (s, 1H), 7,22 (d, *J* = 2,0 Hz, 1H), 7,09 (s, 1H), 7,04 - 6,98 (m, 1H), 6,94 - 6,59 (m, 2H), 4,30 (s, 1H), 4,19 - 4,14 (m, 1H), 4,11 (s, 1H), 4,09 - 3,99 (m, 2H), 3,86 (s, 3H), 3,76 - 3,66 (m, 2H), 3,59 - 3,54 (m, 2H), 3,47 - 3,42 (m, 1H), 3,18 - 3,11 (m, 2H), 3,08 - 2,99 (m, 2H), 2,91 - 2,81 (m, 5H), 2,75 - 2,70 (m, 1H), 2,23 - 2,12 (m, 2H), 2,07 (s, 2H), 1,98 - 1,91 (m, 4H), 1,88 - 1,78 (m, 2H), 1,23 (s, 6H), 1,12 (s, 6H), 1,05 (t, *J* = 6,8 Hz, 1H)	920,7
94	2-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (500 MHz, DMSO-d7,61) δ = 7,56 - 7,51 (m, 1H), 7,43 - 7,78 (m, 1H), 7,78 - 6,99 (m, 1H), 6,98 - 6,85 (m, 1H), 6,84 - 6,79 (m, 1H), 6,75 - 6,36 (m, 1H), 6,28 - 6,10 (m, 1H), 4,30 - 4,20 (m, 1H), 4,20 - 4,19 (m, 3H), 4,13 - 4,10 (m, 1H), 4,03 - 3,94 (m, 1H), 3,92 - 3,88 (m, 1H), 3,76 - 3,66 (m, 3H), 3,31 - 3,08 (m, 1H), 2,93 - 2,79 (m, 3H), 2,78 - 2,71 (m, 1H), 2,71 - 2,27 (m, 1H), 2,16 (s, 3H), 2,11 - 2,02 (m, 1H), 2,02 - 1,87 (m, 1H), 1,29 - 1,25 (m, 3H)	906,6
95	2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-	1H NMR (500 MHz, DMSO-d6) δ = 8,72 (s, 1H), 7,61 - 7,50 (m, 2H), 7,43 - 7,37 (m, 1H), 7,07 - 6,95 (m, 2H), 6,88 - 6,78 (m, 1H), 6,69 - 6,34 (m, 2H), 5,98 - 5,90 (m, 1H), 6,76 - 5,03 (m, 1H), 4,30 - 4,17 (m,	892,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	5-carboxamida	2H), 4,17 - 4,09 (m, 1H), 4,74 - 4,05 (m, 1H), 3,98 - 3,90 (m, 1H), 4,26 - 3,77 (m, 1H), 3,71 - 3,63 (m, 2H), 3,23 - 3,09 (m, 2H), 2,92 - 2,72 (m, 1H), 2,27 - 2,14 (m, 1H), 2,13 - 1,97 (m, 1H), 1,24 - 1,18 (m, 2H).	
112	2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 8,79 (s, 2H), 7,90 (d, J = 8,8 Hz, 1H), 7,80 - 7,71 (m, 2H), 7,50 (s, 1H), 7,21 (d, J = 2,4 Hz, 1H), 7,10 (s, 1H), 7,00 (d, J = 2,4, 8,8 Hz, 1H), 6,96 - 6,62 (m, 2H), 4,33 - 4,22 (m, 2H), 4,19 - 4,10 (m, 2H), 4,04 (d, J = 9,2 Hz, 1H), 3,86 (s, 7H), 3,77 - 3,66 (m, 4H), 3,61 - 3,55 (m, 2H), 3,29 - 3,23 (m, 4H), 3,00 - 2,90 (m, 2H), 2,89 - 2,71 (m, 4H), 2,10 - 2,04 (m, 2H), 2,02 (s, 7H), 1,21 (s, 6H), 1,11 (s, 6H)	1004,8
113	2-[4-[1-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (500 MHz, DMSO-d6) δ = 7,62 - 7,51 (m, 1H), 7,46 - 7,78 (m, 2H), 7,78 - 6,94 (m, 2H), 6,91 - 6,85 (m, 1H), 6,84 - 6,78 (m, 1H), 6,71 - 6,35 (m, 1H), 5,91 - 7,15 (m, 1H), 4,94 - 4,77 (m, 1H), 5,80 - 4,27 (m, 3H), 4,19 - 4,10 (m, 2H), 4,04 - 3,96 (m, 1H), 3,93 - 3,80 (m, 1H), 3,78 - 3,67 (m, 3H), 2,99 - 2,57 (m, 1H), 2,37 - 2,16 (m, 3H), 2,13 - 2,71 (m, 2H), 2,71 - 1,77 (m, 1H), 1,25 (s, 3H), 2,53 - 1,22 (m, 1H), 1,20 - 1,06 (m, 1H), 0,45 - 0,98 (m, 3H)	1003,6
114	6-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidil]-N-[3-(3-cloro-4-	*1*H NMR (9,2 Hz, DMSO-$d_{7,88}$) δ = 7,81 (s, 1H), 7,78 - 7,73 (m, 1H), 7,50 - 7,38 (m, 2H), 7,27 - 7,24 (m, 2H), 7,13 - 7,28 (m, 1H), 7,28 - 7,01 (m, 2H), 6,95 - 6,63 (m, 1H), 4,55 - 4,44	1003,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	cianofenoxi)-2,2,4,4-tetrametilciclobutil]piridazina-3-carboxamida	(m, 1H), 4,41 - 4,30 (m, 2H), 4,23 - 4,09 (m, 1H), 4,04 - 3,96 (m, 1H), 3,86 - 3,67 (m, 1H), 3,62 - 3,53 (m, 1H), 3,26 - 3,22 (m, 1H), 3,18 - 3,05 (m, 3H), 2,92 - 2,81 (m, 3H), 2,80 - 2,69 (m, 2H), 2,12 - 2,07 (m, 1H), 2,02 - 1,88 (m, 1H), 1,80 - 1,70 (m, 1H), 1,65 - 1,50 (m, 1H), 1,25 - 1,20 (m, 1H).	
115	6-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]piridina-3-carboxamida	1,24 (d, J=15,38 Hz, 12 H) 1,81 - 1,90 (m, 4 H) 1,94 - 2,01 (m, 1 H) 2,02 - 2,13 (m, 6 H) 2,18 (s, 1 H) 2,20 - 2,31 (m, 1 H) 2,74 - 2,92 (m, 6 H) 3,01 - 3,10 (m, 2 H) 3,19 - 3,34 (m, 1 H) 3,63 - 3,93 (m, 4 H) 3,96 (d, J=1,88 Hz, 3 H) 4,05 (s, 1 H) 4,10 - 4,35 (m, 5 H) 4,39 - 4,52 (m, 2 H) 4,62 - 4,85 (m, 1 H) 6,06 (d, J=8,13 Hz, 1 H) 6,37 - 6,58 (m, 1 H) 6,67 - 6,70 (m, 1 H) 6,81 (dd, J=8,76, 2,38 Hz, 1 H) 6,86 - 6,91 (m, 1 H) 6,96 - 7,09 (m, 2 H) 7,38 - 7,44 (m, 1 H) 7,60 (s, 2 H) 7,92 (dd, J=9,01, 2,50 Hz, 1 H) 8,50 - 8,62 (m, 1 H)	1002,6
116	4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,70H NMR (8,9 Hz, DMSO-d6) δ 7,53 (d, J = 8,8 Hz, 1H), 7,10 - 7,01 (m, 1H), 6,99 (d, J = 2,4 Hz, 1H), 6,94 (d, J = 9,0 Hz, 2H), 6,92 - 6,88 (m, 3H), 6,83 - 7,38 (m, 1H), 6,72 - 6,38 (m, 1H), 6,12 (d, J = 8,3 Hz, 1H) 4,87 - 4,69 (m, 1H), 4,21 - 4,12 (m, 1H), 3,98 (t, J = 2,0 Hz, 1H), 3,91 - 4,19 (m, 1H), 3,83 (br s, 1H), 3,35 (br d, J =11,2 Hz, 1H), 2,97 - 2,72 (m, 2H), 2,35 - 2,22 (m, 1H), 2,16 - 2,04 (m, 1H), 2,04 - 1,93 (m, 1H), 1,92-1,81 (m, 1H), 1,26 (d, J = 17,4 Hz,	1001,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		3H), 0,91 (d, J = 7,4 Hz, 2H).	
117	6-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]piridazina-3-carboxamida	δ 8,16 (d, J = 9,2 Hz, 1H), 7,97-7,71 (m, 2H), 7,59-7,52 (m, 2H), 7,41 (d, J = 6,0 Hz, 1H), 6,80 (s, 1H), 6,38 (s, 1H), 4,52 (brs, 1H), 3,63 (s, 2H), 3,99 (brs, 2H), 3,98-3,80 (m, 2H), 3,66 (s, 3H), 3,21-2,95 (m, 2H), 2,94-2,63 (m, 2H), 2,34-1,85 (m, 16H), 1,29-1,21 (m, 2H).	989,6
118	2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1,22 (s, 6 H) 1,26 (s, 6 H) 1,95 - 2,13 (m, 7 H) 2,13 - 2,28 (m, 3 H) 2,75 (br t, *J*=5,50 Hz, 1 H) 2,77 - 2,96 (m, 4 H) 3,23 (br t, *J*=12,69 Hz, 1 H) 3,64 - 3,84 (m, 5 H) 3,96 (d, *J*=2,25 Hz, 3 H) 4,05 (s, 1 H) 4,10 - 4,29 (m, 4 H) 4,38 - 4,55 (m, 4 H) 4,65 - 4,79 (m, 1 H) 5,96 (d, *J*=8,13 Hz, 1 H) 6,37 - 6,71 (m, 1 H) 6,81 (dd, *J*=8,69, 2,44 Hz, 1 H) 6,86 - 6,89 (m, 1 H) 6,96 - 7,07 (m, 2 H) 7,39 - 7,43 (m, 1 H) 7,52 - 7,60 (m, 2 H) 8,71 (s, 2 H).	975,5
119	2-[4-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidina-1-carbonil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,5-7,6 (m, 2H), 7,42 (d, 1H, J=6,4 Hz), 7,06 (d, 1H, J=21,6 Hz), 6,9-7,0 (m, 2H), 6,81 (dd, 1H, J=2,4, 8,8 Hz), 6,55 (dt, 1H, J=11,1, 55,6 Hz), 5,96 (d, 1H, J=8,4 Hz), 4,9-5,0 (m, 1H), 4,7-4,9 (m, 3H), 4,60 (t, 1H, J=8,4 Hz), 4,4-4,5 (m, 2H), 4,2-4,3 (m, 1H), 4,1-4,2 (m, 2H), 4,05 (s, 1H), 3,97 (d, 3H, J=2,1 Hz), 3,6-4,0 (m, 4H), 3,0-3,2 (m, 2H), 2,8-3,0 (m, 2H), 2,7-2,8 (m, 2H), 2,4-2,6 (m, 1H), 2,0-2,2 (m, 5H), 1,7-1,9 (m, 4H), 1,24 (d, 12H, J=14,4 Hz)	975,7
120	2-[4-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-	$_1$H NMR (400 MHz, DMSO-d*6*) δ = 8,75 (s, 1H), 7,89 - 8,11 (m, 1H), 7,76 - 7,75	966,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(m, 2H), 7,52 - 7,21 (m, 2H), 6,99 - 7,28 (m, 1H), 7,28 - 7,13 (m, 2H), 4,75 - 4,73 (m, 1H), 4,50 - 4,49 (m, 1H), 4,28 - 4,02 (m, 2H), 3,84 - 4,97 (m, 1H), 3,74 - 3,71 (m, 1H), 3,53 - 3,52 (m, 1H), 3,18 - 3,17 (m, 1H), 2,85 - 2,84 (m, 1H), 2,74 - 2,73 (m, 4H), 2,15 - 2,99 (m, 3H), 2,07 - 2,06 (m, 2H), 1,95 - 1,91 (m, 1H), 1,73 - 1,72 (m, 1H), 1,50 - 1,49 (m, 1H), 1,21 - 6 (m, 1H), 1,22 - 6 (m, 1H).	
122	2-[4-[4-[5-acetil-3-[7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 8,75 (s, 2H), 7,89 (d, *J* = 8,8 Hz, 1H), 7,71 (d, *J* = 9,2 Hz, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,11 (d, *J* = 7,2 Hz, 1H), 7,03 - 6,98 (m, 1H), 6,97 - 6,65 (m, 2H), 6,65 - 6,60 (m, 1H), 4,74 (br d, *J* = 12,4 Hz, 2H), 4,55 - 4,43 (m, 1H), 4,40 - 4,31 (m, 1H), 4,28 (s, 1H), 4,21 - 4,07 (m, 3H), 4,03 (d, *J* = 8,8 Hz, 1H), 3,80 - 3,66 (m, 2H), 3,61 - 3,51 (m, 2H), 3,25 - 3,20 (m, 1H), 3,13 - 2,99 (m, 3H), 2,87 (br t, *J* = 6,0 Hz, 1H), 2,81 (br t, *J* = 5,6 Hz, 2H), 2,78 - 2,65 (m, 2H), 2,07 (s, 2H), 2,00 - 1,82 (m, 6H), 1,73 (br d, *J* = 12,2 Hz, 3H), 1,58 - 1,41 (m, 2H), 1,21 (s, 6H), 1,10 (s, 6H)	923,4
127	2-[4-[4-[5-acetil-3-(6-ciano-3,4-dihidro-2H-quinolin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	620, *8,74*H NMR (400 MHz, DMSO-d*6*) δ = 7,31 - 7,27 (m, 1H), 7,25 - 7,17 (m, 1H), 6,97 - 8,22 (m, 1H), 6,79 - 6,82 (m, 1H), 6,47 - 6,39 (m, 3H), 5,98 - 5,99 (m, 2H), 4,87 (br d, *J* =13,2 Hz, 1H), 4,81 - 4,70 (m, 1H), 4,33 - 4,26 (m, 1H), 4,22 - 4,09 (m, 1H), 4,05 – 4,83 (m, 1H), 3,98 - 3,88	898,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		(m, 1H), 3,81 - 3,59 (m, 1H), 3,32 - 3,19 (m, 3H), 3,14 - 3,03 (m, 1H), 2,90 - 2,80 (m, 3H), 2,79 (s, 1H), 2,70 (s, 2H), 2,25 - 2,16 (m, 1H), 1,98 - 1,83 (m, 1H), 1,26 - 1,22 (m, 1H).	
128	2-[4-[4-[5-acetil-3-(3,4-dihidro-2H-1,6-naftiridin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d6) δ = 8,76 (s, 2H), 8,14 (s, 1H), 8,06 (s, 1H), 7,98 - 7,93 (m, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,72 (d, *J* = 9,2 Hz, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,04 - 6,98 (m, 1H), 6,41 - 6,32 (m, 1H), 4,74 (br d, *J* = 12,8 Hz, 2H), 4,49 (br d, *J* = 11,2 Hz, 1H), 4,44 - 4,35 (m, 1H), 4,29 (s, 1H), 4,24 - 4,13 (m, 3H), 4,03 (d, *J* = 9,2 Hz, 1H), 3,81 - 3,71 (m, 2H), 3,65 - 3,58 (m, 2H), 3,23 (br s, 1H), 3,07 (br t, *J* = 11,6 Hz, 3H), 2,89 (br s, 1H), 2,82 - 2,74 (m, 3H), 2,73 - 2,66 (m, 1H), 2,09 (s, 2H), 2,03 - 1,89 (m, 6H), 1,73 (br d, *J* = 11,2 Hz, 3H), 1,57 - 1,42 (m, 2H), 1,21 (s, 6H), 1,11 (s, 6H)	874,4
129	2-[4-[4-[5-acetil-3-(3,4-dihidro-2H-quinolin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	620, 1H NMR (400 MHz, DMSO-d6) δ = 7,72 - 9,31 (m, 1H), 7,21 - 8,46 (m, 1H), 7,06 - 6,95 (m, 1H), 6,95 - 6,85 (m, 1H), 6,60 - 7,80 (m, 3H), 6,45 - 6,34 (m, 2H), 4,74 (br d, J =13,2 Hz, 1H), 4,55 - 4,44 (m, 1H), 4,40 - 4,24 (m, 1H), 4,22 - 4,12 (m, 1H), 4,11 – 3,98 (m, 1H), 3,81 - 3,64 (m, 1H), 3,58 - 3,48 (m, 1H), 3,26 - 3,16 (m, 3H), 3,14 - 3,01 (m, 1H), 2,89 - 2,65 (m, 3H), 2,07 (s, 1H), 1,83 (s, 2H), 1,74 - 2,78 (m, 1H), 1,59 - 1,42 (m, 1H), 1,21 - 1,11 (m, 1H).	873,4
150	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-	(DMSO-d6) δ = 8,74 (s, 2H), 8,14 (s, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,70 (d, *J* =	909,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	9,2 Hz, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,12 (d, *J* = 7,6 Hz, 1H), 7,04 - 6,98 (m, 1H), 6,98 - 6,59 (m, 3H), 4,73 (br d, *J* = 13,2 Hz, 2H), 4,29 (s, 1H), 4,15 - 3,98 (m, 4H), 3,78 - 3,65 (m, 2H), 3,61 - 3,55 (m, 2H), 2,97 (br t, *J* = 11,2 Hz, 4H), 2,87 - 2,79 (m, 3H), 2,21 (br d, *J* = 6,8 Hz, 2H), 2,14 - 1,91 (m, 10H), 1,83 (br t, *J* = 11,2 Hz, 5H), 1,21 (s, 6H), 1,11 (s, 6H), 1,06 - 0,97 (m, 2H)	
152	3-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-1,2,4-triazina-6-carboxamida	(DMSO-d_6) δ = 8,71 (s, 1H), 8,11 (d, *J* = 9,2 Hz, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,75 (s, 1H), 7,50 (s, 1H), 7,24 (d, *J* = 2,4 Hz, 1H), 7,10 (s, 1H), 7,06 - 6,99 (m, 1H), 6,95 - 6,63 (m, 2H), 4,96 - 4,53 (m, 2H), 4,44 (s, 1H), 4,24 - 4,10 (m, 2H), 4,07 - 3,96 (m, 2H), 3,87 (s, 3H), 3,79 - 3,66 (m, 2H), 3,63 - 3,56 (m, 2H), 3,17 - 3,05 (m, 2H), 2,99 - 2,90 (m, 2H), 2,89 - 2,71 (m, 4H), 2,19 (br d, *J* = 6,0 Hz, 2H), 2,09 - 1,82 (m, 14H), 1,22 (s, 6H), 1,17 - 1,06 (m, 8H)	990,7
155	2-[4-[[4-[5-acetil-3-(6-ciano-3,4-dihidro-2H-quinolin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(400 MHz, DMSO-d6, ppm) δ 8,18 (s, 1H), 7,29 (s, 1H), 7,25-7,16 (m, 3H), 6,97 (s, 1H), 6,88-6,72 (m, 1H), 6,49-4,30 (m, 3H), 4,30-5,94 (m, 3H), 4,01-4,85 (m, 1H), 4,37-4,09 (m, 3H), 4,07-3,87 (m, 1H), 3,81-3,62 (m, 1H), 3,19-2,69 (m, 1H), 2,42-2,14 (m, 7H), 2,12-2,01 (m, 1H), 2,00-1,73 (m, 1H), 1,25-1,22 (m, 3H), 1,20-1,13 (m, 3H).	884,6
157	2-[4-[[4-[5-acetil-3-(3,4-dihidro-2H-1,6-naftiridin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-	(DMSO-d6) δ = 8,81 (s, 2H), 8,21 (s, 1H), 8,10 (s, 1H), 8,02 - 7,94 (m, 2H), 7,76 (d, *J* = 9,2 Hz, 1H),	860,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	7,27 (d, *J* = 2,4 Hz, 1H), 7,09 - 7,04 (m, 1H), 6,46 - 6,36 (m, 1H), 4,80 (br d, *J* = 13,2 Hz, 2H), 4,35 (s, 1H), 4,28 - 4,23 (m, 2H), 4,14 - 4,06 (m, 2H), 3,82 (br t, *J* = 5,8 Hz, 1H), 3,77 (br t, *J* = 5,4 Hz, 1H), 3,72 - 3,60 (m, 3H), 3,07 - 2,99 (m, 4H), 2,92 (br t, *J* = 5,2 Hz, 1H), 2,87 - 2,81 (m, 2H), 2,27 (br d, *J* = 6,8 Hz, 2H), 2,18 - 2,00 (m, 9H), 1,96 - 1,83 (m, 5H), 1,27 (s, 6H), 1,17 (s, 6H), 1,13 - 1,03 (m, 2H)	
158	2-[4-[[4-[5-acetil-3-(3,4-dihidro-2H-quinolin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (500 MHz, DMSO-d6) δ = 8,58 (s, 1H), 7,08 - 6,88 (m, 2H), 6,87 - 6,77 (m, 1H), 6,70 - 6,50 (m, 3H), 7,71 - 5,93 (m, 1H), 4,95 - 4,78 (m, 2H), 4,04 - 4,03 (m, 1H), 4,30 - 4,02 (m, 1H), 5,65 - 3,89 (m, 2H), 3,87 - 3,48 (m, 1H), 3,17 - 3,03 (m, 1H), 3,01 - 2,90 (m, 1H), 3,27 - 2,73 (m, 1H), 2,89 - 2,68 (m, 2H), 2,41 - 2,14 (m, 3H), 2,09 - 2,00 (m, 1H), 1,98 - 1,85 (m, 1H), 1,25 - 1,22 (m, 1H), 1,20 - 1,15 (m, 2H).	859,5
160	2-[4-[2-[3-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (500 MHz, DMSO-2H) δ = 7,62 - 7,34 (m, 1H), 7,06 - 6,93 (m, 2H), 7,82 - 6,81 (m, 1H), 7,72 - 2,4 (m, 1H), 6,42 (br d, J = 2,0 Hz, 1H), 5,93 (br d, J = 8,0 Hz, 1H), 4,92 - 4,77 (m, 1H), 4,27 - 3,99 (m, 1H), 3,95 - 7,06 (m, 1H), 3,88 - 5,44 (m, 3H), 3,77 - 3,60 (m, 2H), 2,95 - 4,02 (m, 1H), 2,88 - 2,66 (m, 1H), 2,28 - 2,20 (m, 3H), 2,16 - 2,01 (m, 1H), 1,84 - 1,79 (m, 1H), 1,68 (br s, 1H), 1,48 - 1,37 (m, 3H), 1,23 - 2,53 (m, 3H), 1,20 - 1,13 (m, 1H).	1108,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
161	2-[4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]etil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,63 - 7,51 (m, 2H), 7,42 (d, J = 5,6 Hz, 1H), 7,09 - 6,95 (m, 3H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,55 (dt, J = 8,4, 55,6 Hz, 1H), 5,93 (d, J = 8,4 Hz, 1H), 5,01 - 4,81 (m, 1H), 4,26 (s, 1H), 4,16 - 4,07 (m, 3H), 4,06 - 3,99 (m, 2H), 3,97 - 3,93 (m, 6H), 3,89 (br t, J = 5,6 Hz, 1H), 3,83 - 3,68 (m, 5H), 2,99 - 2,84 (m, 4H), 2,79 - 2,68 (m, 2H), 2,61 - 2,49 (m, 6H), 2,21 - 2,00 (m, 6H), 1,24 (d, J = 13,2 Hz, 12H)	488,9 ± 2
162	2-[4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d6) δ = 7,60 - 7,48 (m, 1H), 7,42 - 7,78 (m, 1H), 7,11 - 6,92 (m, 3H), 6,85 - 6,77 (m, 1H), 6,70 - 6,38 (m, 1H), 5,92 - 7,11 (m, 1H), 4,87 - 4,82 (m, 1H), 5,99 - 4,25 (m, 1H), 4,16 - -4,07 (m, 1H), 5,28 - 4,04 (m, 1H), 4,04 - 3,95 (m, 1H), 3,94 - 3,84 (m, 2H), 3,76 - 3,61 (m, 6H), 2,95 (s, 3H), 2,98 - 2,83 (m, 2H), 2,83 - 2,63 (m, 3H), 2,17 - 2,02 (m, 5H), 1,81 - 2,30 (m, 2H), 1,45 - 1,35 (m, 2H), 1,35 - 1,10 (m, 6H).	975,8
163	2-[4-[2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-oxo-etil]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	δ = 8,68 (s, 2H), 7,62 - 7,51 (m, 2H), 7,42 (d, J = 7,2 Hz, 1H), 7,06 (d, J = 22,0 Hz, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,90 (d, J = 4,8 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,55 (dt, J = 11,2, 55,6 Hz, 1H), 5,94 (br d, J = 8,4 Hz, 1H), 4,99 - 4,80 (m, 3H), 4,74 - 4,63 (m, 1H), 4,54 - 4,38 (m, 3H), 4,32 - 4,09 (m, 3H), 4,05 (s, 1H), 3,96 (d, J = 2,4 Hz, 4H), 3,83 - 3,67 (m, 3H), 3,02 - 2,85 (m, 4H), 2,81 - 2,67 (m, 2H), 2,25 - 2,04 (m,	989,6

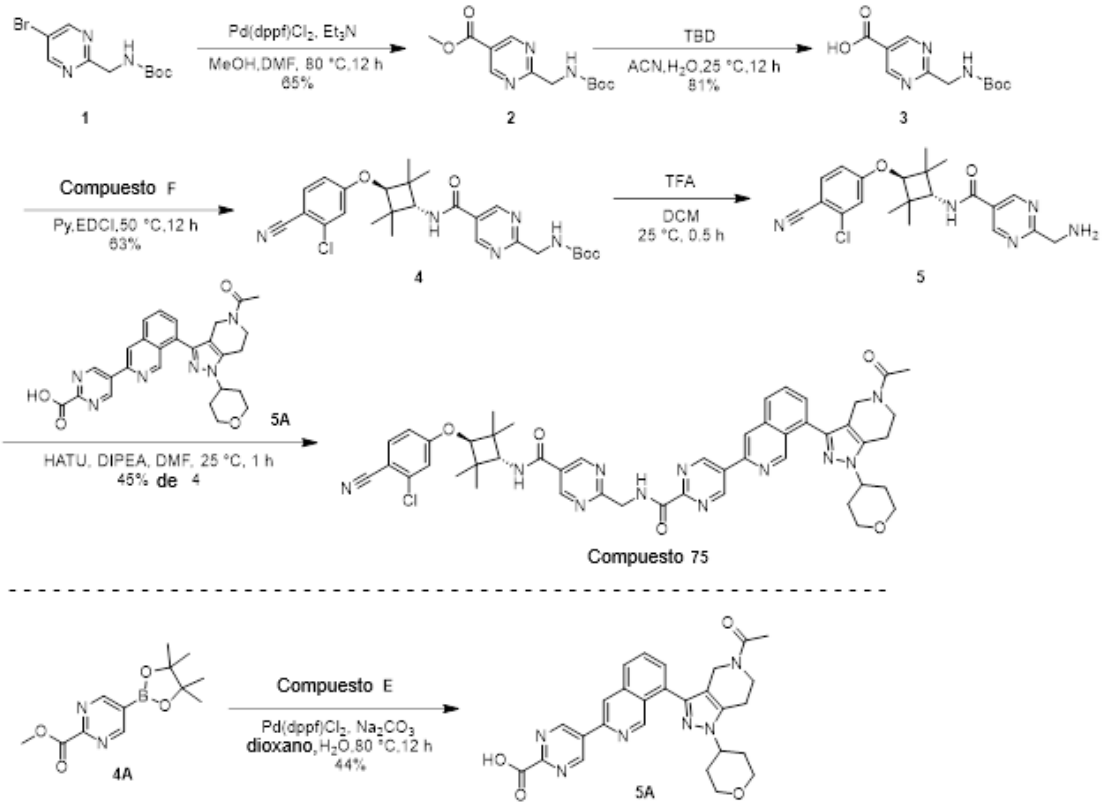
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		8H), 1,96 - 1,85 (m, 2H), 1,24 (d, J = 13,6 Hz, 14H)	
165	2-[4-[2-[3-[5-acetil-3-[2-fluoro-4-(1-metilpirazol-4-il)anilino]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]azetidin-1-il]-2-oxo-etil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ=8,70 (s, 2 H) 7,65 - 7,91 (m, 2 H) 7,53 - 7,60 (m, 2 H) 7,15 - 7,24 (m, 2 H) 6,97 (d, *J*=2,40 Hz, 1 H) 6,81 (dd, *J*=8,80, 2,40 Hz, 1 H) 6,02 (br t, *J*=7,60 Hz, 1 H) 5,81 - 5,94 (m, 1 H) 4,89 - 5,01 (m, 1 H) 4,77 - 4,88 (m, 1 H) 4,60 - 4,71 (m, 1 H) 4,41 - 4,59 (m, 3 H) 4,32 (s, 1 H) 4,14 (d, *J*=8,00 Hz, 1 H) 4,06 (s, 1 H) 4,01 (br d, *J*=3,20 Hz, 4 H) 3,94 (d, *J*=1,60 Hz, 3 H) 3,91 (br s, 1 H) 3,70 - 3,79 (m, 1 H) 3,27 (br d, *J*=6,40 Hz, 2 H) 2,75 (br d, *J*=4,80 Hz, 5 H) 2,68 (br t, *J*=5,60 Hz, 1 H) 2,14 - 2,24 (m, 3 H) 1,27 (s, 6 H) 1,22 (s, 6 H).	918,5
169	2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]propoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d6) δ = 7,50 (s, 1H), 7,40 - 8,11 (m, 1H), 7,07 - 6,94 (m, 2H), 6,90 - 6,77 (m, 2H), 6,71 - 7,28 (m, 1H), 7,28 - 5,89 (m, 2H), 4,29 - 4,17 (m, 1H), 4,16 - 4,09 (m, 1H), 5,55 - 4,05 (m, 2H), 4,00 - 3,93 (m, 1H), 3,92 - 3,86 (m, 1H), 3,77 - 3,55 (m, 1H), 3,54 - 3,43 (m, 1H), 3,24 - 2,92 (m, 1H), 2,91 - 2,78 (m, 3H), 2,77 - 2,71 (m, 1H), 2,67 - 2,47 (m, 2H), 2,30 - 2,13 (m, 1H), 2,11 - 1,96 (m, 1H), 1,95 - 1,84 (m, 1H), 1,60 - 1,36 (m, 1H), 1,25 - 1,22 (m, 1H).	1033,7
170	2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-	*δ* = 8,70 (d, J = 2,4 Hz, 2H), 7,57 (d, J = 8,8 Hz, 1H), 7,53 (d, J = 6,0 Hz, 1H), 7,40 (d, J = 6,8 Hz, 1H), 7,07 - 6,98 (m, 1H), 6,96 (d, J = 2,4 Hz, 1H), 6,91 - 6,83 (m, 1H), 6,80 (dd, J = 2,4, 8,8 Hz, 1H), 6,69 - 6,36 (m, 1H), 6,05 - 5,90 (m, 1H),	1019,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	5-carboxamida	4,31 - 4,14 (m, 3H), 4,13 - 3,99 (m, 3H), 3,95 (d, J = 2,0 Hz, 3H), 3,89 (br t, J = 5,6 Hz, 1H), 3,75 - 3,67 (m, 4H), 3,66 - 3,54 (m, 3H), 3,32 - 3,12 (m, 2H), 2,93 - 2,68 (m, 6H), 2,54 - 2,35 (m, 2H), 2,32 - 2,23 (m, 2H), 2,17 - 2,00 (m, 9H), 1,93 (ddd, J = 3,2, 6,4, 9,6 Hz, 2H), 1,64 (dtd, J = 4,0, 8,4, 12,4 Hz, 2H), 1,23 (d, J = 14,4 Hz, 12H).	
171	2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]propil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6):δ = 8,74 (s, 2H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,74 (s, 1H), 7,69 (br d, *J* = 9,2 Hz, 1H), 7,49 (s, 1H), 7,21 (d, *J* = 2,0 Hz, 1H), 7,10 (s, 1H), 7,04 - 6,97 (m, 1H), 6,95 - 6,61 (m, 2H), 4,71 (br d, *J* = 12,4 Hz, 2H), 4,28 (s, 1H), 4,20 - 4,10 (m, 2H), 4,08 - 3,95 (m, 2H), 3,86 (s, 3H), 3,78 - 3,65 (m, 2H), 3,63 - 3,54 (m, 2H), 3,10 - 2,78 (m, 8H), 2,72 (br s, 1H), 2,14 - 1,66 (m, 13H), 1,55 - 1,44 (m, 1H), 1,31 - 0,88 (m, 19H).	1017,8
172	2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 8,73 (s, 2H), 7,90 (d, J = 8,8 Hz, 1H), 7,75 (s, 1H), 7,69 (d, J = 9,2 Hz, 1H), 7,49 (s, 1H), 7,21 (d, J = 2,4 Hz, 1H), 7,10 (s, 1H), 7,00 (d, J = 2,3, 8,8 Hz, 1H), 6,95 - 6,62 (m, 2H), 4,71 (d, J = 12,8 Hz, 2H), 4,55 - 4,46 (m, 1H), 4,39 - 4,26 (m, 2H), 4,15 (d, J = 19,2 Hz, 2H), 4,07 - 3,96 (m, 2H), 3,86 (s, 3H), 3,79 - 3,66 (m, 2H), 3,62 - 3,54 (m, 2H), 3,24 - 3,11 (m, 1H), 3,04 - 2,93 (m, 2H), 2,89 - 2,80 (m, 3H), 2,79 - 2,64 (m, 2H), 2,32 (d, J = 7,2 Hz, 2H), 2,08 (s, 3H), 2,00 - 1,84 (m, 6H), 1,82 - 1,68 (m, 3H), 1,21 (s, 6H), 1,11 (s, 7H)	1017,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
173	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]metoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(400 MHz, DMSO-d_6, ppm) δ 8,76 (s, 1H), 7,90 (s, 1H), 7,77-7,68 (m, 3H), 7,49 (s, 1H), 7,21-7,09 (m, 1H), 7,04-4,30 (m, 3H), 4,30-6,58 (m, 3H), 4,29-4,14 (m, 1H), 4,06-3,93 (m, 2H), 3,86-3,15 (m, 1H), 3,80-3,65 (m, 1H), 3,62-3,47 (m, 1H), 2,90-2,70 (m, 4H), 2,07-1,73 (m, 1H), 1,63-1,51 (m, 1H), 1,50-1,39 (m, 3H), 1,25-1,05 (m, 3H).	1004,7
174	2-[4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (500 MHz, DMSO-d6) δ = 7,44 - 7,37 (m, 1H), 7,08 - 6,95 (m, 2H), 6,91 - 6,84 (m, 1H), 6,81 - 7,64 (m, 1H), 6,35 (br d, J = 8,0 Hz, 1H), 4,84 (br d, J = 13,2 Hz, 1H), 4,30 - 4,09 (m, 1H), 3,98 - 3,88 (m, 1H), 3,82 - 3,58 (m, 1H), 3,09 - 5,44 (m, 3H), 3,00 - 2,77 (m, 2H), 2,75 - 4,02 (m, 1H), 2,53 - 2,41 (m, 1H), 2,32 - 2,23 (m, 3H), 2,17 - 2,13 (m, 1H), 2,11 - 2,04 (m, 1H), 1,95 (br s, 1H), 1,88 - 1,78 (m, 3H), 1,53 - 1,45 (m, 3H), 1,25 - 1,22 (m, 1H).	1003,6
175	2-[4-[2-[4-[5-acetil-3-[7-cloro-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	7,70 (d, J = 6,3 Hz, 1H), 7,57 (d, J = 8,1 Hz, 1H), 7,15 (d, J = 2,0 Hz, 1H), 6,96 (d, J = 8,6 Hz, 1H), 6,81 (dd, J = 2,4, 8,6 Hz, 1H), 5,94 (d, J = 8,1 Hz, 1H), 4,86 (d, J = 13,2 Hz, 1H), 4,77 (s, 4H), 4,02 (s, 4H), 3,97 - 3,76 (m, 2H), 3,70 - 3,58 (m, 1H), 3,26 - 3,14 (m, 1H), 2,99 (br d, J = 11,6 Hz, 1H), 2,88 - 2,71 (m, 5H), 2,34 - 2,27 (m, 2H), 2,26 - 2,16 (m, 3H), 2,11 (br t, J = 10,5 Hz, 1H), 1,25 (d, J = 6,0 Hz, 7H).	1001,5
176	2-[4-[2-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-	δ=8,70 (s, 2 H) 7,58 (d, *J*=8,80 Hz, 1 H) 7,52 - 7,56 (m, 1 H) 7,35 - 7,40 (m, 1	981,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-oxo-etil]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	H) 6,94 - 7,03 (m, 2 H) 6,81 (dd, *J*=8,80, 2,40 Hz, 1 H) 6,35 - 6,40 (m, 1 H) 5,93 (d, *J*=8,40 Hz, 1 H) 4,87 (br d, *J*=12,80 Hz, 2 H) 4,70 - 4,80 (m, 1 H) 4,28 (s, 1 H) 4,10 - 4,16 (m, 3 H) 4,04 (s, 2 H) 3,93 - 3,96 (m, 3 H) 3,88 - 3,93 (m, 1 H) 3,76 (br t, *J*=5,20 Hz, 1 H) 3,58 - 3,70 (m, 2 H) 3,13 - 3,27 (m, 1 H) 3,00 (br t, *J*=11,60 Hz, 2 H) 2,63 - 2,91 (m, 5 H) 2,28 - 2,35 (m, 2 H) 2,23 (s, 3 H) 2,19 (br d, *J*=12,80 Hz, 3 H) 2,08 (br d, *J*=3,20 Hz, 1 H) 2,00 - 2,05 (m, 4 H) 1,89 - 1,98 (m, 3 H) 1,60 - 1,67 (m, 2 H) 1,25 (s, 6 H) 1,22 (s, 6 H).	
188	2-[[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]triazol-1-il]metil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 9,09 (s, 2H), 8,25 (d, *J* = 9,2 Hz, 1H), 8,11 (s, 1H), 7,89 (d, *J* = 8,8 Hz, 1H), 7,74 (s, 1H), 7,49 (s, 1H), 7,22 (d, *J* = 2,4 Hz, 1H), 7,09 (s, 1H), 7,05 - 6,99 (m, 1H), 6,96 - 6,62 (m, 2H), 5,92 (s, 2H), 4,29 (s, 1H), 4,20 - 4,10 (m, 2H), 4,08 - 3,97 (m, 2H), 3,86 (s, 3H), 3,76 - 3,66 (m, 2H), 3,64 (s, 2H), 3,61 - 3,55 (m, 2H), 3,02 - 2,91 (m, 2H), 2,89 - 2,70 (m, 4H), 2,16 (br t, *J* = 11,6 Hz, 2H), 2,07 (s, 2H), 2,03 - 1,91 (m, 5H), 1,89 - 1,81 (m, 2H), 1,21 (s, 6H), 1,11 (s, 6H)	987,4

[00547] Ejemplo 19: Síntesis de 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-N-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metil]pirimidina-2-carboxamida (**Compuesto 75**)



[00548] La síntesis de **3A** fue reportada en US2018/99940 A1.

[00549] La síntesis de **4A** fue reportada en EP3412669 A1.

[00550] A una solución de N-[(5-bromopirimidin-2-il)metil]carbamato de ter-butilo (500 mg, 1,74 mmol, 1,0 eq), Et_3N (878 mg, 8,68 mmol, 1,21 ml, 5,0 eq) en MeOH (5 ml), DMF (5 ml) se agregó $Pd(dppf)Cl_2$ (254 mg, 347 µmol, 0,2 eq) bajo N_2. La suspensión se desgasificó y se purgó con H2 3 veces. La mezcla de reacción se agitó a 50 oC durante 12 h. La mezcla de reacción se inactivó con agua (20 ml) y se extrajo con acetato de etilo (20 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 0/1). El compuesto metil 2-[(tert-butoxicarbonilamino)metil]pirimidina-5-carboxilato (300 mg, 1,12 mmol, 65 % de rendimiento) se obtuvo como un sólido blanco.

[00551] ^{1}H NMR (400 MHz, CLOROFORMO-d) δ = 9,24 - 5,67 (m, 2H), 4,68 (s, 2H), 3,99 (s, 3H), 1,49 (s, 3H)

[00552] **LC-MS:** MS (ESI^+): t_R = 0,453 min, m/z = 168,0 [M - 100]

[00553] A una solución de N-[(5-bromopirimidin-2-il)metil]carbamato de ter-butilo (500

mg, 1,74 mmol, 1,0 eq), Et_3N (878 mg, 8,68 mmol, 1,21 ml, 5,0 eq) en MeOH (5 ml), DMF (5 ml) se agregó $Pd(dppf)Cl_2$ (254 mg, 347 µmol, 0,2 eq) bajo N_2. La suspensión se desgasificó y se purgó con H2 3 veces. La mezcla de reacción se agitó a 50 oC durante 12 h. La mezcla de reacción se inactivó con agua (20 ml) y se extrajo con acetato de etilo (20 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 0/1). El compuesto metil 2-[(tert-butoxicarbonilamino)metil]pirimidina-5-carboxilato (300 mg, 1,12 mmol, 65 % de rendimiento) se obtuvo como un sólido blanco.

[00554] ^{1}H NMR (400 MHz, CLOROFORMO-d) δ = 9,24 - 5,67 (m, 2H), 4,68 (s, 2H), 3,99 (s, 3H), 1,49 (s, 3H)

[00555] **LC-MS:** MS (ESI^+): t_R = 0,453 min, m/z = 168,0 [M - 100]

[00556] A una solución de ácido 2-[(tert-butoxicarbonilamino)metil]pirimidina-5-carboxílico (210 mg, 829 µmol, 1,0 eq), 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (325 mg, 829 µmol, 1,0 eq) en Py (5 ml) se le agregó EDCI (476 mg, 2,49 mmol, 3,0 eq). La mezcla se agitó a 50 °C durante 12 h. La mezcla de reacción se concentró al vacío para obtener el producto crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 0/1). El compuesto ter-butil N-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metil]carbamato (270 mg, 525,28 µmol, 63 % de rendimiento) se obtuvo como un sólido blanco.

[00557] ^{1}H NMR (400 MHz, DMSO-d6) δ 7,58 (br. s, 1H), 6,98 (d, J = 2,4 Hz, 1H), 6,82 (d, J = 8,4 Hz, 1H), 6,17 (dd, J = 5,63, 2,1 Hz, 1H), 4,66 (d, J = 5,2 Hz, 1H), 4,17 (d, J = 8,4 Hz, 1H), 4,08 (s, 1H), 1,49 (s, 9H), 1,27 (s, 12H).

[00558] **LC-MS:** MS (ESI^+): t_R = 0,597 min, m/z = 458,1 [M - 55]

[00559] A una solución de N-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metil]carbamato de ter-butilo (45 mg, 87,55 µmol, 1,0 eq) en DCM (3 ml) se le agregó TFA (767 mg, 6,73 mmol, 0,5 ml, 76 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se concentró al vacío para obtener el producto crudo. El compuesto 2-(aminometil)-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (42 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[00560] **LC-MS:** MS (ESI^+): t_R = 0,473 min, m/z = 414,1 [$M + H^+$]

[00561] A una solución de ácido 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-

pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirimidina-2-carboxílico (41 mg, 83,35 µmol, 1,0 eq), 2-(aminometil)-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (42 mg, 83,35 µmol, 1,0 eq) en DMF (3 ml) se le agregó DIPEA (53 mg, 416 µmol, 72 µl, 5,0 eq) y HATU (47 mg, 125 µmol, 1,5 eq). La mezcla se agitó a 25 °C durante 1 hora. La mezcla de reacción se concentró al vacío para obtener el producto crudo. El residuo se purificó mediante HPLC preparativa (condición FA; columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua(FA)-ACN]; gradiente: 55 %-75 % B durante 15 min). El compuesto 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-N-[[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]metil]pirimidina-2-carboxamida (34,22 mg, 38,26 µmol, 45 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00562] **^{1}H NMR** (400 MHz, CLOROFORMO-*d*):δ = 9,91 (s, 1H), 9,65 (d, J = 4,8 Hz, 2H), 9,19 - 9,11 (m, 3H), 8,24 (d, J = 9,6 Hz, 1H), 8,03 (s, 1H), 7,97 (dd, J = 8,8, 14,4 Hz, 1H), 7,83 (td, J = 7,6, 11,6 Hz, 1H), 7,66 (dd, J = 7,2, 18,0 Hz, 1H), 7,59 (d, J = 8,8 Hz, 1H), 6,98 (d, J = 2,4 Hz, 1H), 6,82 (dd, J = 2,4, 8,8 Hz, 1H), 6,24 (br d, J = 7,2 Hz, 1H), 5,10 (d, J = 5,2 Hz, 2H), 4,68 (s, 1H), 4,52 (s, 1H), 4,38 - 4,26 (m, 1H), 4,19 (br d, J = 8,0 Hz, 3H), 4,09 (s, 1H), 4,04 (br t, J = 5,6 Hz, 1H), 3,87 (t, J = 6,0 Hz, 1H), 3,59 (br t, J = 12,4 Hz, 2H), 3,01 - 2,81 (m, 2H), 2,58 - 2,34 (m, 2H), 2,25 - 2,07 (m, 3H), 2,03 - 1,96 (m, 2H), 1,28 (d, J = 17,6 Hz, 12H)

[00563] **LC-MS:** MS (ESI$^+$): t_R = 2,372 min, m/z = 894,5 [M + H$^+$]

[00564] Preparación de **5A**

[00565] Una mezcla de [8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil] trifluorometanosulfonato (100 mg, 190 µmol, 1,0 eq), 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirimidina-2-carboxilato de metilo (60 mg, 228 µmol, 1,2 eq), $Pd(dppf)Cl_2$ (6,98 mg, 9,53 µmol, 0,05 eq), Na_2CO_3 (60 mg, 571 µmol, 3,0 eq) y en dioxano (3 ml), agua (0,3 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 80 °C durante 12 h bajo N_2. La mezcla de reacción se concentró al vacío para obtener el producto crudo. El residuo se purificó mediante TLC preparativa (SiO_2, diclorometano: metanol =10:1).El residuo se purificó mediante HPLC preparativa (condición de HCl; columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(HCl)-ACN]; gradiente: 15 %-45 % B durante 10 min). El compuesto ácido 5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirimidina-2-carboxílico (42 mg, 84,25 µmol, 44 % de rendimiento) se obtuvo como un sólido blanco.

[00566] ^{1}H NMR (400 MHz, DMSO-**d**6) δ = 10,06 - 9,73 (m, 1H), 8,83 (br t, J = 8,4 Hz,

1H), 8,01 - 7,92 (m, 3H), 7,83 - 7,67 (m, 3H), 4,59 (br t, J = 8,3 Hz, 1H), 4,52 - 4,44 (m, 1H), 4,04 - 4,01 (m, 3H), 3,58 - 3,48 (m, 3H), 2,98 - 3,13 (m, 1H), 2,86 - 2,82 (m, 1H), 2,23 - 2,08 (m, 4H), 2,05 - 1,92 (m, 3H).

[00567] **LC-MS:** MS (ESI$^+$): t_R = 0,424 min, m/z = 499,2 [M + H$^+$]

[00568] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en los ejemplos 12, 13, 14 y 19.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
72	2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]oximetil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,7-10,0 (m, 1H), 9,09 (d, 2H, J=3,6 Hz), 8,6-8,8 (m, 1H), 8,35 (ddd, 1H, J=2,4, 8,6, 18,8 Hz), 8,02 (s, 1H), 7,9-7,9 (m, 1H), 7,7-7,8 (m, 1H), 7,5-7,7 (m, 2H), 7,12 (d, 1H, J=8,8 Hz), 6,97 (d, 1H, J=2,0 Hz), 6,81 (dd, 1H, J=2,4, 8,8 Hz), 6,1-6,3 (m, 1H), 5,77 (s, 2H), 4,67 (s, 1H), 4,50 (s, 1H), 4,2-4,4 (m, 1H), 4,16 (br d, 3H, J=8,8 Hz), 4,0-4,1 (m, 2H), 3,85 (t, 1H, J=5,6 Hz), 3,57 (br t, 2H, J=12,4 Hz), 2,8-3,0 (m, 2H), 2,44 (dq, 2H, J=4,7, 12,4 Hz), 2,22 (s, 1H), 2,08 (s, 1H), 1,97 (br d, 2H, J=12,0 Hz), 1,26 (d, 13H, J=15,6 Hz)	866,5
74	2-[2-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirimidin-2-il]etil-metil-amino]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d6) δ = 9,99 (s, 1 H) 9,47 (s, 2 H) 8,72 (s ancho, 2 H) 8,63 (s, 1 H) 8,03 (d, J=8,00 Hz, 1 H) 7,84 - 7,96 (m, 2 H) 7,60 - 7,76 (m, 2 H) 7,19 (d, J=2,40 Hz, 1 H) 6,97 (dd, J=8,80, 2,40 Hz, 1 H) 4,57 (s, 2 H) 4,39 - 4,53 (m, 1 H) 4,23 (s, 1 H) 4,18 (t ancho, J=7,20 Hz, 2 H) 3,96 - 4,04 (m, 3 H) 3,79 - 3,88 (m, 2 H) 3,53 (br t, J=12,00 Hz, 2 H) 3,35 - 3,36 (m, 1 H) 3,28 (br s, 2 H) 3,17 (s, 3 H) 2,94 - 3,00 (m, 1 H) 2,12 - 2,23 (m, 2 H) 2,11 (s, 2 H) 2,01 (s, 1 H) 1,95 (br dd, J=7,20, 4,80 Hz, 2 H) 1,14 (s, 6 H) 1,05 (s, 6 H).	894,5
77	2-[3-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-	δ = 9,89 (d, J = 10,8 Hz, 1H), 9,28 (br d, J = 10,4 Hz,	921,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]propil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H), 9,05 (s, 2H), 8,58 (td, J = 2,4, 8,0 Hz, 1H), 8,36 - 8,25 (m, 2H), 8,20 (d, J = 7,2 Hz, 1H), 7,94 (dd, J = 8,4, 12,0 Hz, 1H), 7,80 (q, J = 8,0 Hz, 1H), 7,67 - 7,59 (m, 1H), 7,56 (dd, J = 1,2, 8,8 Hz, 1H), 6,96 (s, 1H), 6,79 (br d, J = 8,8 Hz, 1H), 6,22 (br d, J = 8,0 Hz, 1H), 4,72 - 4,47 (m, 2H), 4,36 - 4,25 (m, 1H), 4,22 - 4,12 (m, 3H), 4,08 - 4,00 (m, 2H), 3,87 (br t, J = 5,6 Hz, 1H), 3,67 - 3,53 (m, 4H), 3,21 (t, J = 7,2 Hz, 2H), 2,99 - 2,84 (m, 2H), 2,51 - 2,39 (m, 2H), 2,31 - 2,23 (m, 2H), 2,23 - 2,07 (m, 3H), 1,98 (br d, J = 13,2 Hz, 2H), 1,29 - 1,19 (m, 12H).	
78	2-[2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]etil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,86 (s, 1 H) 9,29 (dd, *J*=7,20, 1,60 Hz, 1 H) 9,08 (s, 2 H) 8,70 (br d, *J*=4,40 Hz, 1 H) 8,51 - 8,59 (m, 1 H) 8,29 (dd, *J*=8,00, 3,20 Hz, 1 H) 8,16 (d, *J*=10,80 Hz, 1 H) 7,91 (dd, *J*=14,00, 8,40 Hz, 1 H) 7,79 (dt, *J*=11,60, 7,60 Hz, 1 H) 7,59 - 7,66 (m, 1 H) 7,58 (d, *J*=8,80 Hz, 1 H) 6,98 (d, *J*=2,40 Hz, 1 H) 6,81 (dd, *J*=8,80, 2,40 Hz, 1 H) 6,30 - 6,41 (m, 1 H) 4,67 (s, 1 H) 4,51 (s, 1 H) 4,25 - 4,37 (m, 1 H) 4,12 - 4,22 (m, 3 H) 3,98 - 4,11 (m, 4 H) 3,86 (br t, *J*=5,60 Hz, 1 H) 3,58 (br t, *J*=12,00 Hz, 2 H) 3,42 (br t, *J*=6,00 Hz, 2 H) 2,83 - 2,99 (m, 2 H) 2,45 (br d, *J*=12,00 Hz, 2 H) 2,05 - 2,26 (m, 3 H) 1,92 - 2,03 (m, 2 H) 1,30 (s, 6 H) 1,25 (s, 6 H).	907,6
79	2-[[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]metil]-N-[3-	9,88H NMR (3,6 Hz, DMSO-d6) δ = 9,18 - 9,05 (m, 1H), 8,62 (d, J = 8,0 Hz, 1H), 8,36 (s, 1H), 7,83 - 3,2 (m, 2H), 8,20 - 7,56 (m, 1H), 7,94 (dd, J = 8,0, 13,2 Hz,	893,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H), 7,37 - 7,85 (m, 1H), 7,69 - 7,54 (m, 1H), 6,98 (d, J = 2,4 Hz, 1H), 6,81 - 6,68 (m, 1H), 6,18 (br d, J = 7,2 Hz, 1H), 5,06 (d, J = 5,6 Hz, 1H), 4,68 - 4,52 (m, 1H), 4,37 - 4,26 (m, 1H), 4,18 - 4,43 (m, 1H), 4,11 - 3,98 (m, 1H), 3,87 - 3,59 (m, 2H), 2,99 - 2,93 (m, 1H), 2,88 - 2,73 (m, 1H), 2,56 - 2,39 (m, 1H), 2,28 - 2,06 (m, 1H), 2,04 - 1,94 (m, 1H), 1,29 - 1,25 (m, 1H)	
131	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[[rac-(3S)-1-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]pirrolidin-3-il]oximetil]pirimidina-5-carboxamida	δ=9,84 - 9,90 (m, 1 H) 9,29 - 9,37 (m, 1 H) 9,13 (s, 1 H) 9,09 (s, 1 H) 8,50 - 8,58 (m, 1 H) 8,14 - 8,21 (m, 1 H) 7,88 - 8,07 (m, 2 H) 7,79 (dt, *J*=12,00, 7,60 Hz, 1 H) 7,54 - 7,66 (m, 2 H) 6,97 (s, 1 H) 6,80 (br d, *J*=8,80 Hz, 1 H) 6,19 - 6,46 (m, 1 H) 4,85 - 4,95 (m, 1 H) 4,75 - 4,83 (m, 1 H) 4,67 (s, 1 H) 4,52 (s, 1 H) 4,43 (br d, *J*=3,20 Hz, 1 H) 4,24 - 4,36 (m, 1 H) 4,10 - 4,22 (m, 4 H) 4,01 - 4,09 (m, 3 H) 3,81 - 3,99 (m, 3 H) 3,58 (br t, *J*=12,00 Hz, 2 H) 2,84 - 2,99 (m, 2 H) 2,38 - 2,53 (m, 2 H) 2,24 - 2,35 (m, 1 H) 2,22 (s, 1 H) 2,11 - 2,18 (m, 1 H) 2,09 (s, 2 H) 1,98 (br d, *J*=12,80 Hz, 2 H) 1,27 - 1,32 (m, 6 H) 1,24 (br d, *J*=5,20 Hz, 6 H).	482,4 $[M+H^+]$
137	2-[4-[[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 9,83 (s, 1H), 8,75 (s, 2H), 8,40 (s, 1H), 8,12 (d, J = 11,6 Hz, 2H), 7,93 - 7,86 (m, 2H), 7,83 - 7,76 (m, 1H), 7,72 (d, J = 8,8 Hz, 1H), 7,61 - 7,48 (m, 1H), 7,21 (d, J = 2,4 Hz, 1H), 7,00 (dd, J = 2,4, 8,8 Hz, 1H), 4,75 (br d, J = 13,6 Hz, 2H), 4,61 - 4,53 (m, 2H), 4,51 - 4,40 (m, 1H), 4,28 (s, 1H), 4,11 (br d, J = 6,4 Hz, 2H), 4,03 (br d, J = 9,2 Hz,	922,5

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		3H), 3,87 - 3,77 (m, 2H), 3,52 (br t, J = 11,2 Hz, 2H), 3,06 - 2,79 (m, 5H), 2,31 - 2,00 (m, 6H), 2,00 - 1,90 (m, 2H), 1,70 - 1,60 (m, 2H), 1,23 - 1,08 (m, 13H)	
138	2-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d6): δ = 9,81 (s, 1H), 8,71 (s, 2H), 8,40 (s, 1H), 8,12 (d, J = 12,8 Hz, 2H), 7,92 - 7,84 (m, 2H), 7,82 - 7,75 (m, 1H), 7,69 (br d, J = 9,2 Hz, 1H), 7,59 - 7,47 (m, 1H), 7,20 (d, J = 2,4 Hz, 1H), 6,99 (dd, J = 2,4, 8,8 Hz, 1H), 4,55 (br s, 2H), 4,50 - 4,41 (m, 1H), 4,34 (br t, J = 5,2 Hz, 2H), 4,27 (s, 1H), 4,16 - 4,07 (m, 2H), 4,01 (br d, J = 9,2 Hz, 3H), 3,89 (br t, J = 5,2 Hz, 2H), 3,86 - 3,78 (m, 2H), 3,66 - 3,59 (m, 1H), 3,53 - 3,45 (m, 4H), 2,98 - 2,81 (m, 2H), 2,18 - 2,01 (m, 5H), 1,95 (br d, J = 8,0 Hz, 2H), 1,83 (br d, J = 8,8 Hz, 2H), 1,44 - 1,34 (m, 2H), 1,21 - 1,06 (m, 12H).	952,5
139	2-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,6-10,0 (m, 1H), 8,69 (s, 2H), 8,09 (s, 1H), 7,7-8,0 (m, 3H), 7,4-7,7 (m, 2H), 6,97 (d, 1H, J=2,4 Hz), 6,81 (dd, 1H, J=2,4, 8,6 Hz), 5,93 (d, 1H, J=8,0 Hz), 4,86 (d, 2H, J=12,8 Hz), 4,68 (s, 1H), 4,51 (s, 1H), 4,2-4,4 (m, 3H), 4,1-4,2 (m, 3H), 4,0-4,1 (m, 2H), 3,85 (t, 1H, J=6,0 Hz), 3,57 (t, 2H, J=12,0 Hz), 2,8-3,0 (m, 4H), 2,4-2,5 (m, 2H), 2,1-2,2 (m, 3H), 1,8-2,0 (m, 7H), 1,23 (d, 15H, J=13,2 Hz)	936,6
140	2-[4-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-	($DMSO-d_6$) δ = 9,96 (s, 1H), 9,34 (d, *J* = 2,0 Hz, 1H), 8,74 (s, 2H), 8,57 - 8,48 (m, 2H), 8,04 (d, *J* = 8,4 Hz, 1H), 7,91 - 7,85 (m, 2H), 7,73 - 7,61 (m, 2H), 7,41 (d, *J* = 8,0 Hz, 1H), 7,21 (d, *J* = 2,4 Hz,	467,4 $[M+H^+]$

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	tetrametilciclobutil]pirimidina-5-carboxamida	1H), 7,00 (dd, *J* = 2,4, 8,8 Hz, 1H), 4,74 (d, *J* = 12,8 Hz, 2H), 4,57 (s, 2H), 4,53 - 4,43 (m, 1H), 4,28 (s, 1H), 4,03 (d, *J* = 9,2 Hz, 3H), 3,89 - 3,78 (m, 2H), 3,53 (t, *J* = 11,6 Hz, 2H), 3,02 - 2,95 (m, 3H), 2,90 - 2,82 (m, 1H), 2,77 (d, *J* = 6,8 Hz, 2H), 2,20 - 2,10 (m, 5H), 2,03 - 1,94 (m, 3H), 1,72 (d, *J* = 11,2 Hz, 2H), 1,21 (s, 8H), 1,10 (s, 6H)	
141	2-[4-[2-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,23 (s, 1H), 8,55 (d, *J* = 8,3 Hz, 1H), 8,35 (s, 1H), 8,13 (s, 1H), 8,09 (s, 1H), 7,90 (d, *J* = 8,4 Hz, 1H), 7,85 (d, *J* = 8,9 Hz, 1H), 7,82 - 7,75 (m, 2H), 7,52 (d, *J* = 6,4 Hz, 1H), 7,38 (d, *J* = 2,3 Hz, 1H), 7,30 (d, *J* = 9,6 Hz, 1H), 7,27 (d, *J* = 1,1 Hz, 1H), 7,19 - 7,10 (m, 2H), 4,59 - 4,49 (m, 1H), 4,45 (br d, *J* = 13,0 Hz, 2H), 3,92 (s, 3H), 3,88 - 3,80 (m, 1H), 3,66 (s, 3H), 3,39 (s, 3H), 3,36 - 3,32 (m, 1H), 3,06 - 2,92 (m, 4H), 2,20 (br d, *J* = 6,8 Hz, 2H), 2,15 - 2,05 (m, 4H), 1,94 - 1,77 (m, 9H), 1,68 - 1,58 (m, 2H), 1,56 - 1,44 (m, 2H), 1,17 - 1,02 (m, 2H)	947,8
141	2-[4-[2-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,23 (s, 1H), 8,55 (d, *J* = 8,3 Hz, 1H), 8,35 (s, 1H), 8,13 (s, 1H), 8,09 (s, 1H), 7,90 (d, *J* = 8,4 Hz, 1H), 7,85 (d, *J* = 8,9 Hz, 1H), 7,82 - 7,75 (m, 2H), 7,52 (d, *J* = 6,4 Hz, 1H), 7,38 (d, *J* = 2,3 Hz, 1H), 7,30 (d, *J* = 9,6 Hz, 1H), 7,27 (d, *J* = 1,1 Hz, 1H), 7,19 - 7,10 (m, 2H), 4,59 - 4,49 (m, 1H), 4,45 (br d, *J* = 13,0 Hz, 2H), 3,92 (s, 3H), 3,88 - 3,80 (m, 1H), 3,66 (s, 3H), 3,39 (s, 3H), 3,36 - 3,32 (m, 1H), 3,06 - 2,92 (m, 4H), 2,20 (br d, *J* =	474,4 $[M+H^+]$

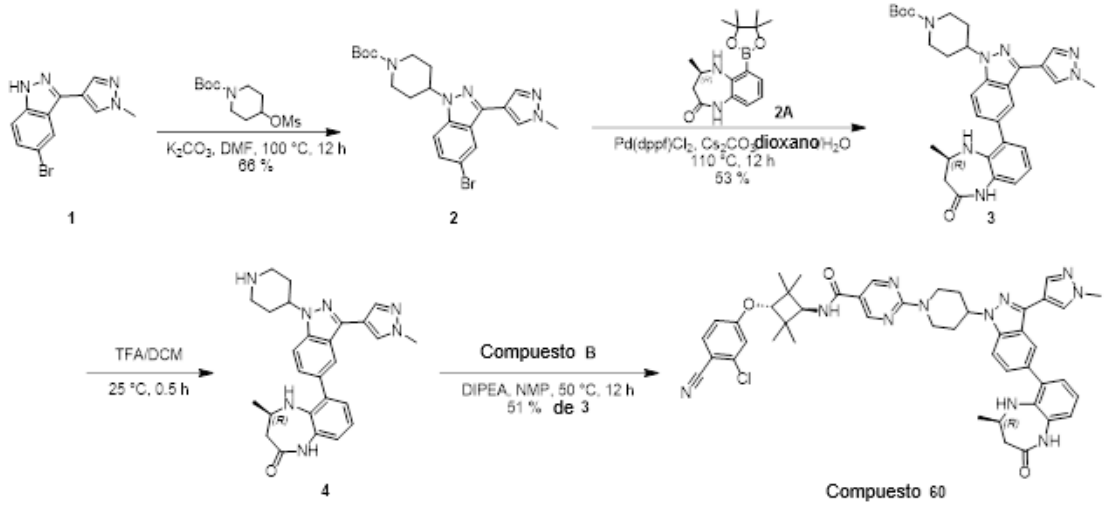
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		6,8 Hz, 2H), 2,15 - 2,05 (m, 4H), 1,94 - 1,77 (m, 9H), 1,68 - 1,58 (m, 2H), 1,56 - 1,44 (m, 2H), 1,17 - 1,02 (m, 2H)	
142	2-[4-[2-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]propil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxam	δ = 9,84 (d, J = 7,2 Hz, 1H), 9,25 (br s, 1H), 8,68 (s, 2H), 8,52 - 8,32 (m, 1H), 8,11 (d, J = 10,4 Hz, 1H), 7,91 (dd, J = 8,4, 14,0 Hz, 1H), 7,77 (td, J = 7,6, 11,2 Hz, 1H), 7,64 - 7,54 (m, 2H), 7,33 (br d, J = 7,6 Hz, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,80 (dd, J = 2,4, 8,8 Hz, 1H), 5,91 (d, J = 8,0 Hz, 1H), 4,81 (br t, J = 12,4 Hz, 2H), 4,72 - 4,46 (m, 2H), 4,36 - 4,24 (m, 1H), 4,18 (br d, J = 11,2 Hz, 2H), 4,12 (d, J = 8,0 Hz, 1H), 4,06 - 4,00 (m, 2H), 3,86 (t, J = 5,6 Hz, 1H), 3,58 (br t, J = 12,0 Hz, 2H), 3,17 (br dd, J = 1,6, 4,4 Hz, 1H), 2,94 (br t, J = 5,6 Hz, 1H), 2,90 - 2,81 (m, 3H), 2,53 - 2,40 (m, 2H), 2,25 - 2,06 (m, 3H), 2,01 - 1,91 (m, 3H), 1,91 - 1,83 (m, 1H), 1,75 (br d, J = 13,2 Hz, 1H), 1,56 - 1,47 (m, 2H), 1,36 (d, J = 6,8 Hz, 3H), 1,23 (d, J = 12,4 Hz, 12H), 1,21 - 1,13 (m, 2H).	481,5 [M+H+]
143	2-[4-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metoximetil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,97 (s, 1H), 9,35 (d, J = 2,0 Hz, 1H), 8,75 (s, 2H), 8,66 - 8,54 (m, 2H), 8,05 (d, J = 8,0 Hz, 1H), 7,95 - 7,83 (m, 2H), 7,74 - 7,55 (m, 3H), 7,21 (d, J = 2,4 Hz, 1H), 7,00 (dd, J = 2,4, 8,8 Hz, 1H), 4,78 (br d, J = 13,2 Hz, 2H), 4,64 (s, 2H), 4,57 (br s, 2H), 4,52 - 4,43 (m, 1H), 4,28 (s, 1H), 4,03 (br d, J = 9,2 Hz, 3H), 3,89 - 3,77 (m, 2H), 3,53 (br t, J = 12,0 Hz, 2H), 3,45 (d, J = 6,4 Hz, 2H), 3,08 - 2,94 (m, 3H), 2,85 (br t, J = 5,2 Hz, 1H), 2,21 - 2,08 (m, 4H), 2,06 - 1,93 (m,	482,4 ± 2

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		4H), 1,89 - 1,79 (m, 2H), 1,26 - 1,15 (m, 8H), 1,10 (s, 6H)	
144	2-[4-[3-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]butil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,82 (d, 1H, J=8,4 Hz), 9,23 (dd, 1H, J=2,4, 3,6 Hz), 8,68 (s, 2H), 8,37 (dt, 1H, J=2,3, 7,8 Hz), 8,09 (d, 1H, J=11,2 Hz), 7,90 (dd, 1H, J=8,2, 14,4 Hz), 7,76 (td, 1H, J=7,7, 11,6 Hz), 7,5-7,6 (m, 2H), 7,3-7,3 (m, 1H), 6,96 (d, 1H, J=2,4 Hz), 6,80 (dd, 1H, J=2,4, 8,8 Hz), 5,91 (d, 1H, J=8,0 Hz), 4,81 (d, 2H, J=13,2 Hz), 4,67 (s, 1H), 4,50 (s, 1H), 4,2-4,4 (m, 1H), 4,1-4,2 (m, 3H), 4,0-4,1 (m, 2H), 3,86 (t, 1H, J=5,6 Hz), 3,58 (t, 2H, J=11,6 Hz), 2,8-3,0 (m, 5H), 2,4-2,6 (m, 2H), 2,0-2,3 (m, 3H), 1,98 (d, 2H, J=13,0 Hz), 1,7-1,9 (m, 4H), 1,5-1,6 (m, 2H), 1,36 (d, 3H, J=6,8 Hz), 1,22 (d, 12H, J=11,6 Hz), 1,0-1,2 (m, 3H)	488,6 $[M+H^+]$
179	2-[4-[2-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-carbonil]amino]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	9,88H NMR (4,8 Hz, DMSO-d6) δ = 1,6 - 8,70 (m, 1H), 8,59 (d, J = 8,0 Hz, 1H), 8,33 (s, 1H), 8,22 - 8,10 (m, 2H), 7,93 - 7,56 (m, 1H), 7,80 (dd, J = 8,0, 10,8 Hz, 1H), 7,68 - 7,54 (m, 1H), 6,97 - 7,13 (m, 1H), 6,81 (d, J = 8,4 Hz, 1H), 5,93 - 6,68 (m, 1H), 4,87 (br d, J = 13,6 Hz, 1H), 4,68 (d, J = 8,6 Hz, 1H), 4,31 - 4,74 (m, 1H), 4,22 - 4,10 (m, 1H), 4,08 - 3,99 (m, 1H), 3,87 - 4,16 (m, 1H), 3,66 - 3,52 (m, 2H), 3,04 - 2,83 (m, 4H), 2,54 - 2,38 (m, 1H), 2,24 - 2,07 (m, 1H), 2,02 - 1,89 (m, 1H), 1,79 - 1,67 (m, 1H), 1,24 - 1,21 (m, 1H)	990,5
180	2-[4-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]piridina-2-	9,87H NMR (3,2 Hz, METANOL-d4) δ = 9,25 (s, 1H), 7,88 - 8,73 (m, 1H), 8,63 - 8,57 (m, 1H), 8,37 - 8,31 (m, 1H), 8,18 - 7,32 (m,	482,0 (M479)/

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	carbonil]amino]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H), 8,13 - 8,06 (m, 1H), 7,98 - 7,89 (m, 1H), 7,65 - 7,56 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,84 - 6,79 (m, 1H), 5,96 - 5,29 (m, 1H), 4,84 - 4,63 (m, 1H), 4,50 - 4,67 (m, 1H), 4,28 - 4,51 (m, 3H), 4,42 - 4,24 (m, 2H), 4,23 - 4,10 (m, 1H), 4,07 - 3,95 (m, 1H), 3,91 - 3,78 (m, 2H), 3,66 - 3,50 (m, 2H), 3,38 - 2,93 (m, 1H), 2,93 - 2,82 (m, 3H), 2,57 - 2,41 (m, 3H), 2,41 - 1,66 (m, 2H), 1,25 - 0,97 (m, 12H).	
215	2-[4-[[4-[8-(5-acetil-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ=9,51 - 9,86 (m, 1 H) 8,99 (s, 1 H) 8,70 (s, 2 H) 8,10 (s, 2 H) 7,78 - 7,91 (m, 2 H) 7,73 (br t, *J*=7,20 Hz, 1 H) 7,49 - 7,60 (m, 2 H) 6,95 - 6,99 (m, 1 H) 6,77 - 6,85 (m, 1 H) 5,93 (br d, *J*=7,60 Hz, 1 H) 4,92 (br d, *J*=13,20 Hz, 2 H) 4,63 (s, 1 H) 4,46 (s, 1 H) 4,07 - 4,19 (m, 3 H) 3,98 - 4,06 (m, 2 H) 3,90 (d, *J*=3,60 Hz, 3 H) 3,84 (t, *J*=5,60 Hz, 1 H) 2,91 - 3,00 (m, 2 H) 2,80 - 2,91 (m, 2 H) 2,29 - 2,43 (m, 1 H) 2,21 (s, 1 H) 2,06 (s, 1 H) 1,76 - 1,84 (m, 3 H) 1,29 (s, 1 H) 1,25 (s, 6 H) 1,22 (s, 6 H).	852,6
222	2-[4-[3-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]pirrolidin-1-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (500 MHz, METANOL-d4) δ = 8,68 (s, 1H), 8,26 - 8,15 (m, 1H), 8,10 - 8,02 (m, 1H), 7,86 - 7,75 (m, 1H), 7,74 - 7,64 (m, 1H), 7,61 - 7,54 (m, 1H), 7,54 - 7,44 (m, 1H), 7,00 - 6,95 (m, 2H), 6,77 (d, J = 8,5 Hz, 1H), 4,88 - 5,87 (m, 1H), 4,67 - 4,43 (m, 1H), 4,35 - 4,22 (m, 1H), 4,20 - 4,11 (m, 1H), 4,07 - 4,03 (m, 1H), 4,03 - 3,98 (m, 2H), 3,91 - 3,78 (m, 1H), 3,64 - 3,48 (m, 1H), 3,24 - 3,00 (m, 2H), 2,99 - 2,74 (m, 3H), 2,54 - 2,93 (m, 1H), 2,93 - 2,26 (m,	977,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		1H), 2,22 - 2,20 (m, 1H), 2,16 - 1,88 (m, 2H), 1,26 - 1,22 (m, 6H).	
231	2-[4-[2-[5-[8-(5-acetil-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,80 (d, *J* = 11,6 Hz, 1H), 9,29 (d, *J* = 1,3 Hz, 1H), 8,72 (s, 2H), 8,58 - 8,40 (m, 1H), 8,15 (d, *J* = 9,4 Hz, 1H), 7,94 (dd, *J* = 8,2, 13,6 Hz, 1H), 7,85 - 7,74 (m, 1H), 7,68 - 7,55 (m, 2H), 7,39 (br d, *J* = 8,1 Hz, 1H), 6,99 (d, *J* = 2,4 Hz, 1H), 6,82 (dd, *J* = 2,4, 8,8 Hz, 1H), 5,95 (d, *J* = 8,4 Hz, 1H), 4,89 (br d, *J* = 13,8 Hz, 2H), 4,65 (s, 1H), 4,49 (s, 1H), 4,15 (d, *J* = 8,1 Hz, 1H), 4,08 - 4,00 (m, 2H), 3,94 (d, *J* = 3,4 Hz, 3H), 3,87 (t, *J* = 5,8 Hz, 1H), 3,08 - 2,95 (m, 4H), 2,95 - 2,89 (m, 2H), 2,86 (br t, *J* = 5,5 Hz, 1H), 2,24 - 2,08 (m, 3H), 1,94 (br d, *J* = 12,3 Hz, 2H), 1,86 - 1,79 (m, 3H), 1,30 (br s, 1H), 1,25 (d, *J* = 13,9 Hz, 12H)	877,7

[00569] Ejemplo 20: Síntesis de N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]-1-piperidil]pirimidina-5-carboxamida (**Compuesto 60**)



[00570] La síntesis de 1 se informó en WO2016/55028 A1.

[00571] La síntesis de **2A** fue reportada en Medicinal Chemistry Letters, 2016, vol. 7, # 5, páginas 531 - 536

[00572] A una solución de 5-bromo-3-(1-metilpirazol-4-il)-1H-indazol (1 g, 3,61 mmol, 1,0 eq) y 4-metilsulfoniloxipiperidina-1-carboxilato de ter-butilo (2,02 g, 7,22 mmol, 2,0 eq) en DMF (15 ml) se agregó K_2CO_3 (1,50 g, 10,83 mmol, 3,0 eq). La mezcla de reacción se agitó a 100 °C durante 12 h. La mezcla de reacción se neutralizó añadiendo agua (30 ml) a 0 °C, y luego se diluyó con agua (30 ml) y se extrajo con acetato de etilo (50 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (condiciones FA: columna: Phenomenex luna C18 150*40mm* 15um; fase móvil: [agua (FA) - ACN]; gradiente: 55 % - 85 % B durante 15 min). El compuesto deseado ter-butil 4-[5-bromo-3-(1-metilpirazol-4-il)indazol-1-il]piperidina-1-carboxilato (1,10 g, 2,39 mmol, 66 % de rendimiento) se obtuvo como un sólido blanco.

[00573] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,03 – 7,94 (m, 2H), 7,86 (s, 2H), 7,46 (t, *J* = 7,5 Hz, 2H), 3,22 (s, 2H), 7,33 (d, **J** = 8,9 Hz, 1H), 4,61 – 4,47 (m, 1H), 4,32 – 4,01 (m, 3H), 2,97 – 1,27 (m, 2H), 2,26 – 1,07 (m, 2H), 2,07 – 1,95 (m, 2H).

[00574] **LC-MS:** MS (ESI$^+$): t_R = 0,604 min, m/z = 460,1 [M + H$^+$]

[00575] A una solución de 4-[5-bromo-3-(1-metilpirazol-4-il)indazol-1-il]piperidina-1-carboxilato de ter-butilo (200 mg, 434,44 µmol, 1,0 eq) y (4R)-4-metil-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,4,5-tetrahidro-1,5-benzodiazepin-2-ona (144 mg, 477,88 µmol, 1,1 eq) en dioxano (5 ml) y H_2O (1 ml) se agregó $Pd(dppf)Cl_2$ (32 mg, 43,44 µmol, 0,1 eq) y Cs_2CO_3 (425 mg, 1,30 mmol, 3,0 eq). La mezcla de reacción se agitó a 110 °C durante 12 h en N_2. La mezcla se concentró a presión reducida para obtener un residuo. El compuesto deseado ter-butil 4-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]piperidina-1-carboxilato (130 mg, 233,95 µmol, 53 % de rendimiento) se obtuvo como un sólido amarillo claro.

[00576] **LC-MS:** MS (ESI$^+$): t_R = 0,568 min, m/z = 556,3 [M + H$^+$]

[00577] A una solución de ter-butil 4-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]piperidina-1-carboxilato (130 mg, 233,95 µmol, 1,0 eq) en DCM (5 ml) se le agregó TFA (133 mg, 1,17 mmol, 86,89 µl, 5,0 eq). La mezcla de reacción se agitó a 25 °C durante 0,5 h. La mezcla se concentró hasta secarse. El compuesto (4R)-4-metil-6-[3-(1-metilpirazol-4-il)-1-(4-piperidil)indazol-5-il]-1,3,4,5-tetrahidro-1,5-benzodiazepin-2-ona (133 mg) se obtuvo como un sólido

blanquecino y se utilizó directamente en el siguiente paso sin purificación adicional.

[00578] **LC-MS:** MS (ESI^+): t_R = 0,406 min, m/z = 456,2 [M + H^+]

[00579] A una solución de (4R)-4-metil-6-[3-(1-metilpirazol-4-il)-1-(4-piperidil)indazol-5-il]-1,3,4,5-tetrahidro-1,5-benzodiazepin-2-ona (133 mg) y DIPEA (302 mg, 2,34 mmol, 406,73 µl, 10,0 eq) en NMP (2 ml) se agregó 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (98 mg, 233,51 µmol, 1,0 eq). La mezcla de reacción se agitó a 50 °C durante 12 h. La mezcla de reacción se filtró y se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (condiciones FA: columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua (FA) - ACN]; gradiente: 58 %-88 % B durante 15 min). El compuesto deseado N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]-1-piperidil]pirimidina-5-carboxamida (103,17 mg, 121,24 µmol, 51 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino.

[00580] **RMN de 1H** (400 MHz, $CDCl_3$): δ = 8,76 (s, 2H), 7,98 (s, 1H), 7,86 (s, 1H), 7,82 (s, 1H), 7,64 - 7,54 (m, 2H), 7,45 - 7,35 (m, 2H), 7,08 (dd, J = 1,6, 7,2 Hz, 1H), 7,01 - 6,90 (m, 3H), 6,82 (dd, J = 2,4, 8,8 Hz, 1H), 5,98 (d, J = 8,0 Hz, 1H), 5,11 (d, J = 13,2 Hz, 2H), 4,87 - 4,75 (m, 1H), 4,16 (d, J = 8,0 Hz, 1H), 4,06 (s, 1H), 4,03 - 3,90 (m, 4H), 3,29 (t, J = 11,6 Hz, 2H), 2,78 (dd, J = 4,4, 13,6 Hz, 1H), 2,54 - 2,34 (m, 3H), 2,22 (d, J = 10,0 Hz, 2H), 1,28 (s, 6H), 1,24 (s, 6H), 1,20 (d, J = 6,4 Hz, 3H)

[00581] **LC-MS:** MS (ESI^+): t_R = 2,611 min, m/z = 838,5 [M + H^+]

[00582] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 20.

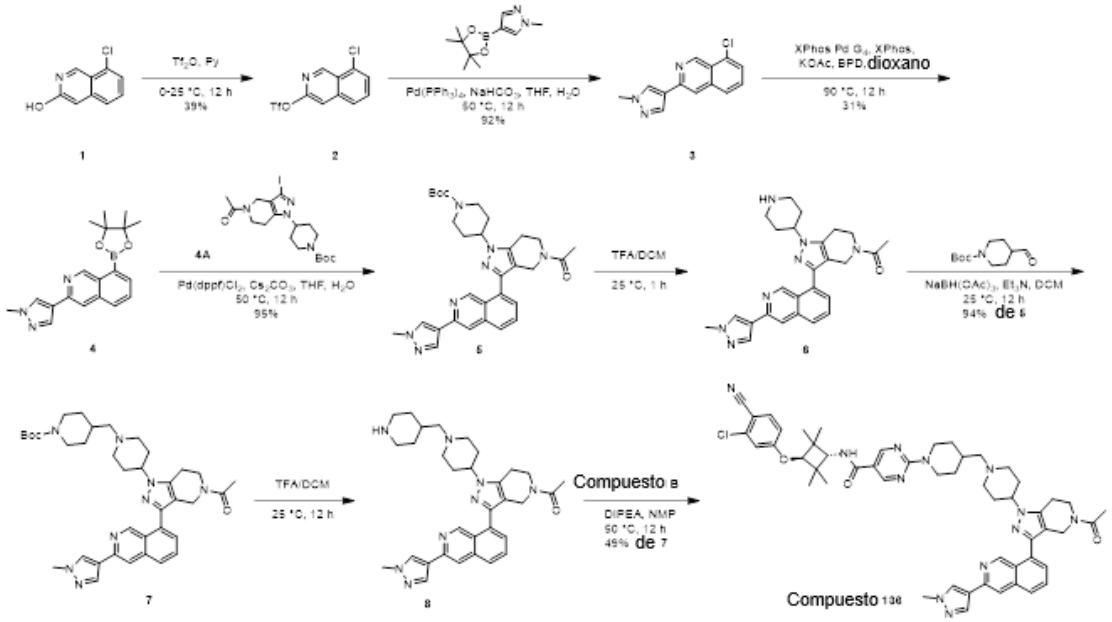
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
47	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[2-[3-(1-metilpirazol-4-il)-5-[rac-(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]indazol-1-il]etoxi]pirimidina-5-carboxamida	δ = 8,88 (s, 2H), 7,87 - 7,73 (m, 3H), 7,58 (d, J = 8,8 Hz, 1H), 7,51 (s, 1H), 7,35 - 7,27 (m, 2H), 7,04 (dd, J = 1,6, 7,2 Hz, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,95 - 6,85 (m, 2H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,11 (d, J = 8,0 Hz, 1H), 5,14 - 4,97 (m, 2H), 4,94 - 4,81 (m, 2H), 4,15 (d, J = 8,0 Hz, 1H), 4,07 (s, 1H), 4,01 (s, 3H), 3,95 (br d, J = 5,6 Hz, 1H), 3,67 (br d, J = 0,8 Hz, 1H), 2,76 (dd, J = 4,6, 13,6 Hz, 1H), 2,44 (dd, J = 6,3, 13,6 Hz, 1H), 1,28 (s, 6H), 1,24 (s, 6H), 1,20 (d, J = 6,2 Hz, 3H)	799,3

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
48	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[metil-[2-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]etil]amino]pirimidina-5-carboxamida	(DMSO-d_6) δ = 9,60 (s, 1H), 8,74 (s, 2H), 8,39 (s, 1H), 7,9-8,0 (m, 3H), 7,71 (d, 1H, J=9,2 Hz), 7,61 (d, 1H, J=8,8 Hz), 7,35 (d, 1H, J=9,6 Hz), 7,22 (d, 1H, J=2,4 Hz), 6,8-7,0 (m, 4H), 4,71 (t, 2H, J=6,4 Hz), 4,29 (s, 1H), 4,0-4,2 (m, 3H), 3,8-3,9 (m, 4H), 3,74 (d, 1H, J=2,4 Hz), 2,97 (s, 3H), 2,61 (dd, 1H, J=4,4, 12,8 Hz), 2,22 (dd, 1H, J=6,0, 13,1 Hz), 1,1-1,2 (m, 12H), 1,05 (d, 3H, J=6,0 Hz)	812,6
49	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[3-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]propoxi]pirimidina-5-carboxamida	δ = 8,90 (s, 2H), 8,01 - 7,85 (m, 2H), 7,79 (s, 1H), 7,58 (d, J = 8,8 Hz, 1H), 7,54 (d, J = 8,8 Hz, 1H), 7,51 (s, 1H), 7,33 (dd, J = 1,6, 8,8 Hz, 1H), 7,05 (dd, J = 2,0, 7,2 Hz, 1H), 6,99 - 6,90 (m, 3H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,09 (d, J = 8,0 Hz, 1H), 4,67 (t, J = 6,4 Hz, 2H), 4,49 (t, J = 6,0 Hz, 2H), 4,15 (d, J = 8,0 Hz, 1H), 4,07 (s, 1H), 3,99 (s, 3H), 3,97 - 3,90 (m, 1H), 3,80 - 3,40 (m, 1H), 2,76 (dd, J = 4,4, 13,2 Hz, 1H), 2,55 (quin, J = 6,4 Hz, 2H), 2,46 (dd, J = 6,4, 13,2 Hz, 1H), 1,26 (d, J = 17,6 Hz, 12H), 1,17 (d, J = 6,4 Hz, 3H).	813,6
50	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[metil-[3-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]propil]amino]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 8,01 (s, 1H), 7,89 (s, 1H), 7,80 (s, 1H), 7,58 (d, J = 8,8 Hz, 1H), 7,53 - 7,42 (m, 2H), 7,36 (dd, J = 1,2, 8,8 Hz, 1H), 7,07 (dd, J = 2,0, 7,2 Hz, 1H), 6,99 - 6,90 (m, 3H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 5,94 (br d, J = 8,0 Hz, 1H), 4,48 (t, J = 7,2 Hz, 2H), 4,13 (d, J = 8,0 Hz, 1H), 4,04 (s, 1H), 4,00 (s, 3H), 3,98 - 3,92 (m, 1H), 3,86 (br t, J = 7,2 Hz, 2H), 3,80 - 3,46 (m, 1H), 3,23 (s, 3H), 2,77 (dd, J = 4,4, 13,2 Hz, 1H), 2,47 (dd, J = 6,4, 13,6 Hz, 1H), 2,39 (quin, J = 6,8 Hz, 2H), 1,23 (d, J = 12,0 Hz, 12H), 1,18 (d, J = 6,4 Hz, 3H).	826,5
54	N-[3-(3-cloro-4-	δ = 8,67 (s, 2H), 8,00 (s, 1H),	1108,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]etoximetil]-1-piperidil]pirimidina-5-carboxamida	7,89 (s, 1H), 7,78 (s, 1H), 7,58 (dd, J = 2,4, 8,4 Hz, 2H), 7,40 - 7,31 (m, 2H), 7,09 (dd, J = 1,6, 7,2 Hz, 1H), 7,01 - 6,89 (m, 3H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,04 (d, J = 8,0 Hz, 1H), 4,82 - 4,71 (m, 2H), 4,60 (t, J = 5,6 Hz, 2H), 4,14 (d, J = 8,0 Hz, 1H), 4,06 (s, 1H), 4,03 - 3,90 (m, 6H), 3,71 - 3,54 (m, 1H), 3,33 - 3,21 (m, 2H), 2,85 (dt, J = 2,4, 13,2 Hz, 2H), 2,74 (dd, J = 4,4, 13,2 Hz, 1H), 2,46 (dd, J = 6,8, 13,6 Hz, 1H), 1,87 - 1,67 (m, 3H), 1,24 (d, J = 15,2 Hz, 12H), 1,16 (d, J = 6,4 Hz, 3H), 1,07 (dq, J = 4,0, 12,8 Hz, 2H).	
55	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[3-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]propil]piperazin-1-il]pirimidina-5-carboxamida	δ = 8,71 (s, 2H), 8,00 (s, 1H), 7,89 (s, 1H), 7,80 (s, 1H), 7,61 - 7,50 (m, 3H), 7,39 (dd, J = 1,1, 8,4 Hz, 1H), 7,07 (dd, J = 1,9, 7,2 Hz, 1H), 7,00 - 6,91 (m, 3H), 6,80 (dd, J = 2,4, 8,8 Hz, 1H), 5,98 (d, J = 8,0 Hz, 1H), 4,54 (br t, J = 6,4 Hz, 2H), 4,13 (br d, J = 8,0 Hz, 2H), 4,05 (s, 2H), 4,03 - 3,97 (m, 4H), 3,97 - 3,92 (m, 1H), 3,39 (t, J = 7,2 Hz, 1H), 2,92 - 2,66 (m, 7H), 2,52 - 2,26 (m, 5H), 1,33 - 1,11 (m, 16H)	881,5
56	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]etil]piperazin-1-il]pirimidina-5-carboxamida	δ = 8,71 (s, 2H), 8,00 (s, 1H), 7,89 (s, 1H), 7,80 (s, 1H), 7,5-7,6 (m, 3H), 7,40 (d, 1H, J=8,4 Hz), 7,07 (dd, 1H, J=1,8, 7,2 Hz), 6,9-7,0 (m, 3H), 6,81 (dd, 1H, J=2,4, 8,8 Hz), 5,96 (d, 1H, J=8,0 Hz), 4,5-4,8 (m, 2H), 4,13 (d, 1H, J=8,0 Hz), 4,05 (s, 1H), 3,9-4,0 (m, 7H), 3,0-3,2 (m, 2H), 2,6-2,9 (m, 5H), 2,46 (dd, 1H, J=6,3, 13,2 Hz), 1,7-1,8 (m, 2H), 1,2-1,3 (m, 15H)	867,5
57	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[3-ciclopropil-5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-	δ = 8,68 (s, 2 H) 7,67 (s, 1 H) 7,57 (d, J=8,8 Hz, 1 H) 7,50 (d, J=8,4 Hz, 1 H) 7,37 (s, 1 H) 7,30 (m, 1 H) 7,08 (m, 1 H) 6,89 - 6,99 (m, 3 H) 6,81 (m, 1 H) 6,02 (d, J=8,4 Hz, 1 H) 4,73 - 4,85 (m, 2 H) 4,50 (t, J=5,6 Hz,	856,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	il]indazol-1-il]etoximetil]-1-piperidil]pirimidina-5-carboxamida	2 H) 4,13 (d, J=8,0 Hz, 1 H) 4,05 (s, 1 H) 3,93 - 4,01 (m, 1 H) 3,86 (t, J=5,2 Hz, 2 H) 3,63 (m, 1 H) 3,20 - 3,30 (m, 2 H) 2,86 (m, 2 H) 2,74 (m, 1 H) 2,46 (m, 1 H) 2,20 (m, 1 H) 1,73 - 1,87 (m, 1 H) 1,64 - 1,69 (m, 2 H) 1,25 (s, 6 H) 1,22 (s, 6 H) 1,18 (d, J=6,4 Hz, 3 H) 1,06 - 1,13 (m, 2 H) 1,02 - 1,06 (m, 4 H)	
58	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[[5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]-3-(1-metilpirazol-4-il)indazol-1-il]metil]-1-piperidil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 8,02 (s, 1H), 7,90 (s, 1H), 7,81 (s, 1H), 7,58 (d, 1H, J=8,8 Hz), 7,4-7,5 (m, 2H), 7,37 (dd, 1H, J=1,2, 8,6 Hz), 7,08 (dd, 1H, J=1,8, 7,3 Hz), 6,9-7,0 (m, 3H), 6,81 (dd, 1H, J=2,4, 8,4 Hz), 5,93 (d, 1H, J=8,0 Hz), 4,92 (br d, 2H, J=13,2 Hz), 4,32 (d, 2H, J=7,2 Hz), 4,13 (d, 1H, J=8,1 Hz), 3,9-4,1 (m, 5H), 2,94 (t, 2H, J=11,9 Hz), 2,78 (dd, 1H, J=4,4, 13,3 Hz), 2,47 (dd, 2H, J=6,6, 13,2 Hz), 1,80 (br d, 2H, J=11,0 Hz), 1,39 (dq, 3H, J=3,7, 12,4 Hz), 1,2-1,3 (m, 15H)	852,4
59	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[3-[3-ciclopropil-5-[(4R)-4-metil-2-oxo-1,3,4,5-tetrahidro-1,5-benzodiazepin-6-il]indazol-1-il]propil]piperazin-1-il]pirimidina-5-carboxamida	*δ* = 8,71 (s, 2 H) 7,69 (s, 1 H) 7,57 (d, *J*=8,4 Hz, 1 H) 7,55 (s, 1 H) 7,49 (d, *J*=8,4 Hz, 1 H) 7,31 (m, 1 H) 7,07 (m, 1 H) 6,90 - 6,99 (m, 3 H) 6,81 (m, 1 H) 5,95 (d, *J*=8,0 Hz, 1 H) 4,43 (t, *J*=6,4 Hz, 2 H) 4,13 (d, *J*=8,0 Hz, 1 H) 4,05 (s, 1 H) 3,95 - 4,00 (m, 1 H) 3,88 - 3,95 (m, 4 H) 2,78 (m, 1 H) 2,44 - 2,52 (m, 5 H) 2,40 (t, *J*=6,4 Hz, 2 H) 2,12 - 2,24 (m, 3 H) 1,25 (s, 6 H) 1,22 (s, 6 H) 1,20 (s, 3 H) 1,02 - 1,09 (m, 4 H)	841,6

[00583] Ejemplo 21: Síntesis de 2-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 136**)



[00584] La síntesis de **1** se describió en el informe de Dalton Transactions, 2008, vol. 8, n.° 4, páginas 491-498.

[00585] A una solución de 8-cloroisoquinolin-3-ol (3,50 g, 19,5 mmol, 1,0 eq) en Py (90 ml) se le agregó Tf_2O (7,15 g, 25,3 mmol, 1,3 eq) a 0 °C. La mezcla se agitó a 25 °C durante 12 h bajo N_2. El residuo se vertió en agua (50 ml). Luego la mezcla se extrajo con acetato de etilo (50 ml×3), se secó en sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 5/1 a 0/1). Se obtuvo el compuesto 8 (2,50 g, 7,62 mmol, 39 % de rendimiento) como un sólido blanco.

[00586] **LC-MS:** MS (ESI^+): t_R = 0,660 min, m/z = 311,9 [M + H^+]

[00587] A una solución de (8-cloro-3-isoquinolil) trifluorometanosulfonato (2,50 g, 8,02 mmol, 1,0 eq) y 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazol (2,00 g, 9,63 mmol, 1,2 eq) en THF (50 ml) y H_2O (10 ml) se añadieron $NaHCO_3$ (2,02 g, 24,1 mmol, 3,0 eq) y $Pd(PPh_3)_4$ (927 mg, 802 µmol, 0,1 eq). La mezcla se agitó a 50 °C durante 12 h bajo N_2. El residuo se vertió en agua (100 ml). Luego la mezcla se extrajo con acetato de etilo (80 ml×3), se secó en sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 (250 × 70 mm, 10 µm); fase móvil: [agua (TFA)-ACN]; gradiente: 23 %-53 % B durante 20 min). Se obtuvo el compuesto 8 (2,03 g, 7,39 mmol, 92 % de rendimiento) como un sólido amarillo.

[00588] **LC-MS:** MS (ESI^+): t_R = 0,533 min, m/z = 244,0 [M + H^+]

[00589] A una solución de 8-cloro-3-(1-metilpirazol-4-il)isoquinolina (1,00 g, 4,10

mmol, 1,0 eq) y 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (1,25 g, 4,92 mmol, 1,2 eq) en dioxano (20 ml) se le agregó KOAc (1,21 g, 12,3 mmol, 3,0 eq) y Xphos Pd G4 (353 mg, 410 µmol, 0,1 eq) y XPhos (196 mg, 410 µmol, 0,1 eq). La mezcla se agitó a 90 °C durante 12 h en N_2. El residuo se vertió en agua (60 ml). Luego la mezcla se extrajo con acetato de etilo (60 ml×3), se secó en sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto 3-(1-metilpirazol-4-il)-8-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)isoquinolina (450 mg, 1,28 mmol, 31 % de rendimiento) se obtuvo como un sólido amarillo.

[00590] **LC-MS:** MS (ESI^+): t_R = 0,541 min, m/z = 336,2 [M + H^+]

[00591] A una solución de 3-(1-metilpirazol-4-il)-8-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)isoquinolina (450 mg, 1,34 mmol, 1,2 eq) y 4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)piperidina-1-carboxilato de ter-butilo (531 mg, 1,12 mmol, 1,0 eq) en THF (20 ml) y H_2O (4 ml) se agregó Cs_2CO_3 (1,09 g, 3,36 mmol, 3,0 eq) y $Pd(dppf)Cl_2$ (164 mg, 224 µmol, 0,2 eq) .La mezcla se agitó a 50 °C durante 12 h bajo N_2. La mezcla de reacción se vertió en agua fría (50 ml). La fase acuosa se extrajo con acetato de etilo (50 ml x 3). La fase orgánica combinada se lavó con salmuera (30 ml x 2), se secó con Na2SO4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150 × 40 mm × 15 µm; fase móvil: [agua(FA)-ACN]; gradiente: 40 %-70 % B durante 15 min). El compuesto ter-butil 4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (600 mg, 1,06 mmol, 95 % de rendimiento) se obtuvo como un aceite amarillo.

[00592] **LC-MS:** MS (ESI^+): t_R = 0,538 min, m/z = 556,5 [M + H^+]

[00593] A una solución de ter-butil 4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (300 mg, 540 µmol, 1,0 eq) en DCM (2 ml) se agregó TFA (768 mg, 6,73 mmol, 12,5 eq). La mezcla se agitó a 25 °C durante 1 h bajo N_2. La mezcla de reacción se concentró para proporcionar un residuo. El compuesto 1-[3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (300 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00594] **LC-MS:** MS (ESI^+): t_R = 0,435 min, m/z = 456,3 [M + H^+]

[00595] 1-[3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg) se agregó a la mezcla de 4-formilpiperidina-1-carboxilato de ter-butilo (56 mg, 263 µmol, 1,5 eq) y Et_3N (178 mg, 1,76 mmol, 10,0

eq) en DCM (3 ml) y se agitó a 25 °C durante 0,5 h. Se agregó $NaBH(OAc)_3$ (186 mg, 878 µmol, 5,0 eq) a la mezcla de reacción anterior y se agitó a 25 °C durante 12 h bajo N_2. El residuo se vertió en agua (20 ml). Luego la mezcla se extrajo con acetato de etilo (20 ml×3), se secó en sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH = 15: 1). El compuesto ter-butil 4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]piperidina-1-carboxilato (120 mg, 165 µmol, 94 % de rendimiento en dos pasos) se obtuvo como un aceite amarillo.

[00596] **LC-MS:** MS (ESI^+): t_R = 0,498 min, m/z = 653,5 [M + H^+]

[00597] A una solución de ter-butil 4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]piperidina-1-carboxilato (120 mg, 165 µmol, 1,0 eq) en DCM (1 ml) se agregó TFA (768 mg, 6,73 mmol, 36,6 eq). La mezcla se agitó a 25 °C durante 1 h bajo N_2. La mezcla de reacción se concentró para proporcionar un residuo. El compuesto 1-[3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-1-[1-(4-piperidilmetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (120 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00598] **LC-MS:** MS (ESI^+): t_R = 0,440 min, m/z = 553,4 [M + H^+]

[00599] A una solución de 1-[3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-1-[1-(4-piperidilmetil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (120 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (91 mg, 216 µmol, 1,2 eq) en NMP (2 ml) se agregó DIPEA (70 mg, 540 µmol, 3,0 eq). La mezcla se agitó a 50 °C durante 12 h bajo N_2. El residuo se vertió en agua (20 ml). Luego la mezcla se extrajo con acetato de etilo (20 ml×3), se secó en sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150 × 25mm × 10um;fase móvil: [agua(FA)-ACN];gradiente:32 %-62 % B durante 10 min) para dar 2-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (86,05 mg, 88,9 µmol, rendimiento del 49 % sobre dos pasos) se obtuvo como un sólido blanquecino.

[00600] 620, ^1H NMR (400 MHz, DMSO-d**6**) δ = 9,78 - 9,60 (m, 1H), 8,69 - 8,05 (m, 1H), 7,87 - 7,76 (m, 1H), 7,75 - 7,65 (m, 1H), 7,61 - 7,55 (m, 3H), 7,54 - 7,42 (m, 1H), 6,97 (br d, J =2,4 Hz, 1H), 6,86 - 6,77 (m, 1H), 6,00 - 5,90 (m, 1H), 4,93 - 4,78 (m, 1H), 4,67 – 4,49 (m, 1H), 4,13 - 4,61 (m, 1H), 4,07 - 3,94 (m, 1H), 3,64 - 3,04 (m, 3H), 3,01 -

2,80 (m, 1H), 2,57 - 2,27 (m, 3H), 2,22 (s, 1H), 2,18 (s, 1H), 2,12 - 2,04 (m, 1H), 2,02 - 1,75 (m, 1H), 1,25 - 1,22 (m, 1H).

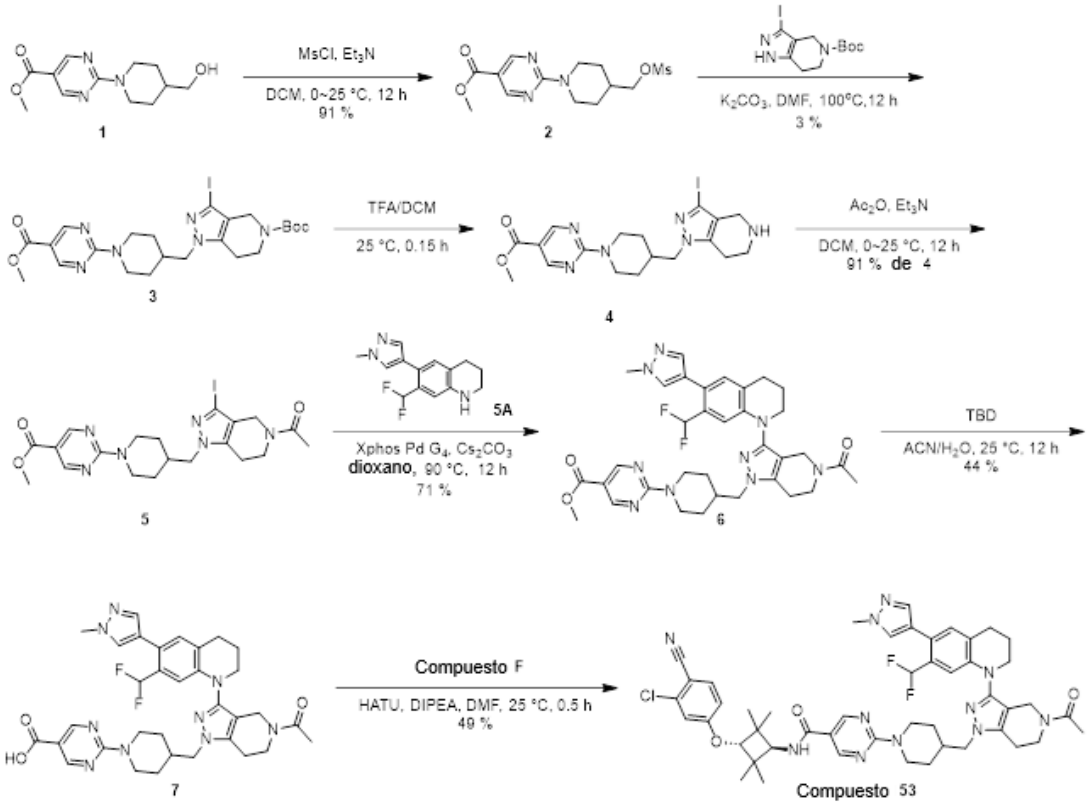
[00601] **LC-MS:** MS (ESI^+): t_R = 1,696 min, m/z = 935,6 [M + H^+]

[00602] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 21.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
142	2-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, METANOL-d4) δ = 8,66 - 8,05 (m, 1H), 7,76 (s, 1H), 7,75 - 7,65 (m, 2H), 7,61 - 7,55 (m, 3H), 7,54 - 7,42 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,86 - 6,77 (m, 1H), 6,00 - 5,90 (m, 1H), 4,93 - 4,78 (m, 1H), 4,67 - 4,49 (m, 1H), 4,13 - 4,22 (m, 1H), 4,07 - 3,94 (m, 2H), 4,00 - 3,84 (m, 1H), 3,64 - 3,04 (m, 3H), 3,01 - 2,80 (m, 1H), 2,57 - 2,85 (m, 3H), 2,85 - 2,22 (m, 2H), 2,18 - 2,14 (m, 1H), 2,12 - 2,04 (m, 1H), 2,02 - 1,79 (m, 1H), 1,79 - 1,25 (m, 1H), 1,42 - 1,22 (m, 2H).	935,6
141	2-[4-[2-[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]etil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (500 MHz, METANOL-d4) δ = 8,38 (s, 1H), 8,09 - 7,99 (m, 1H), 7,85 - 7,76 (m, 1H), 7,74 - 7,66 (m, 1H), 7,57 - 7,32 (m, 1H), 7,52 - 7,42 (m, 1H), 6,96 - 7,21 (m, 1H), 6,85 - 6,77 (m, 2H), 5,90 (d, J = 8,5 Hz, 1H), 4,69 - 4,61 (m, 1H), 4,51 - 4,43 (m, 1H), 4,32 - 4,10 (m, 1H), 4,06 - 4,03 (m, 1H), 4,03 - 3,97 (m, 3H), 3,88 - 3,79 (m, 2H), 3,38 - 3,26 (m, 1H), 3,01 - 2,81 (m, 1H), 2,75 - 2,54 (m, 2H), 2,50 - 2,35 (m, 3H), 2,26 - 2,93 (m, 1H), 2,93 - 1,75 (m, 3H), 1,62 - 1,49 (m, 3H), 1,25 - 1,21 (m, 2H), 1,18 - 1,15 (m, 1H).	949,7

[00603] **Ejemplo 22**: Síntesis de 2-[4-[[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]metil]-1-

piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 53**)



[00604] La síntesis de 1 se informó en WO2006/10750 A1.

[00605] La síntesis de **5A** fue reportada en WO2016/86200 A1.

[00606] La síntesis de **7A** fue reportada en Journal of Medicinal Chemistry, 2023, vol. 66, # 7, páginas 4784 – 4801.

[00607] A una solución de 2-[4-(hidroximetil)-1-piperidil]pirimidina-5-carboxilato de metilo (4 g, 15,92 mmol, 1,0 eq) y Et_3N (8,05 g, 79,59 mmol, 11,08 ml, 5,0 eq) en DCM (50 ml) se agregó MsCl (3,29 g, 28,72 mmol, 2,22 ml, 1,8 eq) a 0 °C. La mezcla de reacción se agitó a 25 °C durante 12 h bajo N_2. La mezcla de reacción se detuvo añadiendo agua (30 ml) a 0 °C, y luego se diluyó con agua (30 ml) y se extrajo con DCM (30 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto deseado, 2-[4-(metilsulfoniloximetil)-1-piperidil]pirimidina-5-carboxilato de metilo (4,8 g, 14,57 mmol, 91 % de rendimiento), se obtuvo como un sólido blanco.

[00608] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8,82 (s, 2H), 4,97 (d, J = 13,6 Hz, 2H), 4,10 (d,

J = 6,4 Hz, 2H), 3,87 (s, 3H), 3,02 (s, 3H), 2,96 (dt, J = 2,4, 12,8 Hz, 2H), 2,20 - 2,05 (m, 1H), 1,90 (d, J = 12,4 Hz, 2H), 1,31 (dq, J = 4,0, 12,4 Hz, 2H).

[00609] **LC-MS:** MS (ESI^+): t_R = 0,476 min, m/z = 330,1 [M + H^+]

[00610] A una solución de ter-butil 3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridina-5-carboxilato (4,8 g, 13,75 mmol, 1,0 eq) y 2-[4-(metilsulfoniloximetil)-1-piperidil]pirimidina-5-carboxilato de metilo (4,80 g, 14,57 mmol, 1,06 eq) en DMF (50 ml) se agregó K_2CO_3 (5,70 g, 41,24 mmol, 3,0 eq). La mezcla de reacción se agitó a 100 °C durante 12 h. La mezcla de reacción se neutralizó añadiendo agua (30 ml) a 0 °C, y luego se diluyó con agua (30 ml) y se extrajo con acetato de etilo (100 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (condiciones FA: columna: Phenomenex luna C18 150*40mm* 15um; fase móvil: [agua (FA) - ACN]; gradiente: 50 % - 80 % B durante 15 min). El compuesto deseado ter-butil 3-iodo-1-[[1-(5-metoxicarbonilpirimidin-2-il)-4-piperidil]metil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato (310 mg, 532,25 µmol, 3 % de rendimiento) se obtuvo como un sólido blanco.

[00611] δ 8,82 - 4,23 (m, 2H), 3,92 - 3,84 (m, 5H), 3,70 (br s, 2H), 2,98 - 2,83 (m, 2H), 2,62 (br s, 2H), 2,37 (br s, 2H), 1,70 (br d, J = 11,2 Hz, 2H), 1,50 (br s, 2H), 1,30 - 1,16 (m, 2H).

[00612] **LC-MS:** MS (ESI^+): t_R = 0,625 min, m/z = 583,1 [M + H^+]

[00613] A una solución de 3-iodo-1-[[1-(5-metoxicarbonilpirimidin-2-il)-4-piperidil]metil]-6,7-dihidro-4H-pirazolo[4,3-c]piridina-5-carboxilato de ter-butilo (310 mg, 532,25 µmol, 1,0 eq) en DCM (10 ml) se agregó TFA (303 mg, 2,66 mmol, 197,68 µl, 5,0 eq). La mezcla de reacción se agitó a 25 °C durante 0,15 h. La mezcla se concentró hasta secarse. El compuesto metil 2-[4-[(3-iodo-4,5,6,7-tetrahidropirazolo[4,3-c]piridin-1-il)metil]-1-piperidil]pirimidina-5-carboxilato (260 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00614] **LC-MS:** MS (ESI^+): t_R = 0,422 min, m/z = 483,2 [M + H^+]

[00615] A una solución de 2-[4-[(3-iodo-4,5,6,7-tetrahidropirazolo[4,3-c]piridin-1-il)metil]-1-piperidil]pirimidina-5-carboxilato de metilo (260 mg, 539,06 µmol, 1,0 eq) y Et_3N (164 mg, 1,62 mmol, 225,09 µl, 3,0 eq) en DCM (10 ml) se agregó Ac_2O (83 mg, 808,60 µmol, 75,94 µl, 1,5 eq) a 0 °C. La mezcla de reacción se agitó a 25 °C durante 12 h. La mezcla de reacción se neutralizó añadiendo agua (20 ml) a 0 °C, y luego se diluyó con agua (30 ml) y se extrajo con DCM (40 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio anhidro,

se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (condiciones FA: columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua (FA) - ACN]; gradiente: 30 % - 60 % B durante 10 min). El compuesto deseado metil 2-[4-[(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)metil]-1-piperidil]pirimidina-5-carboxilato (260 mg, 492,77 µmol, 91 % de rendimiento) se obtuvo como un sólido blanco.

[00616] δ 4,93 - 4,23 (m, 2H), 3,92 - 3,84 (m, 5H), 3,70 (br s, 2H), 2,98 - 2,83 (m, 2H), 2,62 (br s, 2H), 2,37 (br s, 2H), 1,70 (br d, J = 11,2 Hz, 2H), 1,50 (br s, 2H), 1,30 - 1,16 (m, 2H).

[00617] **LC-MS:** MS (ESI^+): t_R = 0,503 min, m/z = 525,2 [$M + H^+$]

[00618] A una solución de 2-[4-[(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)metil]-1-piperidil]pirimidina-5-carboxilato de metilo (500 mg, 953,55 µmol, 1,0 eq) y 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (377 mg, 1,43 mmol, 1,5 eq) en dioxano (10 ml) se añadieron Cs_2CO_3 (932 mg, 2,86 mmol, 3,0 eq) y Xphos Pd G_4 (82 mg, 95,36 µmol, 0,1 eq). La mezcla de reacción se agitó a 90 °C durante 12 h en N_2. La mezcla se concentró a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 1/1 a 10/1). El compuesto deseado metil 2-[4-[[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]metil]-1-piperidil]pirimidina-5-carboxilato (450 mg, 682,10 µmol, 71 % de rendimiento) se obtuvo como un sólido amarillo claro.

[00619] **LC-MS:** MS (ESI^+): t_R = 0,536 min, m/z = 660,4 [$M + H^+$]

[00620] A una solución de 2-[4-[[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]metil]-1-piperidil]pirimidina-5-carboxilato de metilo (250 mg, 378,94 µmol, 1,0 eq) en ACN (6 ml) y H_2O (1 ml) se agregó 3,4,6,7,8,9-hexahidro-2H-pirimido[1,2-a]pirimidina (158 mg, 1,14 mmol, 3,0 eq). La mezcla de reacción se agitó a 25 °C durante 12 h. A la mezcla de reacción se le agregó HCl 1 M hasta alcanzar un pH de 3 a 4, y luego se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (condición HCl: columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (HCl) –CAN]; gradiente: 30 % - 60 % B durante 10 min). El compuesto deseado ácido 2-[4-[[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]metil]-1-piperidil]pirimidina-5-carboxílico (110 mg, 170,36 µmol, 44 % de rendimiento) se obtuvo como un sólido blanco.

[00621] **LC-MS:** MS (ESI^+): t_R = 0,489 min, m/z = 646,3 [M + H^+]

[00622] A una solución de 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (49 mg, 154,87 µmol, 1,0 eq) y DIPEA (100 mg, 774,35 µmol, 134,88 µl, 5,0 eq) en DMF (5 ml) se le agregó ácido 2-[4-[[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]metil]-1-piperidil]pirimidina-5-carboxílico (100 mg, 154,87 µmol, 1,0 eq) y HATU (118 mg, 309,74 µmol, 2,0 eq). La mezcla de reacción se agitó a 45 oC durante 0,5 h. La mezcla de reacción se inactivó con agua (20 ml) y se extrajo con acetato de etilo (20 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (condiciones FA: columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua (FA) - ACN]; gradiente: 58 % - 88 % B durante 10 min). El compuesto deseado 2-[4-[[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]metil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (69,02 mg, 75,97 µmol, 49 % de rendimiento) se obtuvo como un sólido blanco.

[00623] **1H NMR** (400 MHz, $CDCl_3$): δ = 8,70 (s, 2H), 7,64 - 7,50 (m, 2H), 7,41 (d, J = 6,4 Hz, 1H), 7,10 - 6,94 (m, 2H), 6,88 (d, J = 6,8 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,72 - 6,35 (m, 1H), 5,94 (br d, J = 8,0 Hz, 1H), 4,92 (d, J = 13,2 Hz, 2H), 4,37 - 4,10 (m, 3H), 4,05 (s, 1H), 3,96 (d, J = 2,4 Hz, 3H), 3,91 (br t, J = 5,6 Hz, 1H), 3,86 (d, J = 7,2 Hz, 2H), 3,80 - 3,63 (m, 3H), 3,01 - 2,84 (m, 4H), 2,80 - 2,66 (m, 2H), 2,37 - 2,25 (m, 1H), 2,18 (s, 1H), 2,15 - 2,00 (m, 4H), 1,74 (d, J = 8,8 Hz, 2H), 1,24 (d, J = 13,2 Hz, 14H)

[00624] **LC-MS:** MS (ESI^+): t_R = 2,687 min, m/z = 453,9 [M / 2]

[00625] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 22.

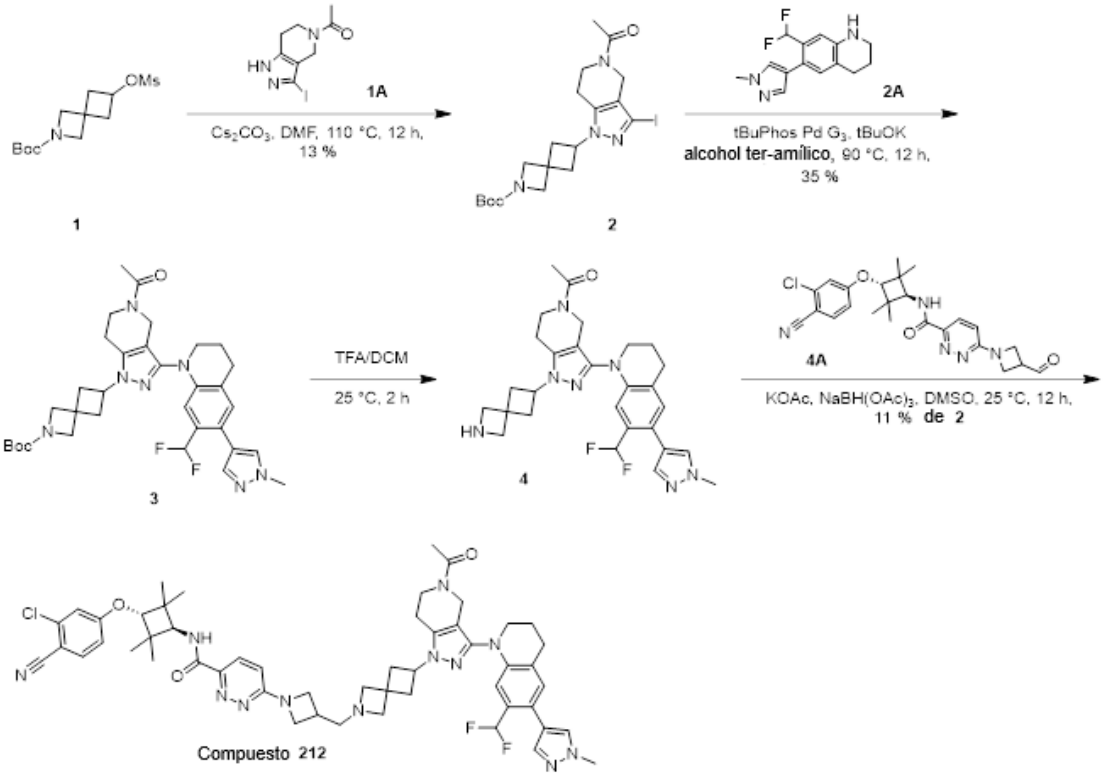
Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
9	2-[4-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]propoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6) δ = 8,76 (s, 2H), 7,89 (d, *J* = 8,8 Hz, 1H), 7,80 - 7,65 (m, 2H), 7,50 (s, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,10 (br s, 1H), 7,04 - 6,98 (m, 1H), 6,96 - 6,60 (m, 2H), 4,32 - 4,19 (m, 3H), 4,17 - 4,09 (m, 2H), 4,07 - 3,99 (m, 3H), 3,86 (s, 3H), 3,76 - 3,64 (m, 2H), 3,61 - 3,51 (m, 3H), 3,49 - 3,40 (m, 4H), 2,83 (br	950,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		d, *J* = 5,6 Hz, 3H), 2,76 - 2,64 (m, 1H), 2,06 (s, 2H), 2,03 - 1,92 (m, 5H), 1,91 - 1,82 (m, 2H), 1,46 - 1,35 (m, 2H), 1,21 (s, 6H), 1,11 (s, 6H)	
43	2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]propoxi]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 8,96 (s, 2 H) 8,04 d, *J*=9,2 Hz, 1 H) 7,90 (d, *J*=8,8 Hz, 1 H) 7,75 (s, 1 H) 7,49 (s, 1 H) 7,22 (d, *J*=2,4 Hz, 1 H) 7,10 (s, 1 H) 7,01 (m, 1 H) 6,61 - 6,94 (m, 2 H) 4,32 - 4,41 (m, 2 H) 4,30 (s, 1 H) 4,10 - 4,17 (m, 3 H) 4,05 - 4,09 (m, 2 H) 3,86 (s, 3 H) 3,62 - 3,72 (m, 3 H) 3,53 - 3,57 (m, 2 H) 2,82 (m, 4 H) 2,22 - 2,27 (m, 2 H) 2,04 (s, 2 H) 1,94 (s, 2 H) 1,22 (s, 6 H) 1,12 (s, 6 H).	867,6
44	2-[3-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]propil-metil-amino]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	*1*H NMR (500 MHz, DMSO-d6) δ = 8,73 - 8,18 (m, 1H), 7,89 - 7,85 (m, 2H), 7,77 - 7,67 (m, 1H), 7,49 - 7,64 (m, 1H), 7,21 (br d, *J* = 2,4 Hz, 1H), 7,10 (br d, J = 9,5 Hz, 1H), 6,94 - 6,60 (m, 1H), 4,28 - 7,31 (m, 1H), 4,16 - 4,08 (m, 1H), 4,05 - 3,97 (m, 3H), 3,86 - 4,17 (m, 2H), 3,73 - 3,64 (m, 1H), 3,61 - 3,56 (m, 1H), 3,17 - 3,13 (m, 3H), 2,86 - 2,81 (m, 1H), 2,80 - 2,76 (m, 1H), 2,69 (br s, 1H), 2,13 - 2,04 (m, 3H), 2,01 - 1,94 (m, 3H), 1,20 - 1,10 (m, 1H).	880,6
45	2-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]etil-metil-amino]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	$_1$H NMR (500 MHz, DMSO-d6) δ = 8,91 - 8,60 (m, 1H), 7,89 - 7,85 (m, 2H), 7,79 - 7,67 (m, 1H), 7,49 - 7,64 (m, 1H), 7,21 (br d, *J* = 8,5 Hz, 1H), 7,00 (br d, *J* = 8,8 Hz, 1H), 6,95 - 6,61 (m, 1H), 4,29 - 7,31 (m, 1H), 4,26 - 4,19 (m, 1H), 4,11 - 3,95 (m, 3H), 3,86 - 4,17 (m, 2H), 3,69 - 3,57 (m, 1H), 3,56 - 3,47 (m, 1H), 3,28 - 3,20 (m,	866,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		3H), 3,05 - 2,92 (m, 1H), 2,87 - 2,77 (m, 1H), 2,64 (br s, 1H), 2,07 - 2,66 (m, 3H), 1,99 - 1,87 (m, 3H), 1,22 - 1,11 (m, 1H).	
46	2-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]etoxi]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6) δ = 8,94 (s, 2H), 7,84 (d, *J* = 8,8 Hz, 1H), 7,78 (br d, *J* = 8,8 Hz, 1H), 7,69 (s, 1H), 7,46 (s, 1H), 7,18 (d, *J* = 2,4 Hz, 1H), 7,09 (s, 1H), 7,04 - 6,99 (m, 1H), 6,88 - 6,56 (m, 2H), 4,79 (t, *J* = 5,6 Hz, 2H), 4,40 (t, *J* = 5,2 Hz, 2H), 4,30 (s, 1H), 4,13 - 4,05 (m, 3H), 3,87 (s, 3H), 3,71 (br t, *J* = 5,2 Hz, 2H), 3,60 - 3,51 (m, 2H), 2,84 (br t, *J* = 5,6 Hz, 4H), 2,10 - 1,91 (m, 5H), 1,25 (s, 6H), 1,16 (s, 6H)	853,6
51	2-[4-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]etoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	8,68 (d, J = 8,6 Hz, 1H), 7,40 (d, J = 6,4 Hz, 1H), 7,10 (d, J = 8,9 Hz, 1H), 6,96 (d, J = 8,6 Hz, 1H), 6,87 (d, J = 3,2 Hz, 1H), 6,80 (d, J = 8,8 Hz, 1H), 6,35 (d, J = 6,2 Hz, 2H), 4,29 - 4,02 (m, 4H), 3,95 (br s, 2H), 3,90 - 3,81 (m, 1H), 3,78 - 3,65 (m, 3H), 3,65 - 3,50 (m, 3H), 2,95 - 2,75 (m, 3H), 2,15 - 2,00 (m, 2H), 1,89 - 1,79 (m, 4H), 1,61 - 1,45 (m, 1H), 1,23 (d, J = 14,4 Hz, 3H).	468,9 ± 2
52	2-[4-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]etil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ=8,71 (d, *J*=2,80 Hz, 2 H) 7,58 (d, *J*=8,80 Hz, 1 H) 7,54 (d, *J*=5,60 Hz, 1 H) 7,41 (d, *J*=6,40 Hz, 1 H) 6,99 - 7,09 (m, 1 H) 6,97 (d, *J*=2,40 Hz, 1 H) 6,86 (s, 1 H) 6,81 (dd, *J*=8,80, 2,40 Hz, 1 H) 6,34 - 6,70 (m, 1 H) 5,89 - 6,04 (m, 1 H) 4,28 (s, 1 H) 4,15 (br s, 2 H) 4,12 (s, 2 H) 4,05 (s, 1 H) 3,96 (s, 3 H) 3,91 (br d, *J*=3,60 Hz, 5 H) 3,65 - 3,82 (m, 3 H) 2,81 - 2,96 (m, 5 H) 2,78 (br t, *J*=5,20 Hz, 1 H) 2,50 - 2,62	921,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		(m, 4 H) 2,17 (s, 1 H) 1,98 - 2,15 (m, 4 H) 1,25 (s, 6 H) 1,22 (s, 6 H).	

[00626] **Ejemplo 23**: Síntesis de 6-[3-[[6-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptan-2-il]metil]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]piridazina-3-carboxamida (**Compuesto 212**)



[00627] La síntesis de **1** se informó en WO2019/8025 A1.

[00628] La síntesis de **2A** se informó en WO2016/86200 A1.

[00629] A una solución de 6-metilsulfoniloxi-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (3,40 g, 11,7 mmol, 2,0 *eq*), 1-(3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridin-5-il)etanona (1,68 g, 5,77 mmol, 1,0 *eq*), Cs_2CO_3 (5,64 g, 17,3 mmol, 3,0 *eq*) en DMF (10 ml). La mezcla se agitó a 110 °C durante 12 h en N_2. La mezcla de reacción se inactivó con agua helada (100 ml) y se extrajo con DCM (100 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex luna C18 150 × 40 mm

× 15 µm; fase móvil: [agua (FA)-ACN]; gradiente: 50 %-80 % B durante 15 min). El compuesto 6-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (352 mg, 724 µmol, 13 % de rendimiento) se obtuvo como un sólido blanco.

[00630] **LC-MS:** MS (ESI^+): t_R = 0,572 min, m/z = 487,2 [M + H^+]

[00631] A una solución de 6-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (160 mg, 329 µmol, 1,0 *eq*), 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (106 mg, 40,3 µmol, 1,2 *eq*), [2-(2-aminofenil)fenil]-metilsulfoniloxi-paladio;diter-butil-[2-(2,4,6-triisopropilfenil)fenil]fosfano (63 mg, 79,0 µmol, 0,2 *eq*) en alcohol terc-amílico (10 ml). A la mezcla se le agregó t-BuOK (1 M, 987 µl, 3,0 *eq*) y se agitó a 90 °C durante 12 h bajo N_2. La mezcla de reacción se vertió en agua (50 ml) y se extrajo con DCM (20 ml) dos veces. Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH = 10:1). El compuesto ter-butil 6-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptano-2-carboxilato (71 mg, 114 µmol, 35 % de rendimiento) se obtuvo como un sólido blanco.

[00632] **LC-MS:** MS (ESI^+): t_R = 0,603 min, m/z = 622,5 [M + H^+]

[00633] A una solución de 6-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (70 mg, 113 µmol, 1,0 *eq*) en DCM (0,5 ml) se agregó TFA (0,5 ml). La mezcla se agitó a 25 °C durante 2 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El compuesto 1- [1-(2-azaespiro [3,3] heptan-6-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c] piridin-5-il] etanona (71 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[00634] **LC-MS:** MS (ESI^+): t_R = 0,493 min, m/z =522,4 [M + H^+]

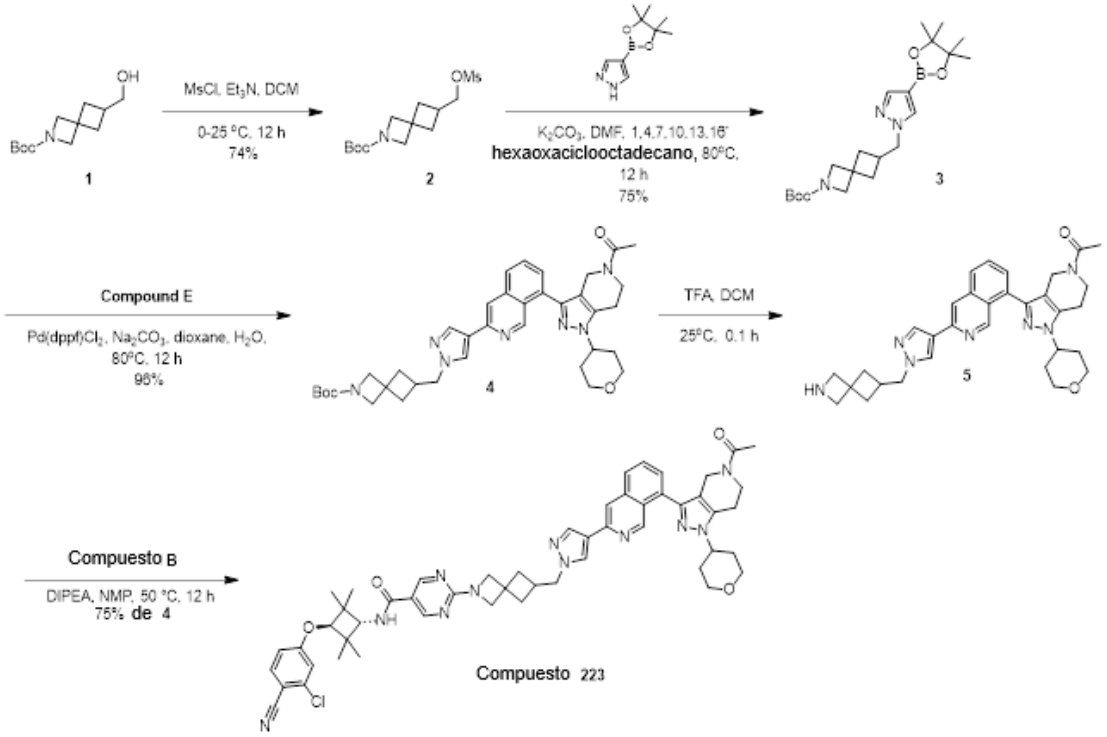
[00635] A una solución de 1-[1-(2-azaespiro[3,3]heptan-6-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (71 mg), N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-6-(3-formilazetidin-1-il)piridazina-3-carboxamida (60 mg, 129 µmol, 1,2 *eq*), KOAc (33 mg, 335 µmol, 3,0 *eq*) en DMSO (1 ml). La mezcla se agitó durante 0,1 h y se agregó $NaBH(OAc)_3$ (71 mg, 335 µmol, 3,0 *eq*). La mezcla se agitó a 25 °C durante 12 h en N_2.

La mezcla de reacción se vertió en agua (50 ml) y se extrajo con DCM (20 ml) dos veces. Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto 6-[3-[[6-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptan-2-il]metil]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]piridazina-3-carboxamida (12 mg, 12,1 µmol, 11 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00636] **^{1}H** (400 MHz, DMSO-d_6) δ = 8,21 (br d, *J* = 9,2 Hz, 1H), 7,90 (d, *J* = 8,4 Hz, 1H), 7,83 (d, *J* = 9,2 Hz, 1H), 7,75 (s, 1H), 7,50 (s, 1H), 7,25 (d, *J* = 2,4 Hz, 1H), 7,11 (br s, 1H), 7,06 - 7,01 (m, 1H), 6,97 - 6,62 (m, 3H), 4,61 (br t, *J* = 8,0 Hz, 1H), 4,45 (s, 1H), 4,22 - 4,07 (m, 4H), 3,99 (d, *J* = 9,0 Hz, 1H), 3,86 (s, 3H), 3,82 - 3,74 (m, 2H), 3,74 - 3,65 (m, 2H), 3,63 - 3,56 (m, 2H), 3,33 - 3,33 (m, 1H), 3,20 (br s, 2H), 2,90 - 2,72 (m, 5H), 2,71 - 2,63 (m, 3H), 2,56 (br t, *J* = 8,0 Hz, 4H), 2,11 - 2,03 (m, 2H), 2,02 - 1,92 (m, 3H), 1,21 (s, 6H), 1,13 (s, 6H).

[00637] **LC-MS:** MS (ESI$^+$): t_R = 2,255 min, m/z =973,6 [M + H$^+$]

[00638] **Ejemplo 24**: Síntesis de 2-[6-[[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 223**)



[00639] A una solución de 6-(hidroximetil)-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (2 g, 8,80 mmol, 1,0 *eq*) en DCM (20 ml) se añadieron Et_3N (4,45 g, 43,99 mmol, 6,12 ml, 5,0 *eq*) y MsCl (1,72 g, 15,02 mmol, 1,16 ml, 1,71 *eq*) a 0 °C. La mezcla se agitó a 25 °C durante 12 h. La mezcla se diluyó con agua helada (80 ml) y se extrajo con acetato de etilo (100 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (100 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 5/0). El compuesto 6-(metilsulfoniloximetil)-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (2 g, 6,55 mmol, 74 % de rendimiento) se obtuvo como un sólido blanco.

[00640] **^{1}H NMR** (400 MHz, CDCl3) δ = 4,16 (d, J = 6,3 Hz, 1H), 3,99 - 3,91 (m, 2H), 3,90 - 3,82 (m, 2H), 3,58 (d, J = 6,4 Hz, 1H), 3,03 (s, 2H), 2,75 - 2,46 (m, 1H), 2,39 - 2,24 (m, 2H), 2,09 - 1,91 (m, 2H), 1,60 (br d, J = 5,1 Hz, 1H), 1,45 (s, 9H)

[00641] A una solución de 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1,27 g, 6,55 mmol, 1,0 *eq*), 6-(metilsulfoniloximetil)-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (2 g, 6,55 mmol, 1,0 *eq*) en DMF (20 ml) se agregó K_2CO_3 (2,72 g, 19,65 mmol, 3,0 *eq*) y 1,4,7,10,13,16-hexaoxaciclooctadecano (173 mg, 654,90 µmol, 0,1 *eq*). La mezcla se agitó a 80 °C durante 30 min. La reacción se diluyó con agua (60 ml) y se extrajo con acetato de etilo (80 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (60 ml x 3), se secaron en sulfato de sodio, se filtraron y se

concentraron hasta secarse. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 12 g, eluyente de gradiente de acetato de etilo/éter de petróleo al 0-20 % a 80 ml/min). El compuesto 6-[[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazol-1-il]metil]-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (2 g, 4,96 mmol, 75 % de rendimiento) se obtuvo como un sólido blanco.

[00642] ^{1}H NMR (400 MHz, CDCl**7,79**): δ 4,13 - 4,09 (m, 2H), 3,93 (s, 2H), 2,70 (t, *J* = 15,5 Hz, 1H), 2,31 - 2,26 (m, 2H), 2,02 - 1,93 (m, 2H), 1,44 (s, 9H).

[00643] **LC-MS:** MS (ESI$^+$): t_R = 0,581 min, m/z = 348,0 [M - 55]

[00644] Una mezcla de 6-[[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazol-1-il]metil]-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (153,79 mg, 381,31 µmol, 2,0 *eq*), [8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil] trifluorometanosulfonato (100 mg, 190,65 µmol, 1,0 *eq*), Pd(dppf)Cl_2 (13,95 mg, 19,07 µmol, 0,1 *eq*), Na_2CO_3 (101,04 mg, 953,27 µmol, 5 *eq*) y H_2O (0,5 ml) en dioxano (5 ml) se desgasificó y purgó con N_2 tres veces, y luego la mezcla se agitó a 80 °C durante 12 h bajo atmósfera de N_2. La reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH=15:1). El compuesto ter-butil 6-[[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]metil]-2-azaespiro[3,3]heptano-2-carboxilato (120 mg, 184,11 µmol, 96,57 % de rendimiento) se obtuvo como un sólido amarillo.

[00645] **LC-MS:** MS (ESI$^+$): t_R = 0,480 min, m/z = 652,5 [M + Na^+]

[00646] A una solución de 6-[[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]metil]-2-azaespiro[3,3]heptano-2-carboxilato de ter-butilo (120 mg, 184,11 µmol, 1,0 *eq*) en DCM (2 ml) se agregó TFA (3,07 g, 26,92 mmol, 2 ml, 146,24 *eq*). La mezcla se agitó a 25 °C durante 0,1 h. La mezcla se concentró al vacío. El compuesto 1-[3-[3-[1-(2-azaespiro[3,3]heptan-6-ilmetil)pirazol-4-il]-8-isoquinolil]-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00647] **LC-MS:** MS (ESI$^+$): t_R = 0,377 min, m/z = 522,4 [M + H^+]

[00648] A una solución de 1-[3-[3-[1-(2-azaespiro[3,3]heptan-6-ilmetil)pirazol-4-il]-8-isoquinolil]-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg, 181,26 µmol, 1,0 *eq*) en NMP (5 ml) se agregó DIPEA (117,14 mg, 906,32 µmol,

157,86 µl, 5,0 *eq*) y 2-cloro-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (76,00 mg, 181,26 µmol, 1,0 *eq*). La mezcla se agitó a 50 °C durante 30 min. La reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. La mezcla se purificó mediante HPLC preparativa (columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua(FA)-ACN]; gradiente: 43 %-73 % B durante 10 min). El compuesto 2-[6-[[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (65,78 mg, 68,36 µmol, 37 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino.

[00649] ^{1}H NMR (400 MHz, DMSO-CDCl3) δ = 9,96 - 9,52 (m, 1H), 8,70 - 8,34 (m, 1H), 8,12 - 8,07 (m, 1H), 8,03 - 7,64 (m, 1H), 7,64 - 7,42 (m, 1H), 7,31 - 7,29 (m, 1H), 7,02 - 6,93 (m, 2H), 6,82 - 7,30 (m, 1H), 6,02 - 5,83 (m, 1H), 4,79 - 4,40 (m, 3H), 4,35 - 4,23 (m, 1H), 4,22 - 4,16 (m, 1H), 4,16 - 4,09 (m, 2H), 4,08 - 4,00 (m, 1H), 3,87 (br s, 1H), 3,68 - 3,51 (m, 1H), 2,99 - 2,84 (m, 3H), 2,54 (br s, 1H), 2,24 - 2,17 (m, 1H), 2,10 - 2,56 (m, 1H), 2,06 (d, **J** = 2,9 Hz, 3H), 1,30 - 1,20 (m, 3H).

[00650] **LC-MS:** MS (ESI$^+$): t_R = 2,675 min, m/z = 934,7 [M + H$^+$]

[00651] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describió en los Ejemplos 23 y 24.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
209	6-[3-[[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-3-azaespiro[5,5]undecan-3-il]metil]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]piridazina-3-carboxamida	δ = 8,41 - 8,37 (m, 1H), 8,18 (d, *J* = 8,8 Hz, 1H), 7,97 (d, *J* = 9,2 Hz, 1H), 7,62 - 7,50 (m, 2H), 7,41 (d, *J* = 5,6 Hz, 1H), 7,07 - 6,95 (m, 2H), 6,93 - 6,78 (m, 2H), 6,59 (d, *J* = 8,8 Hz, 2H), 4,42 - 4,32 (m, 2H), 4,27 (s, 1H), 4,18 (d, *J* = 9,2 Hz, 1H), 4,13 (s, 1H), 4,07 (s, 1H), 4,00 - 3,88 (m, 7H), 3,79 - 3,66 (m, 3H), 3,25 - 3,10 (m, 1H), 2,92 - 2,78 (m, 5H), 2,73 (s, 1H), 2,57 (d, *J* = 8,2 Hz, 4H), 2,22 - 2,15 (m, 2H), 2,10 - 2,02 (m, 5H), 1,97 - 1,84 (m, 6H), 1,80 (s, 4H), 1,28 (s, 6H), 1,21 (s, 6H)	1029,7
216	2-[6-[[6-[5-acetil-3-[7-(difluorometil)-6-(1-	(DMSO-d_6) δ = 8,72 (s, 2H), 7,90 (d, *J* = 8,8 Hz, 1H),	1013,8

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptan-2-il]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	7,75 (s, 1H), 7,73 (br d, *J* = 9,6 Hz, 1H), 7,50 (s, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,13 - 7,08 (m, 1H), 7,03 - 6,97 (m, 1H), 6,96 - 6,60 (m, 2H), 4,60 (br t, *J* = 8,0 Hz, 1H), 4,28 (s, 1H), 4,17 - 4,08 (m, 4H), 4,03 (d, *J* = 9,2 Hz, 1H), 3,99 (s, 2H), 3,86 (s, 3H), 3,74 - 3,64 (m, 2H), 3,62 - 3,56 (m, 2H), 3,26 (br s, 2H), 3,14 (br s, 2H), 2,87 - 2,81 (m, 2H), 2,78 (br t, *J* = 3,2 Hz, 1H), 2,68 - 2,63 (m, 1H), 2,61 - 2,52 (m, 4H), 2,40 (br d, *J* = 6,4 Hz, 2H), 2,29 - 2,22 (m, 2H), 2,18 - 2,11 (m, 1H), 2,06 (s, 2H), 2,01 - 1,93 (m, 3H), 1,91 - 1,85 (m, 2H), 1,20 (s, 6H), 1,10 (s, 6H)	
217	2-[6-[6-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptano-2-carbonil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d6) δ = 8,73 (d, *J* = 2,8 Hz, 2H), 8,13 (s, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,78 - 7,70 (m, 2H), 7,50 (s, 1H), 7,21 (d, *J* = 2,0 Hz, 1H), 7,11 (s, 1H), 7,03 - 6,98 (m, 1H), 6,96 - 6,63 (m, 2H), 4,72 - 4,60 (m, 1H), 4,28 (s, 1H), 4,19 - 4,08 (m, 5H), 4,07 - 3,99 (m, 4H), 3,96 (s, 1H), 3,89 - 3,82 (m, 4H), 3,74 - 3,58 (m, 4H), 3,04 - 2,93 (m, 1H), 2,87 - 2,77 (m, 3H), 2,70 - 2,60 (m, 5H), 2,33 (br t, *J* = 8,8 Hz, 4H), 2,09 - 2,04 (m, 2H), 2,01 - 1,92 (m, 3H), 1,21 (s, 6H), 1,10 (s, 6H)	1027,6
218	2-[6-[6-[5-acetil-3-[7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptano-2-carbonil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-	(DMSO-d6) δ = 8,73 (d, *J* = 2,4 Hz, 2H), 8,13 (s, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,72 (br d, *J* = 8,8 Hz, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,12 (d, *J* = 7,6 Hz, 1H), 7,03 - 6,97 (m, 1H), 6,95 - 6,62 (m, 3H), 4,70 - 4,59 (m, 1H), 4,28 (s, 1H), 4,14 (br d, *J* = 7,6 Hz, 3H), 4,09 (br s,	947,4

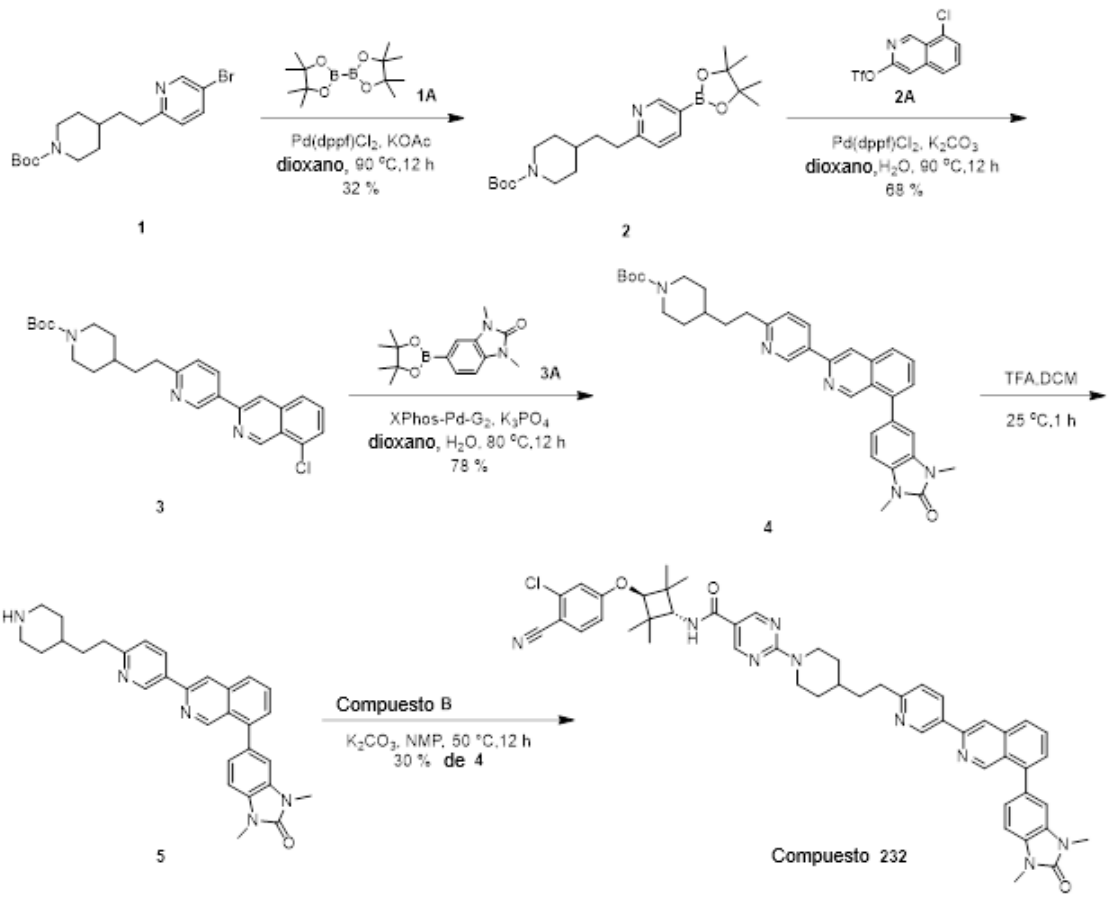
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	5-carboxamida	1H), 4,07 - 4,04 (m, 2H), 4,01 (br d, *J* = 3,2 Hz, 2H), 3,95 (s, 1H), 3,85 (s, 1H), 3,74 - 3,66 (m, 2H), 3,59 (br d, *J* = 6,0 Hz, 2H), 3,03 - 2,91 (m, 1H), 2,90 - 2,71 (m, 4H), 2,64 (br d, *J* = 8,0 Hz, 4H), 2,34 (br t, *J* = 8,8 Hz, 4H), 2,08 - 2,05 (m, 2H), 1,99 - 1,91 (m, 3H), 1,79 - 1,72 (m, 1H), 1,21 (s, 6H), 1,11 (s, 6H)	
219	2-[6-[[6-[5-acetil-3-[7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptan-2-il]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6) δ = 8,72 (s, 2H), 7,89 (d, *J* = 8,8 Hz, 1H), 7,71 (d, *J* = 9,2 Hz, 1H), 7,21 (d, *J* = 2,4 Hz, 1H), 7,11 (d, *J* = 7,6 Hz, 1H), 7,03 - 6,99 (m, 1H), 6,97 - 6,67 (m, 2H), 6,65 (br d, *J* = 6,4 Hz, 1H), 4,58 (br t, *J* = 8,0 Hz, 1H), 4,28 (s, 1H), 4,11 (s, 2H), 4,09 - 4,01 (m, 3H), 4,01 - 3,97 (m, 2H), 3,73 - 3,65 (m, 2H), 3,58 (br d, *J* = 6,0 Hz, 2H), 3,23 (br s, 2H), 3,12 (br s, 2H), 2,86 - 2,74 (m, 3H), 2,65 (br t, *J* = 5,6 Hz, 1H), 2,61 - 2,51 (m, 4H), 2,38 (br d, *J* = 6,8 Hz, 2H), 2,30 - 2,21 (m, 2H), 2,18 - 2,09 (m, 1H), 2,07 - 2,04 (m, 2H), 2,00 - 1,84 (m, 5H), 1,20 (s, 6H), 1,11 (s, 6H)	933,5
220	2-[6-[6-[5-acetil-3-(6-ciano-3,4-dihidro-2H-quinolin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptano-2-carbonil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	$_6$H NMR (400 MHz, DMSO-*d6*) δ = 7,90 - 8,45 (m, 1H), 7,76 – 7,67 (m, 1H), 7,41 (s, 1H), 7,34 - 7,25 (m, 2H), 7,23 - 7,16 (m, 1H), 7,03 – 6,94 (m, 2H), 6,49 – 6,35 (m, 1H), 4,75 – 4,58 (m, 1H), 4,28 – 4,19 (m, 1H), 4,07 – 3,98 (m, 1H), 3,85 - 3,56 (m, 1H), 3,05 – 2,90 (m, 1H), 2,85 - 2,59 (m, 2H), 2,39 - 2,28 (m, 4H), 2,06 (s, 2H), 2,01 1,88 (m, 1H), 1,21 - 1,10 (m, 1H).	922,4
221	2-[6-[[6-[5-acetil-3-(6-ciano-3,4-dihidro-2H-quinolin-1-il)-	*1*H NMR (500 MHz, METANOL-d4) δ = 8,71 (s,	908,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,3]heptan-2-il]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H), 7,72 - 7,82 (m, 1H), 7,65 - 7,55 (m, 1H), 7,37 - 7,32 (m, 1H), 7,29 - 7,21 (m, 1H), 7,15 - 7,10 (m, 1H), 7,01 - 6,94 (m, 1H), 6,51 - 6,40 (m, 2H), 6,73 (d, J = 8,5 Hz, 1H), 4,76 - 4,64 (m, 1H), 4,29 - 4,17 (m, 1H), 4,13 - 4,63 (m, 1H), 4,11 - 4,05 (m, 1H), 3,88 - 3,78 (m, 3H), 3,75 - 3,64 (m, 2H), 3,64 - 3,54 (m, 1H), 3,37 - 3,33 (m, 1H), 2,89 - 2,81 (m, 2H), 2,79 - 2,70 (m, 6H), 2,43 - 2,93 (m, 1H), 2,93 - 2,89 (m, 3H), 2,11 - 2,00 (m, 3H), 1,27 - 2,46 (m, 2H), 1,21 - 0,97 (m, 6H).	
224	2-[6-[[4-[8-(5-acetil-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	10,04 (d, *J* = 8,6 Hz, 1H), 7,59 (d, *J* = 8,1 Hz, 1H), 7,27 (br s, 1H), 6,98 (d, *J* = 2,4 Hz, 1H), 6,82 (d, *J* = 8,1 Hz, 1H), 6,04 (br s, 1H), 4,66 (s, 1H), 4,48 (s, 1H), 4,31 - 4,19 (m, 4H), 4,16 - 4,09 (m, 3H), 4,07 - 4,00 (m, 2H), 3,92 - 3,86 (m, 3H), 2,93 - 2,82 (m, 2H), 2,54 - 2,42 (m, 1H), 2,29 (s, 3H), 2,13 - 2,04 (m, 1H), 1,56 - 1,38 (m, 1H), 1,24 (d, *J* = 11,9 Hz, 3H).	864,7
225	2-[6-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,86 - 9,62 (m, 1H), 8,67 (s, 2H), 8,07 (s, 2H), 7,89 - 7,76 (m, 2H), 7,69 - 7,73 (m, 1H), 7,57 (d, *J* = 8,8 Hz, 1H), 7,54 - 7,43 (m, 1H), 6,96 (d, *J* = 2,4 Hz, 1H), 6,78 - 6,81 (m, 1H), 5,90 - 5,94 (m, 1H), 4,70 - 4,45 (m, 2H), 4,35 - 4,23 (m, 1H), 4,22 - 4,13 (m, 6H), 4,12 - 4,06 (m, 3H), 4,05 - 3,99 (m, 2H), 3,83 (t, *J* = 5,6 Hz, 1H), 3,57 (t, *J* = 12,4 Hz, 2H), 2,97 - 2,81 (m, 2H), 2,51 - 2,34 (m, 4H), 2,27 - 2,19 (m, 2H), 2,14 - 2,01 (m, 4H), 1,98 - 1,85 (m, 4H), 1,24 (s, 6H), 1,21 (s, 6H)	948,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
226	2-[6-[2-[4-[8-(5-acetil-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, METANOL-d4) δ = 8,66 - 8,07 (m, 1H), 7,77 (s, 1H), 7,76 - 7,67 (m, 2H), 7,57 - 7,14 (m, 1H), 7,55 - 7,47 (m, 2H), 6,96 (d, J = 2,4 Hz, 1H), 6,84 - 6,75 (m, 1H), 6,01 - 5,84 (m, 1H), 4,63 - 4,45 (m, 1H), 4,35 - 4,14 (m, 1H), 4,14 - 4,07 (m, 1H), 4,07 - 3,92 (m, 2H), 3,92 - 3,86 (m, 3H), 3,86 - 3,75 (m, 1H), 2,93 - 2,85 (m, 1H), 2,85 - 2,85 (m, 1H), 2,85 - 2,35 (m, 2H), 2,29 - 2,22 (m, 1H), 2,30 - 2,21 (m, 1H), 2,09 - 1,79 (m, 1H), 1,79 - 1,84 (m, 1H), 1,24 - 1,21 (m, 2H).	878,5
227	2-[6-[2-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]etil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	*9,83*H NMR (6,8 Hz, DMSO-*d6*) δ = 8,68 (s, 1H), 8,43 (s, 1H), 8,24 (s, 1H), 8,10 (t, *J* = 11,1 Hz, 1H), 7,87 - 7,93 (m, 1H), 7,72 - 7,79 (m, 1H), 7,63 - 7,22 (m, 2H), 7,22 - 7,28 (m, 1H), 6,96 - 6,91 (m, 2H), 6,78 - 6,81 (m, 1H), 5,93 (br d, *J* = 8,4 Hz, 1H), 4,72 (d, *J* = 8,6 Hz, 1H), 4,24 - 4,14 (m, 1H), 4,13 - 4,07 (m, 1H), 4,06 - 3,99 (m, 1H), 3,86 - 4,14 (m, 1H), 3,54 - 3,60 (m, 3H), 2,94 (s, 3H), 2,90 (s, 3H), 2,53 - 2,35 (m, 1H), 2,24 - 2,32 (m, 1H), 2,21 - 2,08 (m, 1H), 1,98 - 1,84 (m, 1H)	959,4
228	2-[6-[[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d6) δ = 9,25 (s, 1H), 8,69 (d, J = 4,8 Hz, 2H), 8,11 (d, J = 4,8 Hz, 1H), 7,98 - 7,70 (m, 2H), 7,67 - 7,54 (m, 2H), 7,29 - 6,96 (m, 1H), 6,85 - 6,74 (m, 1H), 7,33 - 5,92 (m, 1H), 4,67 - 4,51 (m, 1H), 4,36 – 4,21 (m, 1H), 4,21 - 4,09 (m, 1H), 4,06 - 3,99 (m, 2H), 3,86 - 3,58 (m, 2H), 3,02 - 2,94 (m, 1H), 2,97 - 2,87 (m, 1H), 2,82 - 2,69 (m, 2H), 2,53 – 2,37 (m, 1H),	945,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2,23 - 2,21 (m, 2H), 2,17 - 2,05 (m, 2H), 1,98 - 1,24 (m, 1H).	
229	2-[6-[2-[5-[8-(5-acetil-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]etil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	9,78 (d, J = 8,6 Hz, 1H), 8,41 (d, J = 7,9 Hz, 1H), 8,11 (d, J = 10,8 Hz, 1H), 7,91 (d, J = 8,6 Hz, 1H), 7,76 (dd, J = 8,4, 12,4 Hz, 1H), 7,53 (d, J = 7,9 Hz, 1H), 6,96 (d, J = 2,4 Hz, 1H), 6,80 (br t, J = 8,4 Hz, 2H), 4,63 - 4,47 (m, 1H), 4,14 - 4,07 (m, 2H), 4,06 - 3,99 (m, 1H), 3,91 (br t, J = 6,0 Hz, 2H), 2,90 (br d, J = 5,6 Hz, 2H), 2,83 (s, 3H), 2,44 - 2,35 (m, 2H), 2,29 - 3,11 (m, 3H), 2,21 - 2,05 (m, 3H), 1,97 - 1,88 (m, 2H), 1,23 (br d, J = 12,0 Hz, 3H).	889,7
230	2-[6-[[5-[8-(5-acetil-1-metil-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]metil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ=9,78 (d, *J*=12,00 Hz, 1 H) 9,25 (br s, 1 H) 8,69 (s, 2 H) 8,40 (br d, *J*=5,60 Hz, 1 H) 8,11 (d, *J*=11,20 Hz, 1 H) 7,91 (dd, *J*=14,80, 8,40 Hz, 1 H) 7,76 (dt, *J*=12,40, 7,60 Hz, 1 H) 7,59 (br s, 1 H) 7,57 (d, *J*=8,40 Hz, 1 H) 6,96 (d, *J*=1,60 Hz, 1 H) 6,80 (dd, *J*=8,80, 1,60 Hz, 1 H) 5,92 (d, *J*=8,00 Hz, 1 H) 4,64 (s, 1 H) 4,47 (s, 1 H) 4,23 (s, 2 H) 4,09 - 4,17 (m, 3 H) 3,98 - 4,06 (m, 2 H) 3,92 (d, *J*=2,40 Hz, 3 H) 3,85 (br t, *J*=5,60 Hz, 1 H) 3,00 (br d, *J*=7,20 Hz, 2 H) 2,90 (br t, *J*=5,60 Hz, 1 H) 2,84 (br t, *J*=5,60 Hz, 1 H) 2,75 (dt, *J*=15,60, 7,60 Hz, 1 H) 2,41 (br t, *J*=10,00 Hz, 2 H) 2,21 (s, 1 H) 2,12 (br d, *J*=9,20 Hz, 2 H) 2,04 - 2,08 (m, 2 H) 1,24 (s, 6 H) 1,21 (s, 6 H).	875,6

[00652] Ejemplo 25: Síntesis de N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[8-(1,3-dimetil-2-oxo-bencimidazol-5-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida (**Compuesto 232**)



[00653] La síntesis de **1** se informó en WO2023/38500 A1.

[00654] La síntesis de **2A** fue reportada en Dalton Transactions, 2008, vol. 8, n.° 4, páginas 491-498.

[00655] La síntesis de **3A** fue reportada en WO2017/205536 A2.

[00656] A una solución de 4-[2-(5-bromo-2-piridil)etil]piperidina-1-carboxilato de ter-butilo (3,80 g, 10,20 mmol, 1,0 *eq*) en dioxano (72 ml) se añadieron $Pd(dppf)Cl_2$ (752 mg, 1,00 mmol, 0,1 *eq*), KOAc (3,03 g, 30,81 mmol, 3,0 *eq*) y 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (5,23 g, 20,50 mmol, 2,0 *eq*). La mezcla se agitó a 90 °C durante 12 h en N_2. La solución de reacción se diluyó con agua (15 ml) y se extrajo con EtOAc (15 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 50/1 a 5/1). El compuesto ter-butil 4-[2-[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil]etil]piperidina-1-carboxilato (1,40 g, 3,30 mmol, 32 % de rendimiento) se obtuvo como un sólido negro.

[00657] **LC-MS:** MS (ESI$^+$): t_R = 0,808 min, m/z = 416,2 [M + H$^+$]

[00658] A una solución de trifluorometanosulfonato de (8-cloro-3-isoquinolil) (300 mg, 962 µmol, 1,0 *eq*) y 4-[2-[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil]etil]piperidina-1-carboxilato de ter-butilo (400 mg, 962 µmol, 1,0 *eq*) en dioxano (5 ml) y H_2O (0,5 ml) se agregó K_2CO_3 (399 mg, 2,80 mmol, 3,0 *eq*) y Pd(dppf)Cl_2 (70 mg, 96 µmol, 0,1 *eq*) bajo atmósfera de N_2. La mezcla se agitó a 90 °C durante 12 h en atmósfera de N_2. El residuo se diluyó con H_2O (30 ml) y se extrajo con EtOAc (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 10/1 a 0/1). Compuesto 4-[2-[5-(8-cloro-3-isoquinolil)-2-piridil]etil]piperidina-1-carboxilato de ter-butilo (300 mg, 663 µmol, 68 % de rendimiento) se obtuvo como un sólido blanco.

[00659] **LC-MS:** MS (ESI$^+$): t_R = 0,566 min, m/z = 451,2 [M + H$^+$]

[00660] A una solución de 4-[2-[5-(8-cloro-3-isoquinolil)-2-piridil]etil]piperidina-1-carboxilato de ter-butilo (240 mg, 530 µmol, 1,0 *eq*) y 1,3-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)bencimidazol-2-ona (198 mg, 690 µmol, 1,3 *eq*) en dioxano (5 ml) y H_2O (1,5 ml) se agregó K_3PO_4 (338 mg, 1,50 mmol, 3,0 *eq*) y XPhos-Pd-G_2 (41 mg, 53 µmol, 0,1 *eq*) bajo atmósfera de N_2 . La mezcla se agitó a 80 °C durante 12 h en atmósfera de N_2. El residuo se diluyó con H_2O (30 ml) y se extrajo con EtOAc (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 10/1 a 0/1). El compuesto ter-butil 4-[2-[5-[8-(1,3-dimetil-2-oxo-benzimidazol-5-il)-3-isoquinolil]-2-piridil]etil]piperidina-1-carboxilato (240 mg, 415 µmol, 78 % de rendimiento) se obtuvo como un sólido blanco.

[00661] **LC-MS:** MS (ESI$^+$): t_R = 0,555 min, m/z = 577,3 [M + H$^+$]

[00662] A una solución de 4-[2-[5-[8-(1,3-dimetil-2-oxo-bencimidazol-5-il)-3-isoquinolil]-2-piridil]etil]piperidina-1-carboxilato de ter-butilo (240 mg, 415 µmol, 1,0 *eq*) en DCM (3 ml) se agregó TFA (1,54 g, 13,40 mmol, 1,0 ml, 32,4 *eq*). La mezcla se agitó a 25 °C durante 1 hora. La mezcla de reacción se concentró a presión reducida para obtener un producto crudo. El compuesto 1,3-dimetil-5-[3-[6-[2-(4-piperidil)etil]-3-piridil]-8-isoquinolil]bencimidazol-2-ona (198 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

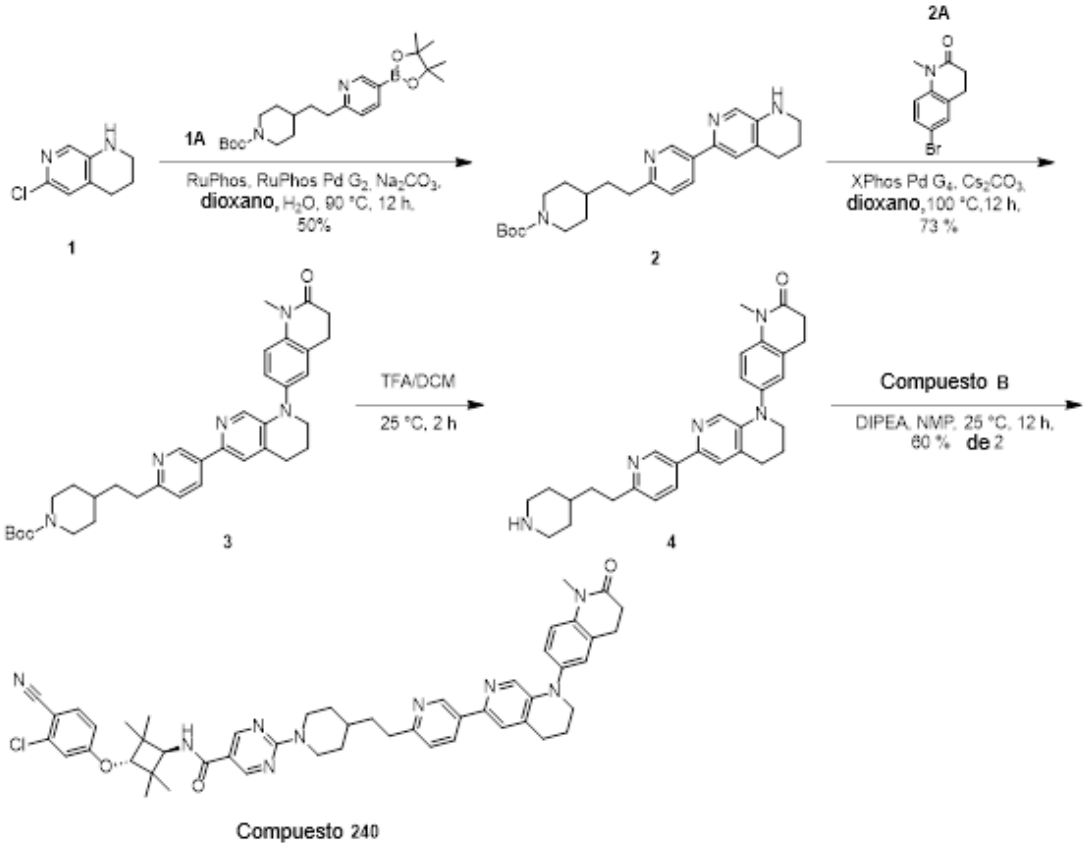
[00663] **LC-MS:** MS (ESI$^+$): t_R = 0,434 min, m/z = 477,2 [M + H$^+$]

[00664] Una mezcla de 1,3-dimetil-5-[3-[6-[2-(4-piperidil)etil]-3-piridil]-8-isoquinolil]bencimidazol-2-ona (99 mg), 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (86 mg, 207 µmol, 1,0 *eq*) y K_2CO_3 (85 mg, 621 µmol, 3,0 *eq*) en NMP (1,5 ml) se agitó a 50 °C durante 12 h. La mezcla de reacción se filtró y concentró a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 58 %-88 % B durante 10 min). Compuesto N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[8-(1,3-dimetil-2-oxo-bencimidazol-5-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida (55 mg, 30 % de rendimiento en dos pasos) se obtuvo como un sólido blanco. .

[00665] ^{1}H NMR (400 MHz, DMSO-**d_6**) δ = 9,38 - 9,27 (m, 1H), 8,75 – 8,57 (m, 1H), 8,47 (s, 1H), 8,04 - 7,67 (m, 2H), 7,92 - 7,83 (m, 1H), 7,73 – 7,58 (m, 2H), 7,47 – 7,40 (m, 1H), 7,36 – 7,32 (m, 1H), 7,30 – 7,26 (m, 1H), 7,21 – 7,00 (m, 1H), 4,75 - 4,28 (m, 1H), 4,03 – 3,41 (m, 6H), 2,98 - 2,90 (m, 2H), 2,89 - 2,82 (m, 2H), 1,85 (s, 2H), 1,73 1,58 (m, 1H), 1,21 - 1,05 (m, 1H).

[00666] **LC-MS:** MS (ESI$^+$): t_R = 2,298 min, m/z = 859,3 [M + H$^+$]

[00667] **Ejemplo 26**: Síntesis de N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[1-(1-metil-2-oxo-3,4-dihidroquinolin-6-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil] etil]-1-piperidil] pirimidina-5-carboxamida (**Compuesto 240**)



[00668] La síntesis de **1** fue reportada en WO2022/20342 A1.

[00669] A una solución de 6-cloro-1,2,3,4-tetrahidro-1,7-naftiridina (200 mg, 1,19 mmol, 1,0 *eq*), 4-[2-[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil] etil] piperidina-1-carboxilato de ter-butilo (1,33 g, 3,20 mmol, 2,7 *eq*), diciclohexil-[2-(2,6-diisopropoxifenil)fenil]fosfano (55 mg, 119 µmol, 0,1 *eq*), [2-(2-aminofenil)fenil]-cloropaladio;diciclohexil-[2-(2,6-diisopropoxifenil)fenil]fosfano (92 mg, 119 µmol, 0,1 *eq*) en dioxano (6,5 ml) se agregó Na_2CO_3 (2 M, 1,8 ml, 3,0 *eq*) en H_2O (1,8 ml) bajo N_2. La mezcla se agitó a 90 °C durante 12 h. La mezcla se vertió en agua helada (0,1 l) y se extrajo con EtOAc (0,1 l dos veces). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto ter-butil 4-[2-[5-(1,2,3,4-tetrahidro-1,7-naftiridin-6-il)-2-piridil] etil] piperidina-1-carboxilato (253 mg, 599 µmol, 50 % de rendimiento) se obtuvo como un sólido amarillo.

[00670] **LC-MS:** MS (ESI^+): t_R = 0,553 min, m/z = 582,6 [M + H^+]

[00671] A una solución de 4-[2-[5-(1,2,3,4-tetrahidro-1,7-naftiridin-6-il)-2-piridil] etil] piperidina-1-carboxilato de ter-butilo (200 mg, 473 µmol, 1,0 *eq*), 6-bromo-1-metil-3,4-

dihidroquinolin-2-ona (140 mg, 583 µmol, 1,2 *eq*), Xphos Pd G4 (40 mg, 46,5 µmol, 1,0 *eq*), Cs_2CO_3 (312 mg, 958 µmol, 2,0 *eq*) en dioxano (8 ml). La mezcla se agitó a 100 °C durante 12 h en N_2. La mezcla de reacción luego se vertió en agua (50 ml) y se extrajo con DCM (20 ml). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex Luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 37 %-67 % B durante 10 min). El compuesto ter-butil 4-[2-[5-[1-(1-metil-2-oxo-3,4-dihidroquinolin-6-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil] etil] piperidina-1-carboxilato (201 mg, 346 µmol, 73 % de rendimiento) se obtuvo como un sólido amarillo.

[00672] **LC-MS:** MS (ESI^+): t_R = 0,554 min, m/z = 582,6 [M + H^+]

[00673] A una solución de 4-[2-[5-[1-(1-metil-2-oxo-3,4-dihidroquinolin-6-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil] etil] piperidina-1-carboxilato de ter-butilo (100 mg, 172 µmol, 1,0 *eq*) en DCM (1 ml) se agregó TFA (0,5 ml). La mezcla se agitó a 25 °C durante 2 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El compuesto 1-metil-6-[6-[6-[2-(4-piperidil) etil]-3-piridil]-3,4-dihidro-2H-1,7-naftiridin-1-il]-3,4-dihidroquinolin-2-ona (102 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00674] **LC-MS:** MS (ESI^+): t_R = 0,469 min, m/z =482,4 [M + H^+]

[00675] A una solución de 1-metil-6-[6-[6-[2-(4-piperidil)etil]-3-piridil]-3,4-dihidro-2H-1,7-naftiridin-1-il]-3,4-dihidroquinolin-2-ona (51 mg), 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (54 mg, 129 µmol, 1,5 *eq*) en NMP (1 ml) se agregó DIPEA (33 mg, 257 µmol, 45,0 µl, 3,0 e*q*). La mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se vertió en 50 ml de agua helada a 0 °C y luego se extrajo con DCM (20 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 50 %-80 % B durante 10 min). El compuesto N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[1-(1-metil-2-oxo-3,4-dihidroquinolin-6-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil] etil]-1-piperidil] pirimidina-5-carboxamida (44,87 mg, 51,4 µmol, 60 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[00676] **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 9,03 (d, *J* = 2,4 Hz, 1H), 8,75 (s, 2H), 8,27 (br d, *J* = 8,0 Hz, 1H), 7,90 (d, *J* = 8,8 Hz, 1H), 7,85 (s, 1H), 7,74 - 7,66 (m, 2H), 7,39 (br

d, *J* = 8,4 Hz, 1H), 7,25 - 7,19 (m, 3H), 7,18 - 7,13 (m, 1H), 7,03 - 6,97 (m, 1H), 4,75 (br d, *J* = 13,2 Hz, 2H), 4,29 (s, 1H), 4,03 (d, *J* = 9,2 Hz, 1H), 3,66 - 3,58 (m, 2H), 3,27 (s, 3H), 2,99 - 2,91 (m, 2H), 2,89 (br d, *J* = 4,4 Hz, 4H), 2,86 - 2,80 (m, 2H), 2,60 - 2,54 (m, 2H), 2,06 - 1,97 (m, 2H), 1,83 (br d, *J* = 11,2 Hz, 2H), 1,72 - 1,54 (m, 3H), 1,21 (s, 6H), 1,11 (s, 8H)

[00677] LC-MS: MS (ESI$^+$): t_R = 2,182 min, m/z =864,6 [M + H$^+$]

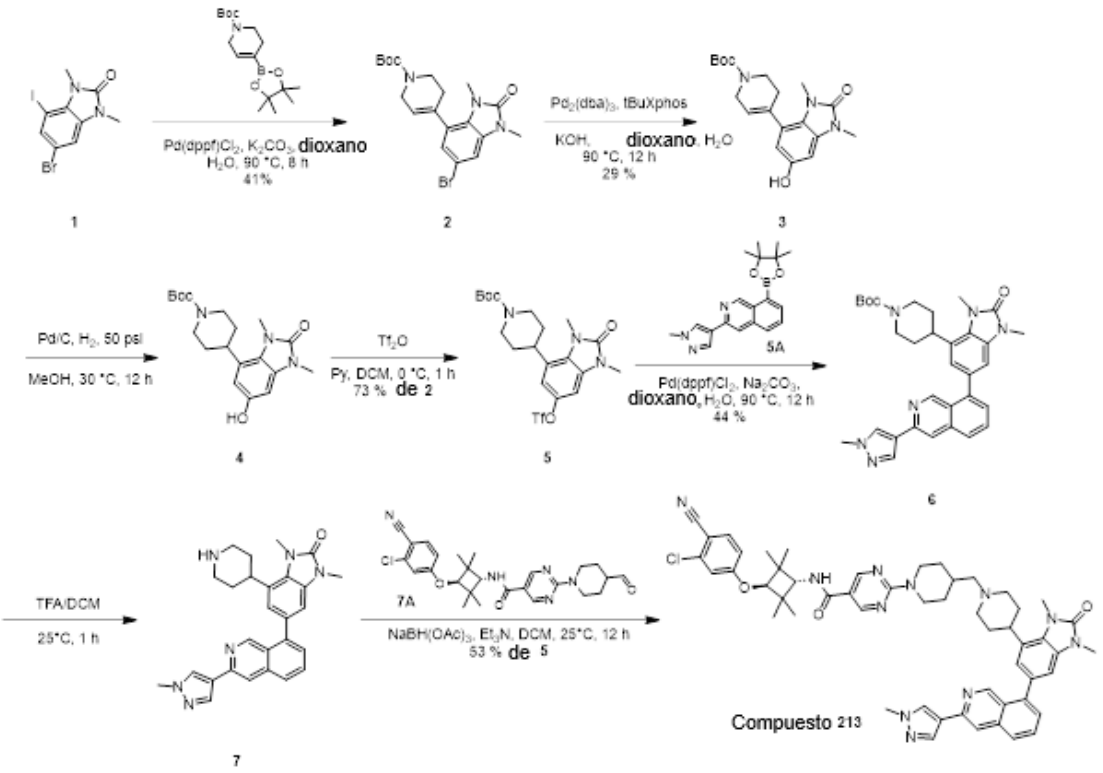
[00678] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en los ejemplos 25 y 26.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS (M+H)$^+$:**
233	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[7-(difluorometil)-1-(1,3-dimetil-2-oxo-bencimidazol-5-il)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida	$_1$H NMR (400 MHz, DMSO-d6) δ = 8,75 - 8,38 (m, 1H), 8,21 – 8,11 (m, 1H), 7,90 (s, 1H), 7,74 - 7,55 (m, 2H), 7,34 - 7,29 (m, 1H), 7,25 – 7,20 (m, 2H), 7,17 – 7,15 (m, 1H), 7,05 – 6,97 (m, 1H), 6,75 – 6,41 (m, 1H), 4,75 – 4,29 (m, 1H), 3,62 - 3,36 (m, 1H), 3,00 – 2,86 (m, 4H), 2,85 - 2,76 (m, 2H), 2,10 - 1,99 (m, 2H), 1,84 (s, 2H), 1,72 1,58 (m, 1H), 1,21 - 1,11 (m, 1H).	913,4
234	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[1-(1,3-dimetil-2-oxo-bencimidazol-5-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridilo]etil]-1-piperidilo]pirimidina-5-carboxamida	*1*H NMR (400 MHz, DMSO-d_6) δ = 9,03 - 8,95 (m, 1H), 7,88 - 8,74 (m, 1H), 8,18 - 8,12 (m, 3H), 7,92 - 7,85 (m, 1H), 7,75 - 7,61 (m, 1H), 7,30 - 7,24 (m, 1H), 7,23 - 7,15 (m, 1H), 7,04 - 6,96 (m, 1H), 4,82 - 4,64 (m, 1H), 4,28 - 5,15 (m, 1H), 4,08 - 3,97 (m, 1H), 3,65 - 3,59 (m, 2H), 3,58 - 3,33 (m, 6H), 2,96 (s, 3H), 2,91 - 2,83 (m, 2H), 2,83 - 2,69 (m, 3H), 2,09 - 1,99 (m, 2H), 1,88 - 1,74 (m, 2H), 1,69 - 1,35 (m, 2H), 1,35 - 0,93 (m, 6H).	865,6
235	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[8-(3-metil-2-oxo-1,3-benzotiazol-5-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida	δ = 9,41 (s, 1 H) 9,27 (s, 1 H) 8,70 (s, 2 H) 8,42 (m, 1 H) 8,17 (s, 1 H) 7,96 (d, *J*=8,8 Hz, 1 H) 7,80 (t, *J*=7,6 Hz, 1 H) 7,55 - 7,66 (m, 3 H) 7,31 - 7,41 (m, 2 H) 7,15 - 7,24 (m, 1 H) 6,97 (d, *J*=2,4 Hz, 1 H) 6,81 (m, 1 H) 5,92 (m, 1 H) 4,87 (m, 2 H) 4,13 (d, *J*=8,0 Hz, 1 H) 4,05 (s, 1 H) 3,51 (s, 3 H) 2,89 - 3,06 (m, 4 H) 1,87 - 1,98 (m, 2 H) 1,76 -	863,3

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		1,86 (m, 2 H) 1,66 - 1,72 (m, 1 H) 1,27 - 1,34 (m, 2 H) 1,25 (s, 6 H) 1,22 (s, 6 H).	
236	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[7-(difluorometil)-1-(3-metil-2-oxo-1,3-benzotiazol-5-il)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida	1H NMR (400 MHz, DMSO-d6) δ = 8,65 (s, 1H), 7,66 (d, J = 4,8 Hz, 2H), 7,45 (d, J = 4,8 Hz, 1H), 7,26 - 7,21 (m, 1H), 7,14 - 7,07 (m, 2H), 7,04 - 7,54 (m, 1H), 7,02 - 6,94 (m, 1H), 6,85 - 6,76 (m, 1H), 6,52 - 6,19 (m, 1H), 5,92 – 5,04 (m, 1H), 4,88 - 4,13 (m, 1H), 4,36 - 4,05 (m, 1H), 3,77 - 3,64 (m, 2H), 3,43 - 2,82 (m, 1H), 2,20 - 2,08 (m, 1H), 1,97 - 1,86 (m, 2H), 1,82 – 1,67 (m, 1H), 1,65 - 1,58 (m, 2H), 1,50 - 1,50 (m, 2H), 1,26 - 1,22 (m, 1H).	917,5
237	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[1-(3-metil-2-oxo-1,3-benzotiazol-5-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida	1H NMR (500 MHz, METANOL-d4) δ = 8,64 (s, 1H), 8,54 - 8,18 (m, 1H), 8,13 - 7,99 (m, 1H), 7,58 - 7,43 (m, 1H), 7,50 - 7,42 (m, 1H), 7,41 - 7,32 (m, 1H), 7,27 - 7,21 (m, 1H), 7,14 - 7,07 (m, 2H), 6,97 (d, J = 2,4 Hz, 1H), 6,83 - 6,77 (m, 1H), 5,94 - 5,29 (m, 1H), 4,68 - 4,86 (m, 1H), 4,18 - 4,10 (m, 1H), 4,08 - 4,02 (m, 3H), 3,77 - 3,69 (m, 2H), 3,45 - 3,37 (m, 1H), 3,05 - 2,87 (m, 1H), 3,54 - 2,85 (m, 2H), 2,42 - 2,34 (m, 1H), 2,20 - 2,93 (m, 1H), 2,93 - 1,97 (m, 3H), 1,94 - 1,85 (m, 3H), 1,83 - 1,73 (m, 2H), 1,25 - 1,22 (m, 6H).	868,5
238	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[8-(1-metil-2-oxo-3,4-dihidroquinolin-6-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 8,79 (s, 2H), 7,90 (d, J = 8,8 Hz, 1H), 7,80 - 7,71 (m, 2H), 7,50 (s, 1H), 7,21 (d, J = 2,4 Hz, 1H), 7,10 (s, 1H), 7,00 (d, J = 2,4, 8,8 Hz, 1H), 6,96 - 6,62 (m, 2H), 4,33 - 4,22 (m, 2H), 4,19 - 4,10 (m, 2H), 4,04 (d, J = 9,2 Hz, 1H), 3,86 (s, 7H), 3,77 - 3,66 (m, 4H), 3,61 - 3,55 (m, 2H), 3,29 - 3,23 (m, 4H), 3,00 - 2,90 (m, 2H), 2,89 - 2,71 (m, 4H), 2,10 - 2,04 (m, 2H), 2,02 (s, 7H), 1,21 (s, 6H), 1,11 (s, 6H)	1004,8

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
239	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[2-[5-[7-(difluorometil)-1-(1-metil-2-oxo-3,4-dihidroquinolin-6-il)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]etil]-1-piperidil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 8,75 (s, 2H), 8,39 (d, J = 2,4 Hz, 1H), 7,90 (d, J = 8,8 Hz, 1H), 7,71 (d, J = 9,2 Hz, 1H), 7,61 (d, J = 2,3, 8,0 Hz, 1H), 7,32 (d, J = 8,0 Hz, 1H), 7,23 - 7,14 (m, 4H), 7,05 (s, 1H), 7,01 (d, J = 2,3, 8,8 Hz, 1H), 6,77 - 6,48 (m, 2H), 4,75 (d, J = 13,6 Hz, 2H), 4,29 (s, 1H), 4,03 (d, J = 9,2 Hz, 1H), 3,59 (t, J = 5,2 Hz, 2H), 3,27 (s, 3H), 2,99 - 2,91 (m, 2H), 2,91 - 2,85 (m, 4H), 2,84 - 2,79 (m, 2H), 2,59 - 2,54 (m, 2H), 2,04 - 1,97 (m, 2H), 1,84 (d, J = 12,0 Hz, 2H), 1,70 - 1,58 (m, 3H), 1,21 (s, 6H), 1,15 (s, 2H), 1,11 (s, 6H)	913,7

[00679] Ejemplo 27: Síntesis de N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[[4-[1,3-dimetil-6-[3-(1-metilpirazol-4-il)-8-isoquinolil]-2-oxo-bencimidazol-4-il]-1-piperidil]metil]-1-piperidil]pirimidina-5-carboxamida (**Compuesto 213**)



[00680] La síntesis de **1** fue reportada en Journal of Organic Chemistry, 2018, vol. 83,

17, páginas 10627 - 10635

[00681] La síntesis de **5A** fue reportada en US2019/308978 A1

[00682] La síntesis de **7A** fue reportada en WO2021/249534 A1

[00683] A una solución de 6-bromo-4-iodo-1,3-dimetil-benzimidazol-2-ona (4,00 g, 10,90 mmol, 1,0 *eq*) y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3,6-dihidro-2H-piridina-1-carboxilato de ter-butilo (6,74 g, 21,80 mmol, 2,0 *eq*) en dioxano (82 ml) y H_2O (16 ml) se agregó K_2CO_3 (3,77 g, 27,25 mmol, 2,5 *eq*) y $Pd(dppf)Cl_2$ (1,20 g, 1,63 mmol, 0,1 *eq*) bajo atmósfera de N_2. La mezcla se agitó a 90 °C durante 8 h en atmósfera de N_2. La mezcla se diluyó con agua (50 ml) y se extrajo con EtOAc (60 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (80 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto ter-butil 4-(6-bromo-1,3-dimetil-2-oxo-benzimidazol-4-il)-3,6-dihidro-2H-piridina-1-carboxilato (1,90 g, 4,50 mmol, 41 % de rendimiento) se obtuvo como un aceite amarillo.

[00684] **LC-MS:** MS (ESI^+): t_R = 0,913 min, m/z = 422,1 [$M + H^+$]

[00685] A una mezcla de 4-(6-bromo-1,3-dimetil-2-oxo-benzimidazol-4-il)-3,6-dihidro-2H-piridina-1-carboxilato de ter-butilo (800 mg, 1,89 mmol, 1,0 *eq*) en dioxano (8 ml) y H_2O (8 ml) se añadieron KOH (318 mg, 5,68 mmol, 3,0 *eq*), $Pd_2(dba)_3$ (173 mg, 189 µmol, 0,1 *eq*) y tBuXphos (160 mg, 378 µmol, 0,2 *eq*) bajo N_2. La mezcla se agitó a 90 °C durante 12 h. El pH de la mezcla se ajustó a aproximadamente 4 con HCl (1 M) y la mezcla se extrajo con EtOAc (10 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (10 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : Se obtuvo el compuesto ter-butil 4-(6-hidroxi-1,3-dimetil-2-oxo-benzimidazol-4-il)-3,6-dihidro-2H-piridina-1-carboxilato (201 mg, 559 µmol, 29 % de rendimiento) como un sólido amarillo.

[00686] **LC-MS:** MS (ESI^+): t_R = 0,562 min, m/z = 360,1 [$M + H^+$]

[00687] A una mezcla de ter-butil 4-(6-hidroxi-1,3-dimetil-2-oxo-benzimidazol-4-il)-3,6-dihidro-2H-piridina-1-carboxilato (200 mg, 556 µmol, 1,0 *eq*) en MeOH (10 ml) se agregó Pd/C (100 mg, 10 % de pureza) bajo N_2. La suspensión se desgasificó y se purgó con H_2 3 veces. La mezcla se agitó bajo H_2 (50 psi) a 30 °C durante 12 h. La mezcla de reacción se filtró y se lavó con MeOH (50 ml x 3). El filtrado se concentró para obtener un residuo crudo. El compuesto ter-butil 4-(6-hidroxi-1,3-dimetil-2-oxo-benzimidazol-4-il)piperidina-1-carboxilato (140 mg) se obtuvo como un sólido rojo y se utilizó

directamente en el siguiente paso sin purificación adicional.

[00688] **LC-MS:** MS (ESI^+): t_R = 0,764 min, m/z = 384,1 [M + Na^+]

[00689] A una solución de 4-(6-hidroxi-1,3-dimetil-2-oxo-bencimidazol-4-il)piperidina-1-carboxilato de ter-butilo (140 mg) en DCM (4 ml) se añadieron Py (306 mg, 3,87 mmol, 312 µl, 10,0 *eq*) y Tf_2O (218 mg, 774 µmol, 127 µl, 2,0 *eq*) a 0 °C. La mezcla se agitó a 0 °C durante 1 h. La mezcla de reacción se diluyó con agua (15 ml), se ajustó el pH a aproximadamente 8 con $NaHCO_3$, y se extrajo con DCM (20 ml * 3). Las capas orgánicas combinadas se secaron en Na_2SO_4 anhidro, se filtró el agente secante y el filtrado se concentró a presión reducida para obtener material crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 3/1). El compuesto ter-butil 4-[1,3-dimetil-2-oxo-6-(trifluorometilsulfoniloxi)bencimidazol-4-il]piperidina-1-carboxilato (140 mg, 283 µmol, 73 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00690] **LC-MS:** MS (ESI^+): t_R = 0,900 min, m/z = 516,3 [M + Na^+]

[00691] A una solución de 4-[1,3-dimetil-2-oxo-6-(trifluorometilsulfoniloxi)bencimidazol-4-il]piperidina-1-carboxilato de ter-butilo (140 mg, 283 µmol, 1,0 *eq*) y 3-(1-metilpirazol-4-il)-8-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)isoquinolina (114 mg, 340 µmol, 1,2 *eq*) en dioxano (4 ml) y H_2O (0,8 ml) se agregó $Pd(dppf)Cl_2$ (20 mg, 28 µmol, 0,1 *eq*) y Na_2CO_3 (90 mg, 851 µmol, 3,0 *eq*). La mezcla se agitó a 90 °C durante 12 h en N_2. La mezcla de reacción se inactivó con agua (15 ml) y se extrajo con EtOAc (20 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante TLC preparativa (SiO_2, acetato de etilo/MeOH = 10/1). El compuesto ter-butil 4-[1,3-dimetil-6-[3-(1-metilpirazol-4-il)-8-isoquinolil]-2-oxo-benzimidazol-4-il]piperidina-1-carboxilato (70 mg, 126 µmol, 44 % de rendimiento) se obtuvo como un sólido amarillo.

[00692] **LC-MS:** MS (ESI^+): t_R = 0,790 min, m/z = 553,4 [M + H^+]

[00693] A una solución de 4-[1,3-dimetil-6-[3-(1-metilpirazol-4-il)-8-isoquinolil]-2-oxo-bencimidazol-4-il]piperidina-1-carboxilato de ter-butilo (70 mg, 126 µmol, 1,0 *eq*) en DCM (3 ml) se agregó TFA (1,54 g, 13,4 mmol, 1 ml, 106,2 *eq*). La mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró al vacío. El compuesto 1,3-dimetil-6-[3-(1-metilpirazol-4-il)-8-isoquinolil]-4-(4-piperidil)bencimidazol-2-ona (57 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00694] **LC-MS:** MS (ESI^+): t_R = 0,698 min, m/z = 453,3 [M + H^+]

[00695] A una solución de 1,3-dimetil-6-[3-(1-metilpirazol-4-il)-8-isoquinolil]-4-(4-

piperidil)benzimidazol-2-ona (57 mg) y N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-(4-formil-1-piperidil)pirimidina-5-carboxamida (68 mg, 138 µmol, 1,1 *eq*) en DCM (3 ml) se agregó Et_3N (63 mg, 629 µmol, 87 µl, 5,0 *eq*) y $NaBH(OAc)_3$ (80 mg, 377 µmol, 3,0 *eq*). La mezcla se agitó a 25 °C durante 12 h. La mezcla se concentró al vacío. El residuo se purificó mediante HPLC preparativa (columna: Waters xbridge 150*25mm 10um; fase móvil: [agua (NH_4HCO_3)-ACN]; gradiente: 75 %-95 % B durante 8 min). El compuesto N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[[4-[1,3-dimetil-6-[3-(1-metilpirazol-4-il)-8-isoquinolil]-2-oxo-bencimidazol-4-il]-1-piperidil]metil]-1-piperidil]pirimidina-5-carboxamida (65,82 mg, 67,57 µmol, 53 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00696] ^{1}H NMR (400 MHz, METANOL-**d_6**) δ = 9,22 - 9,44 (m, 1H), 8,76 - 8,69 (m, 1H), 8,34 (s, 1H), 8,15 - 8,05 (m, 2H), 7,93 - 7,84 (m, 2H), 7,81 - 7,74 (m, 1H), 7,71 - 7,64 (m, 1H), 7,54 - 7,46 (m, 1H), 7,28 - 7,23 (m, 1H), 7,23 - 7,18 (m, 1H), 7,16 - 7,11 (m, 1H), 7,04 – 6,95 (m, 2H), 4,78 - 4,60 (m, 2H), 4,27 - 4,44 (m, 2H), 4,06 - 3,96 (m, 2H), 3,91 - 4,13 (m, 2H), 3,96 - 3,37 (m, 3H), 3,30 - 3,20 (m, 2H), 3,01 - 2,83 (m, 4H), 2,22 - 2,12 (m, 2H), 2,11 - 1,99 (m, 2H), 1,90 - 1,70 (m, 1H), 1,20 - 1,10 (m, 1H), 1,05 - 0,92 (m, 1H).

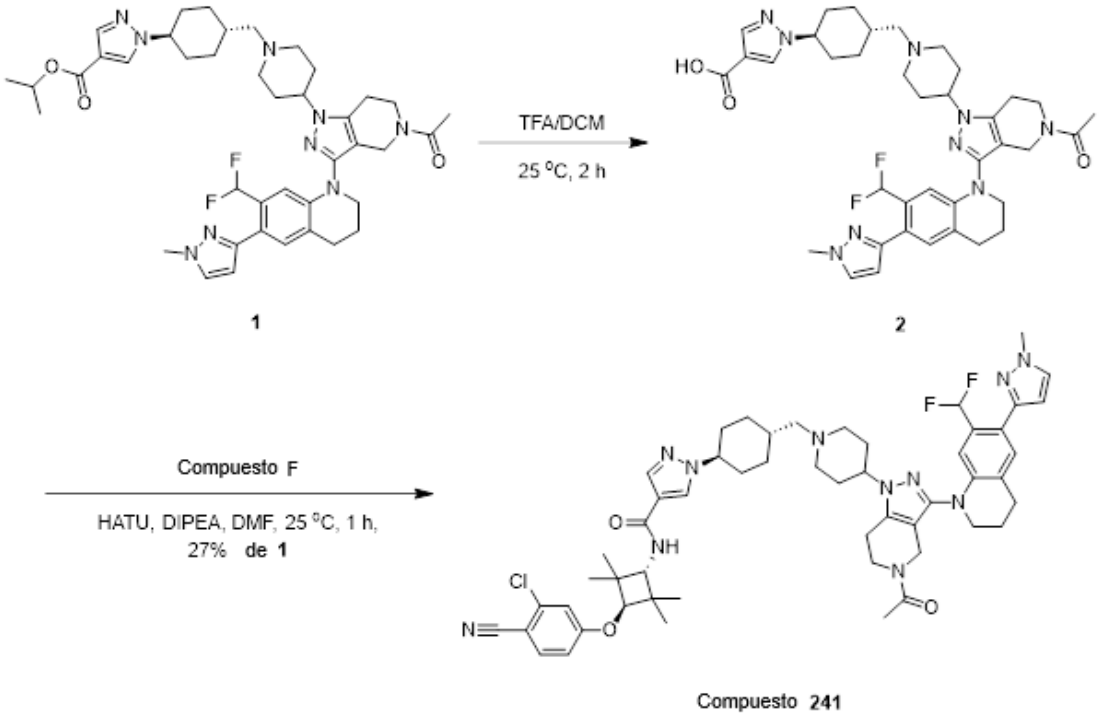
[00697] **LC-MS:** MS (ESI$^+$): t_R = 1,819 min, m/z = 932,7 [M + H$^+$]

[00698] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 27.

Compuesto	**Nombre**	**RMN ^{1}H (400 MHz, DMSO-d6):**	**LC-MS (M+H)$^+$:**
243	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[[4-[1,3-dimetil-6-[3-(1-metilpirazol-4-il)-8-isoquinolil]-2-oxo-bencimidazol-4-il]-3,6-dihidro-2H-piridin-1-il]metil]-1-piperidil]pirimidina-5-carboxamida	δ = 9,24 (s, 1H), 8,79 - 8,70 (m, 2H), 8,33 (s, 1H), 8,14 (s, 1H), 8,10 (d, J = 15,2 Hz, 2H), 7,92 - 7,86 (m, 2H), 7,78 (s, J = 7,7 Hz, 1H), 7,72 - 7,67 (m, 1H), 7,52 (d, J = 6,4 Hz, 1H), 7,33 (d, J = 1,5 Hz, 1H), 7,21 (d, J = 2,3 Hz, 1H), 7,03 - 6,97 (m, 2H), 5,79 (s, 1H), 4,81 - 4,68 (m, 2H), 4,28 (s, 1H), 4,03 (d, J = 9,2 Hz, 1H), 3,91 (s, 3H), 3,40 (d, J = 9,0 Hz, 6H), 3,20 - 3,09 (m, 2H), 3,04 - 2,91 (m, 2H), 2,75 - 2,63 (m, 2H), 2,39 - 2,25 (m, 2H), 2,01 - 1,89 (m, 1H), 1,88 - 1,78 (m, 2H), 1,21 (s, 7H), 1,16 - 0,98 (m, 9H).	930,7
214	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[[4-[6-[7-(difluorometil)-6-(1-metilpirazol-4-il)-	δ 7,92-8,73 (m, 1H), 7,96-7,85 (m, 2H), 7,80-7,65 (m, 2H), 7,25-7,18 (m, 1H), 7,09 (s, 1H), 7,05-6,96 (m, 1H), 6,55 (s, 2H), 4,83-4,63 (m, 2H), 4,28 (brs,	986,7

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
	3,4-dihidro-2H-quinolin-1-il]-1,3-dimetil-2-oxo-bencimidazol-4-il]-1-piperidil]metil]-1-piperidil]pirimidina-5-carboxamida	2H), 4,09-3,96 (m, 2H), 3,72-3,51 (m, 2H), 3,30 (s, 3H), 3,13 (s, 3H), 3,07-2,79 (m, 2H), 2,28-1,95 (m, 2H), 1,93-1,60 (m, 2H), 1,21-1,10 (m, 2H), 1,05-0,94 (m, 2H).	
242	N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-[4-[[4-[6-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1,3-dimetil-2-oxo-bencimidazol-4-il]-3,6-dihidro-2H-piridin-1-il]metil]-1-piperidilo]pirimidina-5-carboxamida	δ 8,00-7,85 (m, 1H), 7,78-7,65 (m, 2H), 7,16-7,04 (m, 2H), 6,92-6,56 (m, 1H), 4,29 (s, 1H), 4,13-3,97 (m, 1H), 3,86 (s, 2H), 3,67-3,53 (m, 2H), 3,35 (brs, 2H), 3,31-3,03 (m, 2H), 3,02-2,93 (m, 2H), 2,86 (s, 3H), 2,58 (s, 3H), 2,41-2,35 (m, 2H), 2,31-2,22 (m, 2H), 2,04-1,97 (m, 2H), 1,88-1,77 (m, 2H), 1,08-1,00 (m, 2H).	984,7

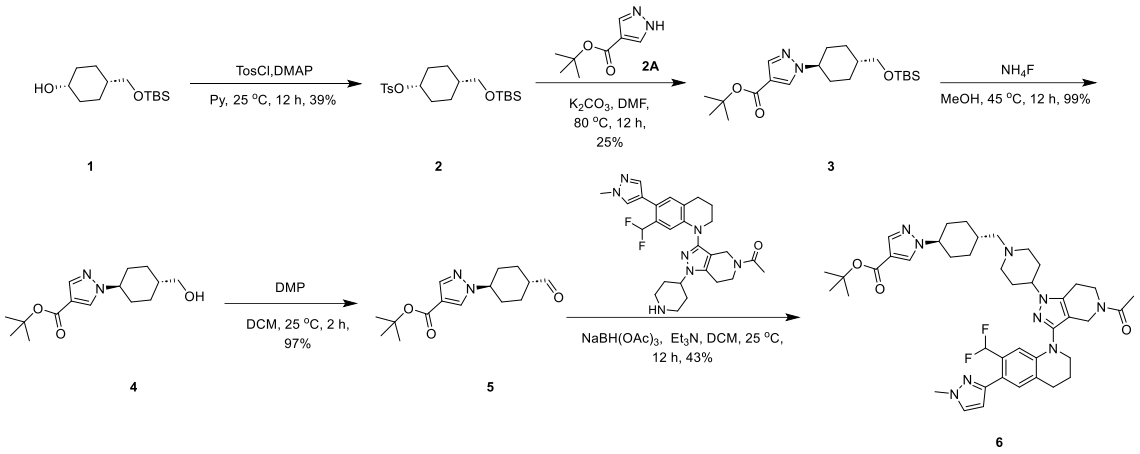
[00699] **Ejemplo 28**: Síntesis de 1-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-3-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]ciclohexil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirazol-4-carboxamida (**Compuesto 241**)



[00700] La síntesis de **2A** fue reportada en Journal of Medicinal Chemistry, 2019, vol.

62, # 24, páginas 11218 – 11231.

[00701] Síntesis de (1)



[00702] A una mezcla de 4-[[ter-butil(dimetil)silil]oximetil]ciclohexanol (2,80 g, 11,5 mmol, 1,0 eq) en Py (50 ml) se le añadieron DMAP (280 mg, 2,30 mmol, 0,2 eq) y TosCl (2,80 g, 14,7 mmol, 1,3 eq). La mezcla se agitó a 25 °C durante 12 h en atmósfera de N_2. La mezcla se inactivó con agua (100 ml) y se extrajo con acetato de etilo (100 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 20/0). El compuesto [4-[[ter-butil(dimetil)silil]oximetil]ciclohexil] 4-metilbencenosulfonato (1,80 g, 4,52 mmol, 39 % de rendimiento) se obtuvo como un aceite incoloro.

[00703] ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 7,80 (t, *J*=8,4 Hz, 2 H) 7,33 (d, *J*=8,0 Hz, 2 H) 3,40 - 2 (m, 1 H) 1,41 - 1,61 (m, 1 H) 2,95 - 1,41 (m, 1 H) 0,88 (br s, 6 H).

[00704] Una mezcla de 1H-pirazol-4-carboxilato de ter-butilo (900 mg, 5,35 mmol, 1,2 eq), [4-[[ter-butil(dimetil)silil]oximetil]ciclohexil] 4-metilbencenosulfonato (1,80 g, 4,52 mmol, 1,0 eq), K_2CO_3 (1,80 g, 13,0 mmol, 2,9 eq) en DMF (40 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 80 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se diluyó con agua (250 ml) y se extrajo con acetato de etilo (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 5/0). El compuesto ter-butil 1-[4-[[ter-butil(dimetil)silil]oximetil]ciclohexil]pirazol-4-carboxilato (450 mg, 1,14 mmol, 25 % de rendimiento) se obtuvo como un aceite incoloro.

[00705] **LC-MS:** MS (ESI$^+$): t_R = 0,768 min, m/z = 395,2 [M + H$^+$]

[00706] Una mezcla de 1-[4-[[ter-butil(dimetil)silil]oximetil]ciclohexil]pirazol-4-carboxilato de ter-butilo (400 mg, 1,01 mmol, 1,0 eq), NH_4F (400 mg, 10,8 mmol, 10,7 eq) en MeOH (20 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 45 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se concentró bajo presión reducida para eliminar el ACN. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 30/1 a 10/1). El compuesto 1-[4-(hidroximetil)ciclohexil]pirazol-4-carboxilato de ter-butilo (280 mg, 999 µmol, 99 % de rendimiento) se obtuvo como un sólido amarillo.

[00707] **LC-MS:** MS (ESI^+): t_R = 0,527 min, m/z = 281,2 [M + H^+]

[00708] Una mezcla de 1-[4-(hidroximetil)ciclohexil]pirazol-4-carboxilato de ter-butilo (280 mg, 999 µmol, 1,0 eq), DMP (560 mg, 1,32 mmol, 1,3 eq) en DCM (10 ml) se desgasificó y se purgó con N2 tres veces, y luego la mezcla se agitó a 25 °C durante 2 h bajo atmósfera de N2. Posteriormente, la mezcla de reacción se neutralizó mediante la adición de una solución saturada equivalente de NaHCO3 (50 ml) y una solución saturada equivalente de Na2SO3 (50 ml) a 0 °C, y luego se extrajo con DCM (40 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (40 ml x3), se secaron en Na2SO4, se filtraron y se concentraron a presión reducida para obtener el residuo crudo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 1/1 a 0/0). Se obtuvo el compuesto 1-(4-formilciclohexil)pirazol-4-carboxilato de ter-butilo (270 mg, 970 µmol, 97 % de rendimiento) como un sólido amarillo.

[00709] LC-MS (ESI): m/z = 279,2 [M+H]+.

[00710] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg, 196 µmol, 1,0 eq), 4-formilpiperidina-1-carboxilato de ter-butilo (50 mg, 234 µmol, 1,2 eq) y Et_3N (218 mg, 2,16 mmol, 11,0 eq) en DCM (5 ml) se agregó $NaBH(OAc)_3$ (210 mg, 991 µmol, 5,1 eq). La mezcla se agitó a 25 °C durante 12 h, y luego se diluyó con DCM (100 ml), se lavó con agua (15 ml × 2), salmuera (15 ml), se secó con sulfato de sodio anhidro, se filtró y se concentró al vacío. El residuo se purificó mediante TLC preparativa (SiO_2, acetato de etilo: MeOH = 10:1). El compuesto ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]piperidina-1-carboxilato (61 mg, 84,9 µmol, 43 % de rendimiento) se obtuvo como un aceite amarillo.

[00711] **LC-MS:** MS (ESI^+): t_R = 0,527 min, m/z = 772,5 [M + H^+]

[00712] Síntesis del compuesto 241

[00713] Una mezcla de ter-butil 1-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-

3-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]ciclohexil] pirazol-4-carboxilato (80 mg, 104 µmol, 1,0 eq), TFA (480 mg, 4,00 mmol, 40,0 eq) en DCM (10 ml) se agitó a 25 °C durante 2 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El compuesto 1-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-3-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]ciclohexil]pirazol-4-ácido carboxílico (85 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

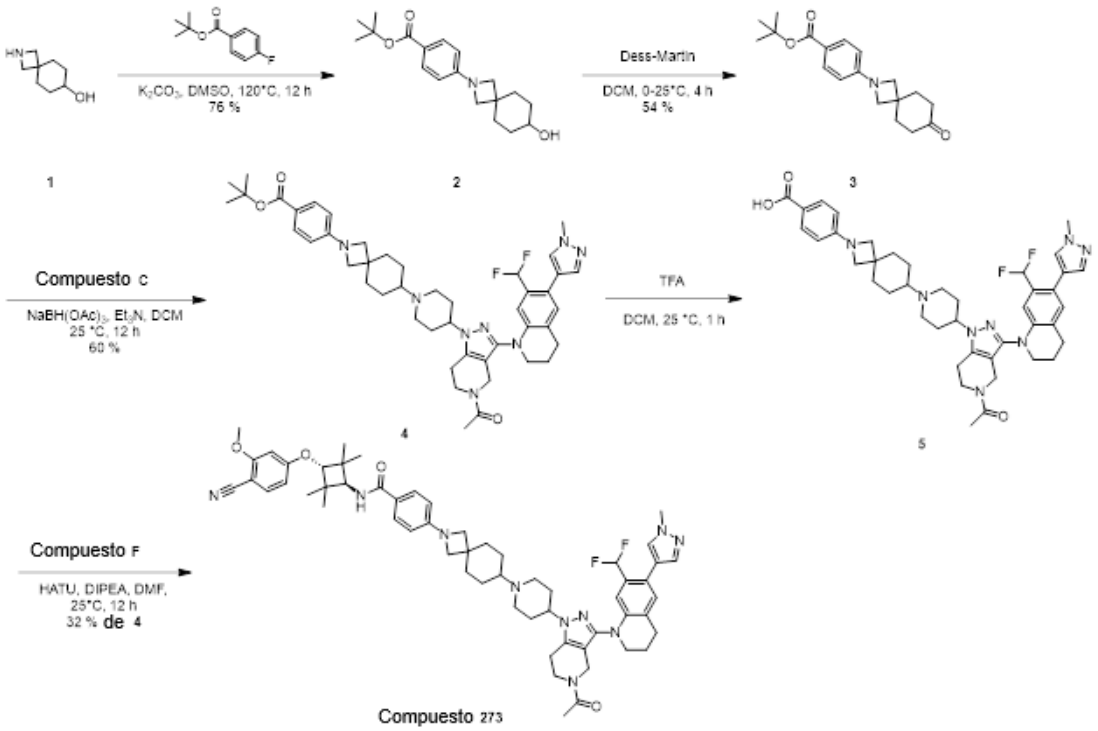
LC-MS: MS (ESI^+): t_R = 0,452 min, m/z = 716,4 [$M + H^+$]

[00714] A una solución de ácido 1-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-3-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]ciclohexil]pirazol-4-carboxílico (84 mg, 101 µmol, 1,0 eq) y 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (50 mg, 179 µmol, 1,8 eq) en DMF (4 ml) se le agregó DIPEA (110 mg, 849 µmol, 8,4 eq) y HATU (59 mg, 155 µmol, 1,5 eq) y se agitó a 25 °C durante 1 h. La mezcla se diluyó con acetato de etilo (100 ml), se lavó con agua (15 ml × 2), salmuera (15 ml), se secó con sulfato de sodio anhidro, se filtró y se concentró al vacío. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto 1-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-3-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]ciclohexil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirazol-4-carboxamida (28,5 mg, 27,4 µmol, 27 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 8,37 (s, 1 H) 7,91 (s, 1 H) 7,72 (s, 1 H) 7,50 - 7,62 (m, 2 H) 7,41 (d, *J*=6,4 Hz, 1 H) 7,03 (d, *J*=20,0 Hz, 1 H) 6,97 (d, *J*=2,4 Hz, 1 H) 6,89 (d, *J*=11,2 Hz, 1 H) 6,81 (m, 1 H) 6,33 - 6,73 (m, 1 H) 5,81 (d, *J*=8,0 Hz, 1 H) 4,28 (s, 1 H) 4,07 - 4,16 (m, 3 H) 3,93 - 4,06 (m, 5 H) 3,91 (m, 1 H) 3,63 - 3,80 (m, 3 H) 3,02 - 3,23 (m, 2 H) 2,78 - 2,94 (m, 1 H) 2,68 - 2,77 (m, 1 H) 2,67 - 2,78 (m, 1 H) 2,65 - 2,79 (m, 1 H) 2,20 - 2,41 (m, 8 H) 1,99 - 2,13 (m, 12 H) 1,68 - 1,83 (m, 3 H) 1,18 - 1,29 (m, 12 H) 1,09 - 1,18 (m, 2 H)

LC-MS: MS (ESI^+): t_R = 1,981 min, m/z = 976,8 [$M + H^+$]

[00715] Ejemplo 29: Síntesis de 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 273**)



[00716] La síntesis de **1** se informó en WO2023/278402 A1

[00717] A una mezcla de 2-azaespiro[3,5]nonan-7-ol (2,89 g, 20,4 mmol, 1,0 *eq*) y 4-fluorobenzoato de ter-butilo (8,03 g, 40,9 mmol, 2,0 *eq*) en DMSO (30 ml) se agregó K_2CO_3 (14,14 g, 102,33 mmol, 5,0 *eq*), la mezcla se agitó a 120 °C durante 12 h. La mezcla de reacción se diluyó con agua (100 ml) y se extrajo con EtOAc (50 ml * 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto 4-(7-hidroxi-2-azaespiro[3,5]nonan-2-il)benzoato de ter-butilo (5,00 g, 15,75 mmol, 76 % de rendimiento) se obtuvo como un sólido blanco. **LC-MS:** MS (ESI^+): t_R = 0,842 min, m/z = 318,4 [M + H^+]

[00718] A una mezcla de 4-(7-hidroxi-2-azaespiro[3,5]nonan-2-il)benzoato de ter-butilo (4,80 g, 15,12 mmol, 1,0 *eq*) en DCM (400 ml) se le agregó Dess-Martin (12,83 g, 30,24 mmol, 9,3 ml, 2,0 *eq*) a 0 °C, la mezcla se agitó a 25 °C durante 4 h. La mezcla de reacción se diluyó con agua (200 ml) y se extrajo con DCM (100 ml * 3). Las capas orgánicas combinadas se secaron en Na_2SO_4 anhidro, se filtró el agente secante y el filtrado se concentró a presión reducida para obtener material crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 20/1 a 2/1). El compuesto 4-(7-oxo-2-azaespiro[3,5]nonan-2-il)benzoato de ter-butilo (2,60 g,

8,24 mmol, 54 % de rendimiento) se obtuvo como un sólido blanco.

^{1}H NMR (400 MHz, CDCl**3**): δ = 7,86 (d, *J* = 8,8 Hz, 1H), 6,39 (d, *J* = 8,8 Hz, 1H), 3,81 (s, 1H), 2,46-2,34 (m, 4H), 2,20-2,11 (m, 4H).

LC-MS: MS (ESI$^+$): t_R = 0,848 min, m/z = 316,5 [M + H$^+$]

[00719] A una mezcla de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (1,50 g, 2,94 mmol, 1,0 *eq*) y 4-(7-oxo-2-azaespiro[3,5]nonan-2-il)benzoato de ter-butilo (1,39 g, 4,42 mmol, 1,5 *eq*) en DCM (30 ml) se agregó Et_3N (1,49 g, 14,72 mmol, 2,1 ml, 5,0 *eq*) y $NaBH(OAc)_3$ (1,87 g, 8,83 mmol, 3,0 *eq*), la mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se diluyó con agua (30 ml), se extrajo con DCM (30 ml * 3). Las capas orgánicas combinadas se secaron en Na_2SO_4 anhidro, se filtró el agente secante y el filtrado se concentró a presión reducida para obtener material crudo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 100/1 a 10/1). El compuesto ter-butil 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]benzoato (1,45 g, 1,79 mmol, 60 % de rendimiento) se obtuvo como un sólido amarillo claro.

[00720] ^{1}H NMR (400 MHz, METANOL-**d$_3$**) δ = 7,88 - 7,79 (m, 1H), 7,58 (s, 1H), 7,44 - 7,37 (m, 1H), 7,08 - 6,94 (m, 1H), 6,86 - 8,19 (m, 1H), 6,72 - 7,83 (m, 1H), 7,83 - 4,10 (m, 1H), 3,97 3,93 (m, 3H), 3,92 - 3,86 (m, 1H), 3,79 - 3,67 (m, 2H), 3,65 - 4,80 (m, 2H), 3,60 - 4,58 (m, 1H), 3,15 - 3,00 (m, 2H), 2,92 - 2,70 (m, 1H), 2,36 - 2,28 (m, 1H), 2,28 - 2,18 (m, 1H), 2,11 - 1,99 (m, 1H), 1,98 - 1,90 (m, 1H), 1,89 - 1,79 (m, 1H), 1,59 - 1,55 (m, 1H), 1,42 - 1,30 (m, 2H).

[00721] **LC-MS:** MS (ESI$^+$): t_R = 0,810 min, m/z = 809,3 [M + H$^+$]

[00722] A una mezcla de 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]benzoato de ter-butilo (1,45 g, 1,79 mmol, 1,0 *eq*) en DCM (10 ml) se agregó TFA (7,68 g, 67,31 mmol, 5 ml, 37,5 *eq*), la mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró para obtener un producto crudo. El compuesto ácido 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]benzoico (1,35 g) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00723] **LC-MS:** MS (ESI$^+$): t_R = 0,728 min, m/z = 753,3 [M + H$^+$]

[00724] A una mezcla de ácido 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-

il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]benzoico (1,35 g) y 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (585 mg, 1,88 mmol, 1,05 *eq*) en DMF (15 ml) se agregó DIPEA (1,16 g, 8,97 mmol, 1,5 ml, 5,0 *eq*) y HATU (818 mg, 2,15 mmol, 1,2 *eq*), la mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se diluyó con agua (60 ml) y se extrajo con EtOAc (50 ml * 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante cromatografía en columna (SiO_2, DCM/MeOH =100/1 a 10/1, $NH_3•H_2O$) para obtener un producto crudo, luego el producto crudo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*40mm* 15um; fase móvil: [agua (FA)-ACN]; gradiente: 40 %-70 % B durante 10 min). El compuesto 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (584,55 mg, 575,61 µmol, 32 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[00725] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8,17 (s, 1H), 7,86 (d, **J** = 4,8 Hz, 2H), 7,64 (d, *J* = 4,8 Hz, 1H), 7,46 - 7,38 (m, 3H), 7,10 - 6,61 (m, 2H), 6,58 - 6,50 (m, 1H), 6,48 - 6,35 (m, 1H), 4,18 - 4,10 (m, 1H), 4,08 - 4,01 (m, 1H), 3,90 – 3,86 (m, 1H), 3,76 - 3,66 (m, 1H), 3,64 - 3,50 (m, 3H), 3,05 - 2,95 (m, 2H), 2,88 - 2,70 (m, 1H), 2,44 - 2,38 (m, 1H), 2,07 - 1,85 (m, 2H), 1,80 – 1,68 (m, 1H), 1,58 - 1,46 (m, 2H), 1,44 - 1,32 (m, 2H), 1,32 - 1,02 (m, 1H).

[00726] **LC-MS:** MS (ESI$^+$): t_R = 2,085 min, m/z = 1009,4 [M + H$^+$]

[00727] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 29.

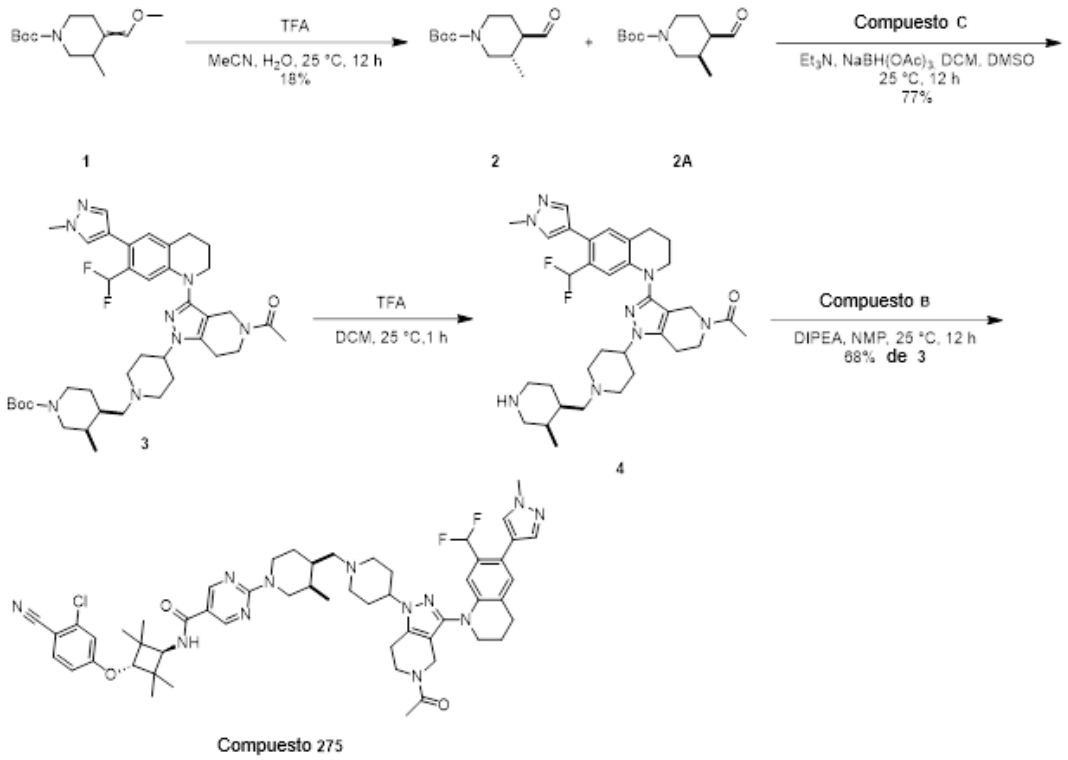
Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS (M+H)$^+$:**
262	4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-7-azaespiro[3,5]nonan-7-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,68 (d, J = 8,4Hz, 1H), 7,54 (d, J = 5,2Hz, 2H), 7,04 (d, J = 8,4Hz, 2H), 6,12 (d, J = 8,4Hz, 1H), 4,29 (s, 1H), 4,12 (s, 2H), 4,05 (s, 1H), 3,96 (brs, 2H), 3,94-3,88 (m, 2H), 3,80-3,63 (m, 2H), 3,30 (s, 2H), 3,25-3,07 (m, 2H), 3,03-2,79 (m, 2H), 2,74-1,67 (m, 2H), 2,32-2,21 (m, 2H), 2,14-2,03 (m, 1H), 1,93-1,76 (m, 8H).	1009,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
274	2-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 11,07 - 11,04 (m, 1 H), 8,69 (s, 2 H), 7,60 - 7,50 (m, 2 H), 7,42 -7,36 (m, 1 H), 7,06 - 6,93 (m, 2 H), 6,89 - 6,74 (m, 2 H), 6,71 - 6,34 (m, 1 H), 5,94 - 5,88 (m, 1 H), 4,24 (s, 1 H), 4,14 - 4,09 (m, 2 H), 4,04 (s, 1 H), 3,95 (s, 3 H), 3,91 - 3,83 (m, 5 H), 3,78 - 3,64 (m, 3 H), 3,23 - 2,93 (m, 2 H), 2,92 - 2,77 (m, 3 H), 2,77 - 2,71 (m, 1 H), 2,50 - 2,11 (m, 6 H), 2,11 - 2,00 (m, 6 H), 1,99 - 1,76 (m, 4 H), 1,60 - 1,49 (m, 3 H), 1,44 - 1,30 (m, 2 H), 1,23 (d, J = 12,0 Hz, 12 H).	1015,6
300	4-[4-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-3-azaespiro[5,5]undecan-3-il]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,70-7,68 (m, 2 H), 7,53-7,52 (d, *J*=4,4 Hz, 1 H), 7,47-7,45 (d, *J*=8,4 Hz, 1 H), 7,41-7,40 (d, *J*=6,0 Hz, 1 H), 7,04-7,02 (m, 1 H), 6,92-6,90 (m, 3 H), 6,70-6,41 (m, 3 H), 6,13 (d, *J*=8,8 Hz, 1 H), 4,27 (s, 1 H), 4,16-4,13 (m, 3H), 3,95-3,94 (m, 4 H), 3,92-3,90 (m, 6H), 3,70-3,68 (m, 3 H), 2,90-2,85 (m, 5 H), 2,85-2,75 (m, 4H), 2,74-2,60 (m, 1 H), 2,25-2,22 (m, 2 H), 2,20-2,10 (m, 7 H), 1,90-1,80 (m, 3 H), 1,80-1,70 (m, 4 H), 1,70-1,60 (m, 4 H), 1,40-1,30 (m, 2 H), 1,25 (d, J = 10,4 Hz, 12 H).	1037,7
301	4-[3-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-3-azaespiro[5,5]undecan-3-il]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,65 (d, J = 8,6 Hz, 1H), 7,53 (d, J = 7,9 Hz, 1H), 7,45 (d, J = 8,8 Hz, 1H), 7,37 (d, J = 8,6 Hz, 1H), 6,83 (dd, J = 6,37, 8,7 Hz, 1H), 6,09 (d, J = 7,9 Hz, 1H), 3,96 (d, J = 2,14 Hz, 1H), 3,86 (br t, J = 6,8 Hz, 2H), 3,77 - 3,66 (m, 1H), 3,39 - 3,29 (m, 2H), 2,92 - 2,83 (m, 1H), 2,79 (br t, J = 6,0 Hz, 2H), 2,73 (br d, J = 5,6 Hz, 2H), 2,39 (s, 4H),	1009,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2,18 - 2,04 (m, 2H), 1,88 - 3,11 (m, 3H), 1,82 - 1,73 (m, 4H), 2,86 - 1,49 (m, 2H), 1,25 (br d, J = 11,2 Hz, 3H).	
310	4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	$_3$H NMR (400 MHz, DMSO-d*6*) δ = 8,65 (s, 1H), 7,73 (d, J = 4,8 Hz, 2H), 7,66 (d, J = 4,8 Hz, 1H), 8,26 - 7,61 (m, 3H), 7,55 - 7,49 (m, 2H), 7,45 - 7,07 (m, 1H), 6,76 - 6,69 (m, 1H), 6,64 - 6,48 (m, 1H), 4,33 - 4,05 (m, 1H), 3,99 – 3,86 (m, 1H), 3,85 - 3,73 (m, 1H), 3,72 - 3,62 (m, 3H), 3,51 - 3,43 (m, 1H), 3,39 - 3,33 (m, 1H), 3,16 - 3,03 (m, 1H), 2,99 - 2,78 (m, 2H), 2,26 – 2,13 (m, 1H), 2,13 - 1,95 (m, 2H), 1,35 - 1,26 (m, 2H), 1,25 - 1,20 (m, 1H).	941,6
333	2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ 7,92-8,72 (m, 1H), 7,65-7,52 (m, 2H), 7,45-7,39 (m, 2H), 7,10-6,94 (m, 1H), 6,78 (s, 1H), 6,74-6,32 (m, 1H), 5,96 (s, 2H), 4,35-4,21 (m, 2H), 4,04 (brs, 2H), 4,03-3,89 (m, 2H), 3,81-3,65 (m, 2H), 3,45 (s, 3H), 3,32 (s, 3H), 2,54-3,05 (m, 2H), 2,93-2,72 (m, 2H), 2,38-2,23 (m, 2H), 2,19-1,97 (m, 2H), 1,30-1,20 (m, 2H).	947,3
334	2-[(3S)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]pirrolidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ 7,61-7,51 (m, 1H), 7,43-7,38 (m, 2H), 7,08-6,95 (m, 2H), 6,90-6,77 (m, 1H), 6,34 (s, 1H), 5,99-5,89 (m, 1H), 4,25 (s, 2H), 4,17-4,09 (m, 2H), 4,00 (brs, 2H), 3,99-3,87 (m, 2H), 3,79-3,66 (m, 2H), 3,50 (s, 1H), 3,36 (s, 1H), 3,26-2,98 (m, 2H), 2,93-2,79 (m, 2H), 2,78-2,70 (m, 2H), 2,39-2,20 (m, 2H), 2,12-1,91 (m, 2H).	961,7
335	2-[(3R)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-	(400 MHz, DMSO-d_6, ppm) δ 8,76 (s, 1H), 7,91-7,88 (m, 3H), 7,78-7,66 (m, 1H),	961,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]pirrolidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	7,49 (s, 1H), 7,23-7,18 (m, 1H), 7,10 (s, 1H), 7,04-6,97 (m, 3H), 6,96-4,29 (m, 4H), 3,86-3,67 (m, 3H), 3,62-3,56 (m, 2H), 2,90-2,65 (m, 1H), 2,24-2,15 (m, 3H), 2,09-1,95 (m, 3H), 1,93-1,77 (m, 1H), 1,27-1,17 (m, 3H), 1,11 (s, 3H).	
336	4-[(3S)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]pirrolidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	1H NMR (500 MHz, METANOL-d7,74) δ = 7,63 (s, 1H), 7,57 - -7,50 (m, 1H), 7,65 - 7,46 (m, 1H), 7,48 - 7,43 (m, 1H), 7,43 - 7,35 (m, 1H), 7,10 - 6,82 (m, 1H), 6,71 - 6,45 (m, 1H), 6,44 - 6,34 (m, 2H), 6,09 (d, J = 8,0 Hz, 1H), 4,29 - 4,09 (m, 1H), 5,42 - 4,05 (m, 1H), 4,02 - 3,86 (m, 1H), 3,82 - 3,66 (m, 1H), 3,65 - 3,49 (m, 3H), 3,44 - 3,15 (m, 2H), 3,14 - 2,98 (m, 1H), 2,94 - 2,79 (m, 1H), 2,79 - 2,72 (m, 2H), 2,39 - 2,22 (m, 4H), 2,210 - 2,93 (m, 1H), 2,93 - 2,03 (m, 3H), 2,02 - 1,93 (m, 3H), 2,58 - 1,27 (m, 2H), 1,24 - 0,97 (m, 6H).	955,7
337	4-[(3R)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]pirrolidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	*1*H NMR (400 MHz, DMSO-d_6) δ = 8,17 (s, 1H), 7,82 - 7,71 (m, 1H), 7,69 - 7,57 (m, 2H), 7,50 - 7,55 (m, 2H), 7,46 - 7,28 (m, 1H), 7,28 - 7,13 (m, 2H), 6,98 - 6,72 (m, 1H), 6,67 - 6,58 (m, 1H), 6,56 - 6,46 (m, 2H), 6,30 - 6,29 (m, 1H), 4,27 - 3,90 (m, 1H), 3,88 - 3,84 (m, 1H), 3,78 - 3,68 (m, 1H), 3,64 - 3,55 (m, 1H), 2,92 - 2,79 (m, 4H), 2,78 - 2,72 (m, 1H), 2,63 - 2,53 (m, 2H), 2,42 - 2,23 (m, 1H), 2,19 - 2,04 (m, 1H), 2,02 - 1,91 (m, 1H), 1,22 - 1,80 (m, 1H), 1,14 - 1,07 (m, 1H).	940,7

[00728] **Ejemplo 30**: Síntesis de 2-[(3R,4R)-4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 275**)



[00729] La síntesis de **1** se informó en WO2006/97292 A1

[00730] A una solución de (4E)-4-(metoximetileno)-3-metil-piperidina-1-carboxilato de ter-butilo (10,00 g, 41,4 mmol, 1,0 *eq*) en MeCN (80 ml) y H_2O (20 ml) se agregó gota a gota TFA (6 ml, 2,0 *eq*) y la mezcla se agitó a 25 °C durante 12 h bajo N_2. La mezcla de reacción se neutralizó mediante la adición de 10 % de $NaHCO_3$ a pH=7,0, y la mezcla se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 20/1 a 10/1). El compuesto ter-butil 4-formil-3-metil-piperidina-1-carboxilato (1,70 g, 7,48 mmol, 18 % de rendimiento) se obtuvo como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-$_d$**9,72**) δ 3,85 (br, 1H), 3,83-3,72 (m, 1H), 3,22-3,06 (m, 1H), 3,05 – 2,79 (m, 1H), 2,59-2,45 (m, 1H), 2,35 (br, 1H), 1,90-1,75 (m, 1H), 1,74-1,64 (m, 1H), 1,46(s, 9H), 0,96-1,20 (m, 1H).

[00731] A una solución de (3R,4R)-4-formil-3-metil-piperidina-1-carboxilato de ter-butilo (1,64 g, 7,22 mmol, 1,0 *eq*), 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona

(3,68 g, 7,22 mmol, 1,0 *eq*) en DCM (40 ml) y DMSO (10 ml) se agregó Et_3N (3,3 ml, 3,3 *eq*) y $NaBH(OAc)_3$ (3,28 g, 15,5 mmol, 2,1 *eq*). La mezcla de reacción se agitó a 45 oC durante 12 h. La mezcla de reacción se inactivó con agua (50 ml) y se extrajo con acetato de etilo (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 2), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 200/1 a 50/1). El compuesto ter-butil (3R,4R)-4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metil-piperidina-1-carboxilato (4,00 g, 5,55 mmol, 77 % de rendimiento) se obtuvo como un sólido blanco.

^{1}H NMR (400 MHz, DMSO-$_d$**7,75**) δ 7,10 (br, 1H), 6,96-6,62 (m, 1H), 4,20-4,10 (m, 2H), 4,06 – 3,90 (m, 1H), 3,86-3,65 (m, 3H), 3,62 (br, 1H), 3,04-2,67 (m, 1H), 2,22-1,93 (m, 11H), 1,82(s, 4H), 1,46-1,14 (m, 1H).

LC-MS: MS (ESI$^+$): t_R = 0,542 min, m/z =721,6 [M + H$^+$]

SFC: t_R = 2,350 min**,** 50 %; t_R = 4,072 min;50 %.

[00732] A una solución de ter-butil (3R,4R)-4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metil-piperidina-1-carboxilato (2,00 g, 2,77 mmol, 1,0 *eq*) en diclorometano (10 ml) se agregó TFA (6,0 ml) y la mezcla se agitó a 25 °C durante 1 h. La mezcla de reacción se concentró a presión reducida para eliminar disolvente. El residuo se diluyó con diclorometano (50 ml), se basificó con una solución saturada de bicarbonato de sodio (pH=8), se extrajo con diclorometano (50 ml × 3), la fase naranja se lavó con salmuera (50 ml), se secó sobre sulfato de sodio anhidro y se concentró a presión reducida para obtener el residuo. El producto crudo 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3-metil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (1,72 g) como un sólido blanco se utilizó en el siguiente paso sin purificación adicional.

LC-MS: MS (ESI$^+$): t_R = 0,467 min, m/z = 621,5 [M + H$^+$]

[00733] A una solución de 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (1,20 g) y 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3-metil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (1,72 g, 2,77 mmol, 1,0 eq) en NMP (7,5 ml) se le agregó DIPEA (1,11 g, 8,61 mmol, 1,5 ml, 3,1 eq) y la mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se detuvo mediante la adición de 50 ml de agua y se extrajo con acetato de etilo (50 ml × 3). Las capas orgánicas combinadas se

lavaron con salmuera (50 ml x 2), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 100/1 a 20/1). El compuesto 2-[(3R,4R)-4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (1893,96 mg, 1,89 mmol, 68 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-$_d$**8,71**) δ 7,89 (d, ^{J} = 8,8 Hz, 1H), 7,75 - 8,06 (m, 1H), 7,69 (d, *J* = 9,2 Hz, 1H), 7,50 (d, *J* = 2,4 Hz, 2H), 7,10 - 7,47 (m, 3H), 7,04 - 6,97 (m, 4H), 6,95 - 6,61 (m, 4H), 4,70 (d, *J* = 13,2 Hz, 1H) 4,58 - 4,28 (m, 1H), 4,20 - 4,10 (m, 1H), 4,02 (t, *J* = 9,2 Hz, 1H), 3,87 - 3,66 (m, 1H), 3,64 (br s, 1H), 3,19 (br d, *J* =11,2 Hz, 1H), 3,07 - 2,96 (m, 2H), 2,95 - 2,71 (m, 1H), 2,24 - 1,92 (m, 1H), 1,85 - 1,45 (m, 1H), 1,41-1,28 (m, 1H), 1,21 (d, *J* = 3,2 Hz, 3H), 1,10 (d, *J* = 6,4 Hz, 2H).

LC-MS: MS (ESI$^+$): t_R = 2,087 min, m/z=1003,3 [M + H$^+$]

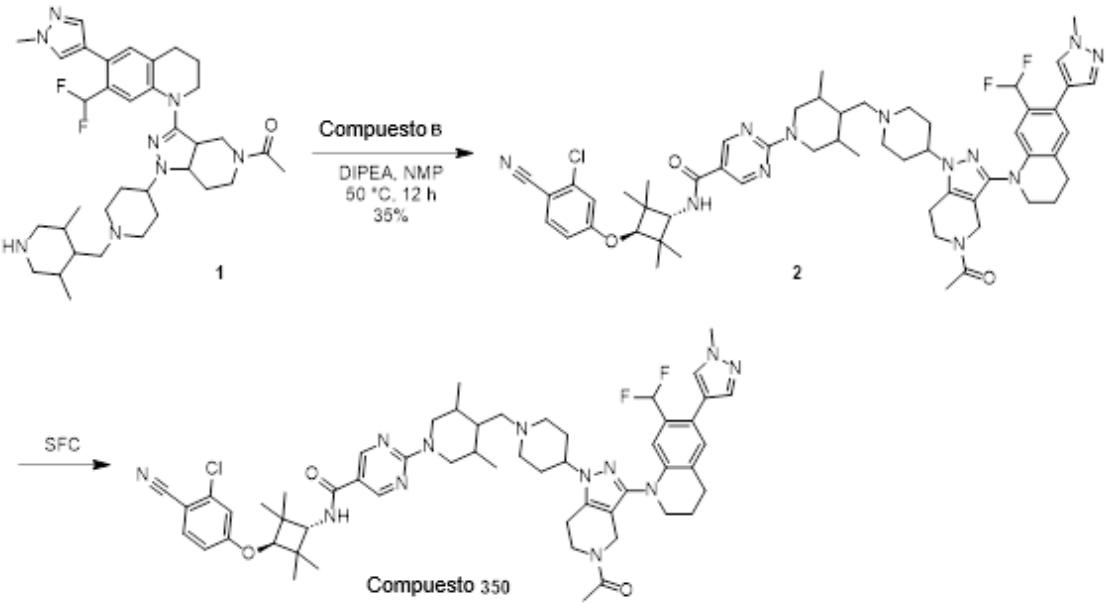
SFC: t_R = 5,963 min, 46 %; t_R = 6,837 min; 54 %.

[00734] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 30.

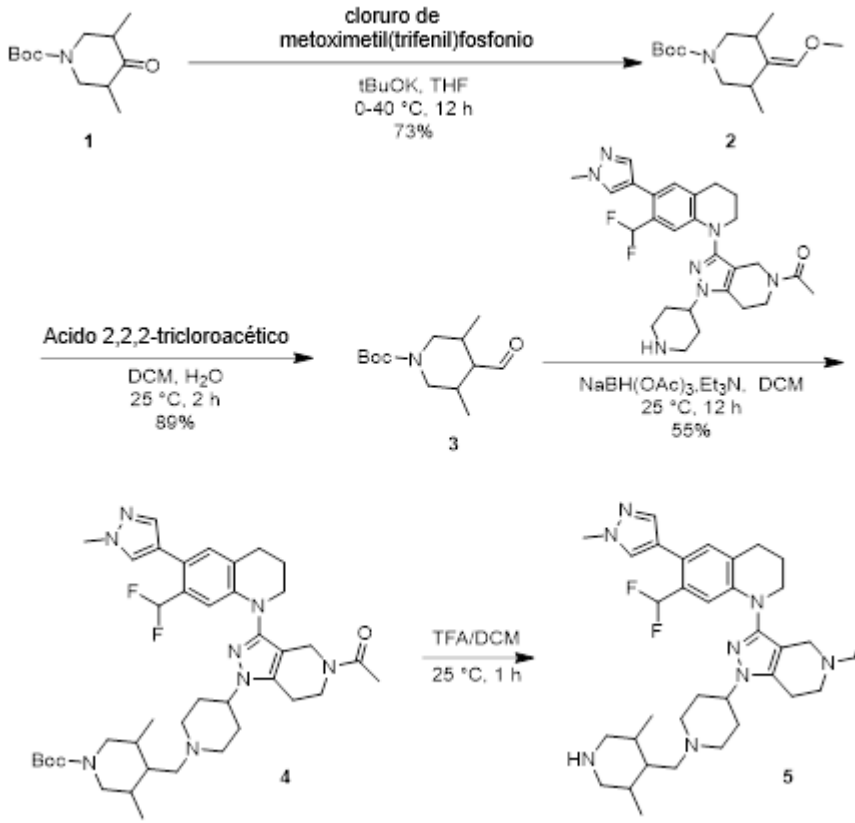
Compuesto	**Nombre**	**^{1}H NMR (300 MHz, DMSO-d_6):**	**LC-MS (M+H)$^+$:**
263	4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,75 (s, 1H), 7,74 - 7,67 (m, 2H), 7,64 (d, J = 8,4 Hz, 1H), 7,50 (s, 1H), 7,46 (d, J = 9,2 Hz, 1H), 7,11 (s, 1H), 6,92 (d, J = 8,8 Hz, 2H), 6,82 - 6,51 (m, 4H), 4,26 (s, 1H), 4,19 - 4,10 (m, 2H), 4,04 (d, J = 9,2 Hz, 2H), 3,90 (s, 3H), 3,87 (s, 3H), 3,76 - 3,66 (m, 3H), 3,65 - 3,57 (m, 3H), 2,95 (d, J = 11,6 Hz, 3H), 2,85 (d, J = 6,0 Hz, 4H), 2,76 (d, J = 18,8 Hz, 1H), 2,20 (s, 2H), 2,09 - 1,94 (m, 10H), 1,92 - 1,78 (m, 3H), 1,52 (s, 2H), 1,22 (s, 6H), 1,14 (s, 6H), 0,88 (d, J = 6,8 Hz, 3H).	997,8
363	2-[(3R,4R)-4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-	δ = 8,72 (s, 2H), 7,91 (d, J = 8,4 Hz, 1H), 7,76 (s, 1H), 7,70 (br d, J = 9,2 Hz, 1H), 7,51 (s, 1H), 7,22 (d, J = 2,4 Hz, 1H), 7,12 (s, 1H), 7,04 -	1003,4

Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
	1-piperidil]metil]-3-metil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	6,99 (m, 1H), 6,97 - 6,65 (m, 2H), 4,75 - 4,67 (m, 1H), 4,63 - 4,55 (m, 1H), 4,29 (s, 1H), 4,20 - 4,11 (m, 2H), 4,07 - 3,99 (m, 2H), 3,88 (s, 3H), 3,78 - 3,67 (m, 2H), 3,64 - 3,55 (m, 2H), 3,21 - 3,10 (m, 2H), 3,07 - 2,97 (m, 2H), 2,94 - 2,81 (m, 4H), 2,79 - 2,72 (m, 1H), 2,21 - 2,15 (m, 2H), 2,09 - 1,96 (m, 10H), 1,84 (br d, J = 9,6 Hz, 2H), 1,51 (br d, J = 10,4 Hz, 1H), 1,40 - 1,30 (m, 1H), 1,22 (d, J = 2,8 Hz, 6H), 1,11 (s, 6H), 0,76 (br d, J = 6,4 Hz, 3H).	
364	2-[(3S,4S)-4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,72 (s, 2H), 7,91 (d, J = 8,4 Hz, 1H), 7,76 (s, 1H), 7,70 (br d, J = 9,2 Hz, 1H), 7,51 (s, 1H), 7,22 (d, J = 2,4 Hz, 1H), 7,12 (s, 1H), 7,04 - 6,99 (m, 1H), 6,97 - 6,65 (m, 2H), 4,75 - 4,67 (m, 1H), 4,63 - 4,55 (m, 1H), 4,29 (s, 1H), 4,20 - 4,11 (m, 2H), 4,07 - 3,99 (m, 2H), 3,88 (s, 3H), 3,78 - 3,67 (m, 2H), 3,64 - 3,55 (m, 2H), 3,21 - 3,10 (m, 2H), 3,07 - 2,97 (m, 2H), 2,94 - 2,81 (m, 4H), 2,79 - 2,72 (m, 1H), 2,21 - 2,15 (m, 2H), 2,09 - 1,96 (m, 10H), 1,84 (br d, J = 9,6 Hz, 2H), 1,51 (br d, J = 10,4 Hz, 1H), 1,40 - 1,30 (m, 1H), 1,22 (d, J = 2,8 Hz, 6H), 1,11 (s, 6H), 0,76 (br d, J = 6,4 Hz, 3H).	1003,4

[00735] Ejemplo 31: Síntesis de 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 350**)



[00736] Síntesis de (1)



[00737] A una solución de metoximetil(trifenil)fosfonio;cloruro (15,08 g, 44,0 mmol, 2,0 eq) en THF (150 ml) se agregó tBuOK (1 M, 66 ml, 3,0 eq) a 0 °C y se agitó a 0 °C durante 1 h. Luego se agregó 3,5-dimetil-4-oxo-piperidina-1-carboxilato de ter-butilo

(5,00 g, 22,0 mmol, 1,0 eq) en THF (30 ml) a 0 °C. La mezcla de reacción se agitó a 40 °C durante 11 h bajo N_2. La mezcla se extrajo con acetato de etilo (300 ml). La fase acuosa se extrajo con agua (100 ml × 3), se secó con sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 5/1 a 2/1). El compuesto 4-(metoximetileno)-3,5-dimetil-piperidina-1-carboxilato de ter-butilo (4,15 g, 16,1 mmol, 73 % de rendimiento) se obtuvo como un aceite incoloro.

[00738] ^{1}H NMR (400 MHz, Cloroformo-**d**) δ 5,79 (s, 1H), 3,88 – 3,49 (m, 1H), 3,14 – 2,72 (m, 3H), 2,28 (d, J = 1,2 Hz, 9H).

[00739] A una solución de 4-(metoximetileno)-3,5-dimetil-piperidina-1-carboxilato de ter-butilo (6,80 g, 26,6 mmol, 1,0 eq) en DCM (120 ml) y H_2O (40 ml) se agregó ácido 2,2,2-tricloroacético (26,11 g, 160 mmol, 6,0 eq). La mezcla se agitó a 25 °C durante 2 h en N_2. Ajustar el pH a 9-10 con $NaHCO_3$ y luego concentrar el sistema, extraer con DCM (300 ml), lavar con agua (100 ml × 3), secar sobre Na_2SO_4, concentrar a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 100/1 a 10/1). El compuesto ter-butil 4-formil-3,5-dimetil-piperidina-1-carboxilato (5,81 g, 23,8 mmol, 89 % de rendimiento) se obtuvo como un aceite incoloro.

[00740] ^{1}H NMR (400 MHz, cloroformo-**d**) δ 10,11 – 9,38 (m, 1H), 4,24 – 3,76 (m, 2H), 2,86 – 3,96 (m, 1H), 2,64 – 2,51 (m, 1H), 2,42 – 2,19 (m, 2H), 1,99 – 1,76 (m, 2H), 1,46 – 2,12 (m, 1H), 1,00 – 1,76 (m, 1H), 0,86 (t, J = 6,4 Hz, 2H).

[00741] A una solución de 4-formil-3,5-dimetil-piperidina-1-carboxilato de ter-butilo (268 mg, 1,11 mmol, 1,3 eq) y 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (435 mg, 854 µmol, 1,0 eq) en DCM (8 ml) se agregó gota a gota Et_3N (864 mg, 8,54 mmol, 10,0 eq) y $NaBH(OAc)_3$ (905 mg, 4,27 mmol, 5,0 eq) a 25 °C bajo N_2. La mezcla se agitó a 25 °C durante 12 h en N_2. El residuo se vertió en agua (30 ml). La fase acuosa se extrajo con DCM (30 ml × 3), se secó con sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150 × 40mm × 15um; fase móvil: [agua(FA)-ACN]; gradiente: 32 %-62 % B durante 10 min). El compuesto ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (364 mg, 471 µmol, 55 % de rendimiento) se obtuvo como un sólido amarillo.

[00742] **LC-MS:** MS (ESI$^+$): t_R = 0,557 min, m/z = 735,4 [M + H$^+$]

[00743] A una solución de ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (364 mg, 471 µmol, 1,0 eq) en DCM (4 ml) se le agregó TFA (1,54 g, 13,5 mmol, 27,3 eq). La mezcla se agitó a 25 °C durante 1 h en N_2. La mezcla de reacción se concentró. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (360 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00744] **LC-MS:** MS (ESI^+): t_R = 0,471 min, m/z = 635,6 [M + H^+]

[00745] Síntesis del compuesto **350**

[00746] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (11 g) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (8,01 g, 19,1 mmol, 1,3 eq) en NMP (100 ml) se agregó DIPEA (5,70 g, 44,1 mmol, 3,0 eq) a 25 °C. La mezcla se agitó a 50 °C durante 12 h bajo N_2. La mezcla se extrajo con acetato de etilo (150 ml). La fase acuosa se extrajo con 300 ml de agua (100 ml × 3), se secó con sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante cromatografía en columna (SiO_2, DCM/MeOH = 100/1 a 10/1) como un sólido amarillo, que posteriormente se separó por SFC (columna: DAICEL CHIRALPAK AD (250 mm × 30 mm, 10 µm); fase móvil: [CO_2-ACN/EtOH (0,1 % NH_3H_2O)]; B%: 40 %, modo de elución isocrática). El compuesto 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (5224,17 mg, 5,08 mmol, 35 % de rendimiento) se obtuvo como un sólido amarillo.

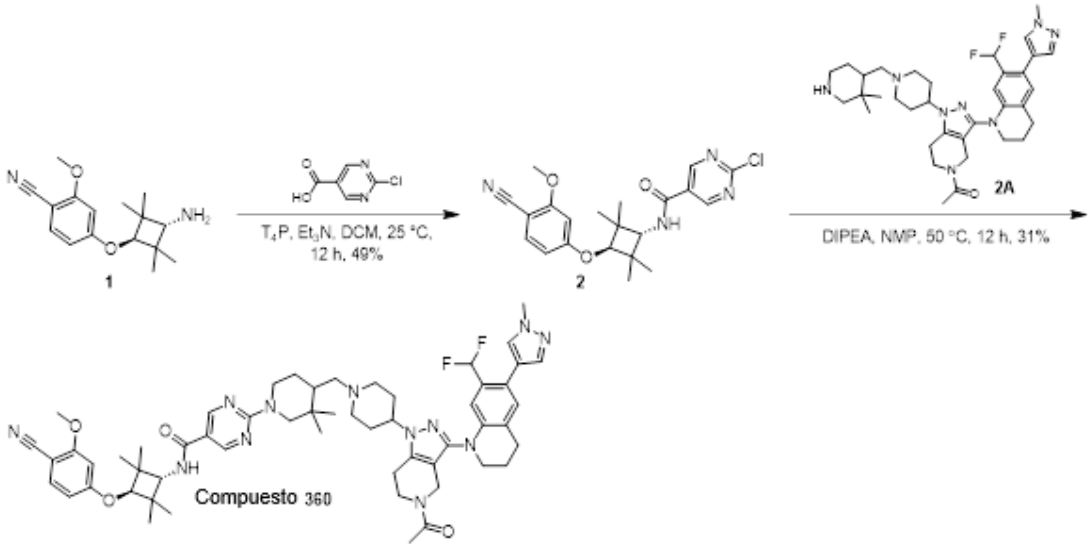
[00747] 620, ^{1}H NMR (400 MHz, DMSO-d**6**) δ = 8,68 - 9,31 (m, 1H), 7,59 - 7,49 (m, 1H), 7,43 - 7,36 (m, 1H), 7,07 - 6,93 (m, 1H), 6,89 - 6,75 (m, 3H), 6,69 - 6,33 (m, 2H), 5,98 (br d, J =8,4 Hz, 1H), 4,29 - 4,08 (m, 1H), 4,07 - 3,98 (m, 1H), 3,97 - 3,85 (m, 1H), 3,77 – 3,64 (m, 1H), 3,42 - 3,29 (m, 1H), 3,07 - 4,42 (m, 1H), 2,93 - 2,69 (m, 3H), 2,35 - 2,15 (m, 1H), 2,10 - 2,00 (m, 3H), 1,86 (s, 1H), 1,24 (s, 2H), 1,21 - 2,78 (m, 1H), 1,01 - 2,57 (m, 1H), 2,41 - 2,29 (m, 1H).

[00748] **LC-MS:** MS (ESI^+): t_R = 3,133 min, m/z =1017,7 [M + H^+]

[00749] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 31.

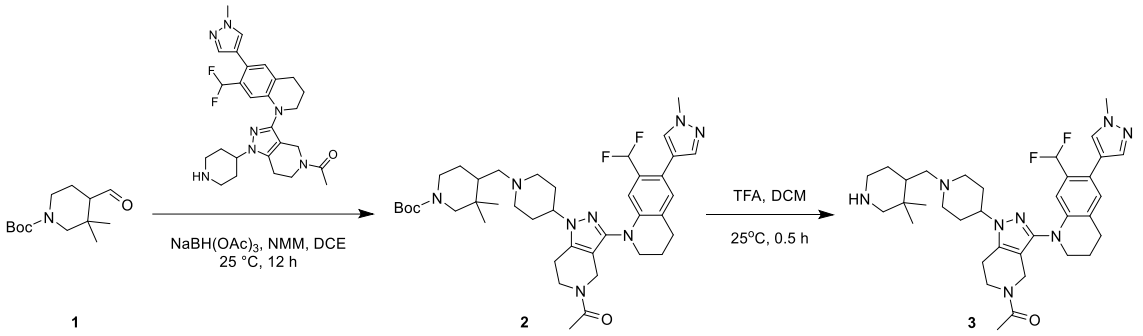
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
327	4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,75-7,63 (m, 1H), 7,58-7,50 (m, 2H), 7,49-7,44 (m, 2H), 7,43-7,37 (m, 1H), 6,86 (s, 1H), 6,70-6,36 (m, 1H), 6,06 (s, 2H), 4,34-4,24 (m, 2H), 4,12 (brs, 2H), 4,08-4,03 (m, 2H), 3,99-3,86 (m, 2H), 3,65 (s, 3H), 3,30 (s, 3H), 3,16-3,02 (m, 2H), 2,94-2,72 (m, 2H), 2,32-2,17 (m, 2H), 2,14-1,98 (m, 2H), 1,93-1,20 (m, 2H).	1011,7

[00750] **Ejemplo 32**: Síntesis de 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 360**)



[00751] La síntesis de **1** se describió en el informe de WO2021/127443 A1

[00752] Síntesis de **2A:**



[00753] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (350 mg, 561,24 µmol, 1 eq, TFA) y NMM (568 mg, 5,61 mmol, 617,04 µl, 10 eq) en DCM (5 ml) se agregó 4-formil-3,3-dimetil-piperidina-1-carboxilato de ter-butilo (270 mg, 1,12 mmol, 1,99 eq) y $NaBH(OAc)_3$ (238 mg, 1,12 mmol, 2 eq). La mezcla de reacción se agitó a 25 °C durante 12 h. La mezcla se concentró hasta secarse. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 0/1 a 10/1). El compuesto ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-piperidina-1-carboxilato (420 mg, crudo) se obtuvo como un sólido blanquecino.

[00754] ^{1}H NMR (400 MHz, DMSO-d_3) δ = 7,53 (s, 1H), 7,40 (d, **J** = 4,8 Hz, 2H), 7,02 (d, J = 4,8 Hz, 1H), 6,92 - 6,81 (m, 1H), 6,52 - 7,71 (m, 2H), 4,29 - 4,09 (m, 1H), 3,99 - 3,87 (m, 1H), 3,79 - 3,67 (m, 1H), 3,21 - 3,09 (m, 1H), 3,07 – 2,95 (m, 1H), 2,92 - 2,78 (m, 1H), 2,74 - 4,27 (m, 1H), 2,60 - 3,96 (m, 3H), 2,52 - 2,35 (m, 1H), 2,32 - 2,13 (m, 1H), 2,11 - 2,03 (m, 2H), 2,01 – 1,90 (m, 1H), 1,84 - 1,75 (m, 2H), 0,97 - 0,90 (m, 2H), 0,79 - 1,21 (m, 1H).

[00755] **LC-MS:** MS (ESI$^+$): t_R = 0,488 min, m/z = 735,4 [M + H$^+$]

[00756] A una solución de ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-piperidina-1-carboxilato (120 mg, 163,28 µmol, 1 eq) en DCM (5 ml) se le agregó TFA (93 mg, 816,42 µmol, 60,65 µl, 5 eq). La mezcla de reacción se agitó a 25 °C durante 0,5 h. La mezcla se concentró hasta secarse. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,3-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (104 mg, crudo) se obtuvo como aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional .

[00757] **LC-MS:** MS (ESI$^+$): t_R = 0,401 min, m/z = 635,4 [M + H$^+$]

[00758] Síntesis del compuesto **360**

[00759] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-metoxibenzonitrilo (2,00 g, 7,29 mmol, 1,0 eq) en diclorometano (20 ml) se añadieron Et_3N (5,90 g, 58,32 mmol, 8,12 ml, 8,0 eq) y ácido 2-cloropirimidina-5-carboxílico (1,16 g, 7,29 mmol, 1,0 eq), T_4P (3,94 g, 10,93 mmol, 1,5 eq). La mezcla se agitó a 25 °C durante 12 h y luego se vertió en agua (50 ml). La capa acuosa se extrajo con DCM (50 ml x 2). La capa orgánica combinada se lavó con salmuera (100 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : Se obtuvo el compuesto 2-cloro-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (1,49 g, 3,59 mmol, rendimiento del 49 %) como un sólido blanco.

[00760] ^{1}H NMR (400 MHz, DMSO-d6) δ 8,30 (d, J = 9,0 Hz, 1H), 7,64 (d, J = 8,5 Hz, 1H), 6,70 (s, 2H), 4,06 (s, 1H), 3,91 (s, 2H), 1,27 (s, 12H).

[00761] **LC-MS:** MS (ESI$^+$): t_R = 0,543 min, m/z = 415,1 [M + H$^+$]

[00762] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,3-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (129 mg, 203,21 µmol, 1,0 eq) en NMP (3 ml) se le agregó DIPEA (210 mg, 1,63 mmol, 283,16 µl, 8,0 eq) y 2-cloro-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (126 mg, 304,82 µmol, 1,5 eq). La mezcla se agitó a 50 °C durante 12 horas. El residuo se vertió en agua (50 ml). La fase acuosa se extrajo con acetato de etilo (50 ml x 2). La capa orgánica combinada se lavó con salmuera (100 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 15/1 a 10/1). El residuo se purificó mediante HPLC preparativa (columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua (FA)-ACN]; gradiente: 30 %-60 % B durante 10 min) para obtener el compuesto deseado. Luego fue liofilizado. El compuesto 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (65,78 mg, 64,26 µmol, 31 % de rendimiento) se obtuvo como un sólido blanco.

[00763] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8,68 (s, 2H), 7,54 (d, J = 5,8 Hz, 1H), 7,46 (d, J = 8,6 Hz, 1H), 7,41 (d, J = 6,6 Hz, 1H), 7,09-6,98 (m, 1H), 6,93-6,84 (m, 1H), 6,69-6,38 (m, 3H), 5,92 (d, J = 8,3 Hz, 1H), 4,87 (d, J = 13,5 Hz, 1H), 4,50 (d, J = 13,0 Hz, 1H), 4,29-4,10 (m, 3H), 4,04 (s, 1H), 3,96 (d, J = 1,9 Hz, 4H), 3,93-3,89 (m, 4H), 3,80-3,66 (m, 3H), 3,25-3,08 (m, 1H), 3,05-2,94 (m, 1H), 2,93-2,84 (m, 3H), 2,82 (t, J = 5,5 Hz, 1H), 2,77-2,69 (m, 2H), 2,51-2,40 (m, 1H), 2,37-2,21 (m, 3H), 2,17 (s, 2H), 2,12-2,02 (m,

5H), 1,98 (d, J = 10,5 Hz, 3H), 1,61-1,56 (m, 1H), 1,44-1,35 (m, 1H), 1,24 (d, J = 7,1 Hz, 12H), 1,05 (s, 3H), 0,79 (s, 3H)

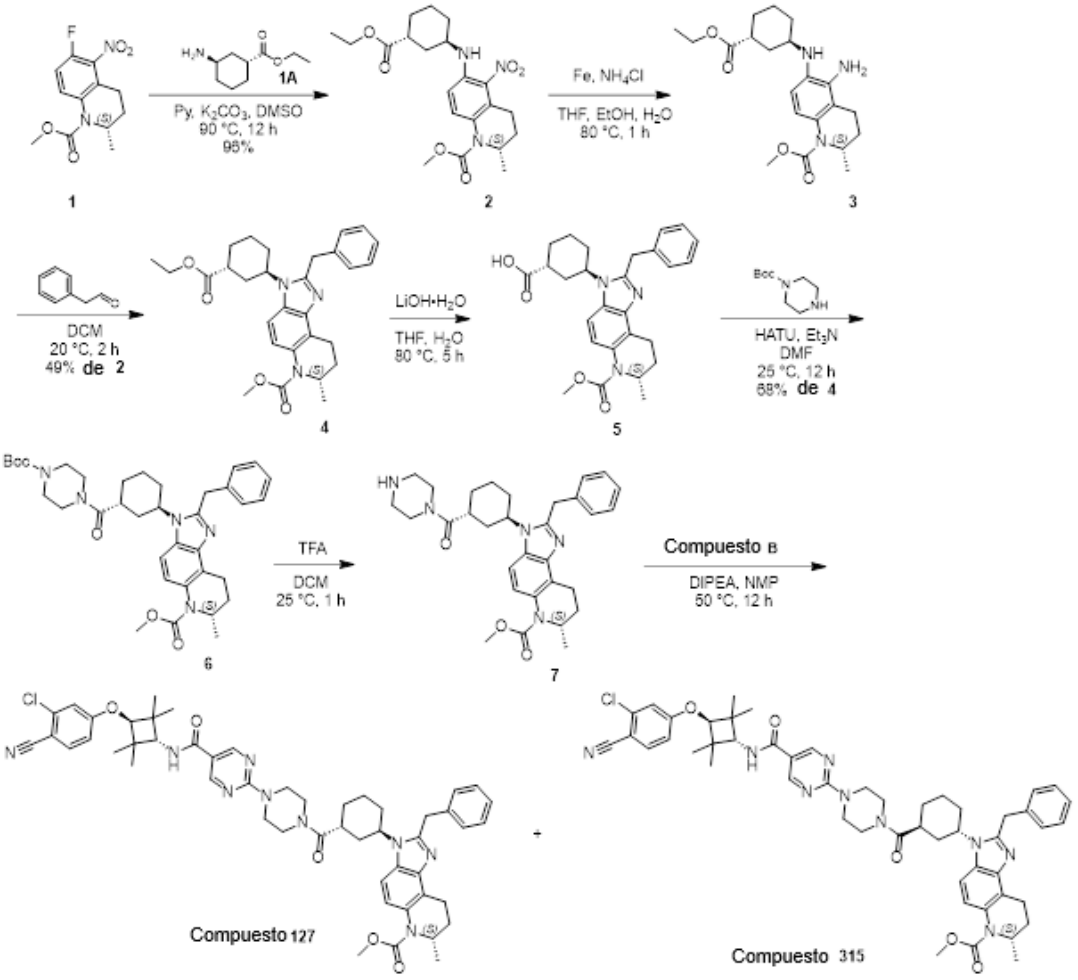
[00764] **LC-MS:** MS (ESI^+): t_R = 3,050 min, m/z = 1013,8 [M + H^+]

[00765] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 32.

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
329	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metoxi-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	8,72H NMR (400 MHz, CLOROFORMO-d) δ = 7,70 (d, J = 9,4 Hz, 1H), 7,21 - 7,10 (m, 2H), 7,04 - 6,98 (m, 1H), 6,96 - 6,63 (m, 4H), 5,09 (br d, J = 13,6 Hz, 1H), 4,83 - 4,71 (m, 1H), 4,29 (s, 1H), 4,20 - 4,10 (m, 4H), 4,07 - 3,98 (m, 1H), 3,86 - 4,14 (m, 2H), 3,66 (s, 1H), 3,55 (s, 1H), 3,24 (s, 2H), 3,02 - 2,81 (m, 8H), 2,71 (s, 1H), 2,25 - 1,92 (m, 12H), 1,90 - 1,80 (m, 2H), 1,56 - 1,47 (m, 4H), 1,42 - 1,32 (m, 4H), 1,21 - 1,11 (m, 2H).	1019,5
331	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metoxi-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ = 8,71 (s, 2 H) 7,58 (d, *J*=8,8 Hz, 1 H) 7,54 (d, *J*=5,2 Hz, 1 H) 7,41 (d, *J*=6,4 Hz, 1 H) 7,03 (d, *J*=20,0 Hz, 1 H) 6,97 (d, *J*=2,4 Hz, 1 H) 6,93-6,85 (m, 1 H) 6,81 (dd, *J*=8,8, 2,4 Hz, 1 H) 6,69-6,38 (m, 1 H) 5,95 (días, *J*=8,4 Hz, 1 H) 4,96-4,73 (m, 1 H) 4,63-4,46 (m, 1 H) 4,28 (s, 1 H) 4,16-4,12 (m, 2 H) 4,05 (s, 1 H) 3,96 (d, *J*=1,6 Hz, 4 H) 3,92-3,88 (m, 1 H) 3,77-3,66 (m, 3 H) 3,46 (s, 3 H) 3,21-3,09 (m, 2 H) 3,07-3,00 (m, 2 H) 2,90-2,84 (m, 2 H) 2,81 (t, *J*=5,6 Hz, 1 H) 2,76-2,73 (m, 1 H) 2,39-2,19 (m, 4 H) 2,17 (s, 2 H) 2,09 (d, *J*=6,0 Hz, 2 H) 2,07-2,02 (m, 3 H) 1,96-1,85 (m, 2 H) 1,80-1,67 (m, 3 H) 1,28 (s, 1 H) 1,26 (s, 6 H) 1,22 (s, 6 H).	1019,7

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
332	4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3-metoxi-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,70 (d, J = 8,6 Hz, 1H), 7,54 (d, J = 5,6 Hz, 1H), 7,46 (d, J = 8,4 Hz, 1H), 7,41 (d, J = 8,6 Hz, 1H), 6,92 (d, J = 8,4 Hz, 1H), 6,87 (d, J = 4,0 Hz, 1H), 6,12 (d, J = 8,0 Hz, 2H), 4,28 - 4,03 (m, 4H), 3,87 (br s, 2H), 3,17 - 3,03 (m, 1H), 3,02 - 2,93 (m, 3H), 2,93 - 2,78 (m, 3H), 2,78 - 2,67 (m, 3H), 2,36 - 2,19 (m, 2H), 2,19 - 2,01 (m, 4H), 1,44 - 1,35 (m, 1H), 1,25 (d, J = 10,0 Hz, 3H).	1013,8
356	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ = 8,68 (s, 2H), 7,59 - 7,53 (m, 2H), 7,44 - 7,38 (m, 1H), 7,06 - 6,99 (m, 1H), 6,97 (d, *J* = 2,4 Hz, 1H), 6,89 - 6,86 (m, 1H), 6,81 (dd, *J* = 2,4, 8,7 Hz, 1H), 6,69 - 6,37 (m, 1H), 5,91 (d, *J* = 8,1 Hz, 1H), 4,86 (d, *J* = 12,9 Hz, 1H), 4,49 (d, *J* = 13,0 Hz, 1H), 4,26 (s, 1H), 4,14 - 4,11 (m, 2H), 4,04 (s, 1H), 3,96 (d, *J* = 2,0 Hz, 3H), 3,91 (t, *J* = 5,7 Hz, 2H), 3,78 - 3,68 (m, 3H), 3,21 - 3,05 (m, 1H), 2,98 - 2,80 (m, 5H), 2,77 - 2,70 (m, 2H), 2,47 - 2,37 (m, 1H), 2,34 - 2,21 (m, 3H), 2,17 (s, 1H), 2,13 - 2,04 (m, 5H), 2,02 - 1,87 (m, 4H), 1,58 - 1,53 (m, 1H), 1,42 - 1,35 (m, 1H), 1,25 (s, 6H), 1,22 (s, 6H), 1,05 (s, 3H), 0,79 (s, 3H)	1017,7

[00766] Ejemplo 33: Síntesis de metil (7S)-2-bencil-3-[(1R,3R)-3-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazina-1-carbonil]ciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (**Compuesto 127**) y metil (7S)-2-bencil-3-[(1S,3S)-3-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazina-1-carbonil]ciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (**Compuesto 315**)



[00767] La síntesis de 1A se informó en WO2023/110936 A1.

[00768] A una solución de metil (2S)-6-fluoro-2-metil-5-nitro-3,4-dihidro-2H-quinolina-1-carboxilato (330 mg, 1,23 mmol, 1,0 eq) y etil (1R,3R)-3-aminociclohexanocarboxilato (316 mg, 1,85 mmol, 1,5 eq) en DMSO (12 ml) se añadieron piridina (292 mg, 3,69 mmol, 298 µl, 3,0 eq) y K_2CO_3 (340 mg, 2,46 mmol, 2,0 eq). La mezcla de reacción se agitó a 90 °C durante 12 h. La mezcla de reacción se diluyó con acetato de etilo (120 ml). La fase acuosa se extrajo con acetato de etilo (40 ml x 3). La fase orgánica combinada se lavó con salmuera (40 ml x 2), se secó con Na2SO4 anhidro, se filtró y se concentró a vacío. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 10/1 a 3/1). El compuesto metil (2S)-6-[[(1R,3R)-3-etoxicarbonilciclohexil]amino]-2-metil-5-nitro-3,4-dihidro-2H-quinolina-1-carboxilato (500 mg, 1,18 mmol, 96 % de rendimiento) se obtuvo como una goma roja.

[00769] **LC-MS:** MS (ESI^+): t_R = 1,066 min, m/z = 420,2 [M - H^+]

[00770] A una mezcla de metil (2S)-6-[[(1R,3R)-3-etoxicarbonilciclohexil]amino]-2-

metil-5-nitro-3,4-dihidro-2H-quinolina-1-carboxilato (400 mg, 954 µmol, 1,0 eq) y NH_4Cl (480 mg, 8,97 mmol, 9,4 eq) en THF (6 ml) y EtOH (6 ml) y H_2O (4 ml) se agregó Fe (480 mg, 8,59 mmol, 490 µl, 9,0 eq). La mezcla de reacción se agitó a 80 °C durante 1 h en N_2. La mezcla de reacción resultante se filtró y se lavó con DCM (~20 ml). La mezcla de reacción se concentró para proporcionar un residuo. El compuesto metil (2S)-5-amino-6-[[(1R,3R)-3-etoxicarbonilciclohexil]amino]-2-metil-3,4-dihidro-2H-quinolina-1-carboxilato (340 mg) se obtuvo como un aceite incoloro y se utilizó directamente en el siguiente paso sin purificación adicional.

[00771] **LC-MS:** MS (ESI^+): t_R = 0,511 min, m/z = 390,3 [$M + H^+$]

[00772] A una mezcla de metil (2S)-5-amino-6-[[(1R,3R)-3-etoxicarbonilciclohexil]amino]-2-metil-3,4-dihidro-2H-quinolina-1-carboxilato (340 mg) en DCM (20 ml) se le agregó 2-fenilacetaldehído (340 mg, 2,83 mmol, 221 µl, 3,2 eq). La mezcla de reacción se agitó a 20 °C durante 2 h en N_2. La mezcla de reacción se concentró para proporcionar un residuo. El residuo se purificó por cromatografía en columna (SiO2, éter de petróleo/acetato de etilo = 5/1 a 2/1). El compuesto metil (7S)-2-bencil-3-[(1R,3R)-3-etoxicarbonilciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (210 mg, 428,9 µmol, 49 % de rendimiento en dos pasos) se obtuvo como una goma incolora.

[00773] **LC-MS:** MS (ESI^+): t_R = 0,578 min, m/z = 490,3 [$M + H^+$]

[00774] A una mezcla de metil (7S)-2-bencil-3-[(1R,3R)-3-etoxicarbonilciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (150 mg, 306 µmol, 1,0 eq) en THF (2 ml) se agregó $LiOH·H_2O$ (129 mg, 3,1 mmol, 10,0 eq) en H_2O (2 ml). La mezcla de reacción se agitó a 80 °C durante 5 h. La mezcla de reacción se concentró para eliminar el THF, se vertió en agua helada (15 ml), se ajustó a pH = 6 con ácido clorhídrico (1 M) a 0 °C y se liofilizó para obtener un residuo. El compuesto ácido (1R,3R)-3-[(7S)-2-bencil-6-metoxicarbonil-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolin-3-il]ciclohexanocarboxílico (140 mg) se obtuvo como un sólido blanquecino y se utilizó directamente en el siguiente paso sin purificación adicional.

[00775] A una mezcla de ácido (1R,3R)-3-[(7S)-2-bencil-6-metoxicarbonil-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolin-3-il]ciclohexanocarboxílico (140 mg) en DMF (6 ml) se le agregó Et_3N (92 mg, 910 µmol, 127 µl, 3,0 eq), piperazina-1-carboxilato de ter-butilo (85 mg, 455 µmol, 1,5 eq) y HATU (231 mg, 607 µmol, 2,0 eq). La mezcla de reacción se agitó a 25 °C durante 12 h. La mezcla de reacción se diluyó con acetato de etilo (80 ml). La fase acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica combinada se lavó con salmuera (20 ml x 2), se secó con Na2SO4 anhidro, se filtró y

se concentró a vacío. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 1 : El compuesto metil (7S)-2-bencil-3-[(1R,3R)-3-(4-tert-butoxicarbonilpiperazina-1-carbonil)ciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (140 mg, 207 µmol, 68 % de rendimiento en dos pasos) se obtuvo como una goma marrón.

[00776] **LC-MS:** MS (ESI$^+$): t_R = 0,574 min, m/z = 630,6 [M + H$^+$]

[00777] A una mezcla de metil (7S)-2-bencil-3-[(1R,3R)-3-(4-tert-butoxicarbonilpiperazina-1-carbonil)ciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (140 mg, 222 µmol, 1,0 eq) en DCM (4 ml) se le agregó TFA (3,07 g, 26,9 mmol, 2 ml, 121,0 eq). La mezcla de reacción se agitó a 25 °C durante 1 h. La mezcla se concentró hasta secarse. El compuesto metil (7S)-2-bencil-7-metil-3-[(1R,3R)-3-(piperazina-1-carbonil)ciclohexil]-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (140 mg) se obtuvo como una goma marrón y se utilizó directamente en el siguiente paso sin purificación adicional.

[00778] **LC-MS:** MS (ESI$^+$): t_R = 0,763 min, 0,777 min, m/z = 530,4 [M + H$^+$]

[00779] A una mezcla de metil (7S)-2-bencil-7-metil-3-[(1R,3R)-3-(piperazina-1-carbonil)ciclohexil]-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (140 mg) en NMP (2 ml) se le agregó DIPEA (141 mg, 1,09 mmol, 189 µl, 5,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (110 mg, 262 µmol, 1,2 eq). La mezcla se agitó a 20 °C durante 12 h. La mezcla de reacción se diluyó con agua (20 ml), se extrajo con EtOAc (20 ml x 15), se secó sobre sulfato de sodio anhidro y se concentró al vacío. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (TFA)-ACN]; gradiente: 45 %-75 % B durante 10 min) y TLC preparativa (acetato de etilo/alcohol metílico = 40/1).

[00780] El compuesto metil (7S)-2-bencil-3-[(1R,3R)-3-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazina-1-carbonil]ciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (27,09 mg, 29,55 µmol, 14 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00781] **^{1}H NMR** (400 MHz, CLOROFORMO-*d*) δ = 8,75 (s, 2 H) 7,58 (d, *J*=8,8 Hz, 1 H) 7,32 - 7,48 (m, 3 H) 7,30 (s, 1 H) 7,24 (s, 2 H) 7,13 - 7,20 (m, 1 H) 6,97 (s, 1 H) 6,81 (m, 1 H) 5,95 (m, 1 H) 5,20 - 5,39 (m, 1 H) 4,75 - 4,85 (m, 1 H) 4,43 - 4,56 (m, 1 H) 4,35 - 4,42 (m, 1 H) 4,14 (d, *J*=7,6 Hz, 1 H) 4,06 (s, 1 H) 3,95 (s, 4 H) 3,79 (s, 3 H) 3,69 - 3,78 (m, 2 H) 3,46 - 3,60 (m, 2 H) 3,24 - 3,37 (m, 1 H) 3,18 (s, 1 H) 2,99 - 3,12 (m, 1 H) 2,20 - 2,39 (m, 2 H) 1,93 - 2,07 (m, 2 H) 1,86 (m, 1 H) 1,74 - 1,81 (m, 1 H) 1,64 - 1,72 (m, 2

H) 1,32 - 1,40 (m, 1 H) 1,25 (d, *J*=14,4 Hz, 12 H) 1,20 (d, *J*=6,4 Hz, 3 H).

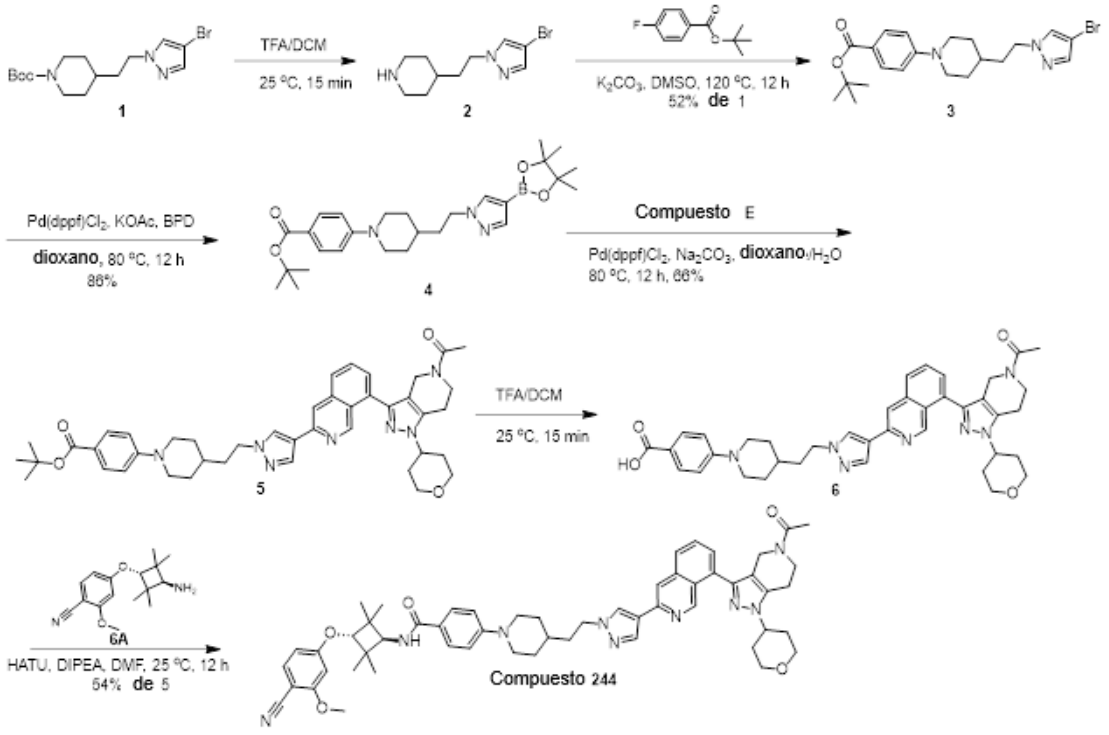
[00782] **LC-MS:** MS (ESI$^+$): t_R = 2,301 min, m/z = 912,4 [M + H$^+$]

[00783] El compuesto metil (7S)-2-bencil-3-[(1S,3S)-3-[4-[5-[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]pirimidin-2-il]piperazina-1-carbonil]ciclohexil]-7-metil-8,9-dihidro-7H-imidazo[4,5-f]quinolina-6-carboxilato (33,33 mg, 36,27 µmol, 17 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00784] **^{1}H NMR** (400 MHz, CLOROFORMO-*d*) δ = 8,75 (s, 2 H) 7,58 (d, *J*=8,8 Hz, 1 H) 7,31 - 7,44 (m, 3 H) 7,30 (s, 1 H) 7,22 - 7,26 (m, 2 H) 7,14 - 7,20 (m, 1 H) 6,97 (d, *J*=2,0 Hz, 1 H) 6,78 - 6,84 (m, 1 H) 5,91 - 5,98 (m, 1 H) 5,21 - 5,40 (m, 1 H) 4,75 - 4,87 (m, 1 H) 4,43 - 4,65 (m, 1 H) 4,31 - 4,42 (m, 1 H) 4,15 (d, *J*=8,0 Hz, 1 H) 4,06 (s, 1 H) 3,89 - 4,03 (m, 4 H) 3,69 - 3,85 (m, 5 H) 3,48 - 3,64 (m, 2 H) 3,23 - 3,38 (m, 1 H) 3,16 - 3,22 (m, 1 H) 3,02 - 3,15 (m, 1 H) 2,21 - 2,35 (m, 2 H) 1,94 - 2,14 (m, 2 H) 1,82 - 1,91 (m, 1 H) 1,64 - 1,81 (m, 3 H) 1,38 - 1,49 (m, 1 H) 1,25 (d, *J*=14,4 Hz, 12 H) 1,18 (d, *J*=6,4 Hz, 3 H).

[00785] **LC-MS:** MS (ESI$^+$): t_R = 2,276 min, m/z = 912,6 [M + H$^+$]

[00786] **Ejemplo 34**: Síntesis de 4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 244**)



[00787] A una solución de ter-butil 4-[2-(4-dimetilpirazol-1-il)fenil]azetidin-1-carboxilato (3,22 g, 8,99 mmol) en DCM (30 ml) se agregó TFA (1,0 ml). La mezcla se agitó a 25 °C

durante 15 minutos. El residuo se filtró y se concentró a presión reducida para obtener un residuo. El compuesto 4-[2-(4-bromopirazol-1-il)etil]piperidina (3,20 g) se obtuvo como un aceite incoloro y se utilizó directamente en el siguiente paso sin purificación adicional.

[00788] **LC-MS:** MS (ESI^+): t_R = 0,365 min, m/z = 258,1 [M + H^+]

[00789] A una solución de 4-[2-(4-bromopirazol-1-il)etil]piperidina (3,20 g), 4-fluorobenzoato de ter-butilo (1,69 g, 8,60 mmol, 1,0 eq) en DMSO (30 ml) se agregó K_2CO_3 (11,88 g, 85,98 mmol, 10,0 eq). La mezcla se agitó a 120 °C durante 30 min. La reacción se diluyó con agua (500 ml) y se extrajo con acetato de etilo (600 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (400 ml x 2), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 20/1 a 5/1). El compuesto ter-butil 4-[4-[2-(4-bromopirazol-1-il)etil]-1-piperidil]benzoato (1,95 g, 4,49 mmol, 52 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00790] ^{1}H NMR (400 MHz, CDCl**3**): δ 7,44 (d, 2H, J=6Hz), 6,85 (t, 2H, J=6Hz), 4,18 (t, 2H, J=7,2Hz), 3,84 (m, 2H), 2,80 (s, 2H), 1,7-2,0 (m, 4H), 1,6-1,6 (m, 9H), 1,4-1,5 (m, 1H), 1,3-1,4 (m, 2H).

[00791] **LC-MS:** MS (ESI^+): t_R = 0,614 min, m/z = 434,1 [M + H^+]

[00792] A una solución de 4-[4-[2-(4-bromopirazol-1-il)etil]-1-piperidil]benzoato de ter-butilo (900 mg, 2,07 mmol, 1,0 eq) en dioxano (10 ml) se añadieron BPD (789 mg, 3,11 mmol, 1,5 eq), Pd(dppf)Cl_2 (152 mg, 207,20 µmol, 0,1 eq) y KOAc (610 mg, 6,22 mmol, 3,0 eq). La mezcla se agitó a 80 °C durante 30 min. La reacción se diluyó con agua (500 ml) y se extrajo con acetato de etilo (600 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (400 ml x 2), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 20/1 a 4/1). El compuesto ter-butil 4-[4-[2-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazol-1-il]etil]-1-piperidil]benzoato (858 mg, 1,78 mmol, 86 % de rendimiento) se obtuvo como un aceite incoloro.

[00793] **LC-MS:** MS (ESI^+): t_R = 0,626 min, m/z = 482,3 [M + H^+]

[00794] A una solución de 4-[4-[2-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazol-1-il]etil]-1-piperidil]benzoato de ter-butilo (138 mg, 285,98 µmol, 1,5 eq), [8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil] trifluorometanosulfonato (100 mg, 190,65 µmol, 1,0 eq) en dioxano (5 ml), H_2O (1 ml) se

agregó $Pd(dppf)Cl_2$ (7 mg, 9,53 µmol, 0,05 eq) y Na_2CO_3 (61 mg, 571,96 µmol, 3,0 eq). La mezcla se agitó a 80 °C durante 30 min. La reacción se diluyó con agua (500 ml) y se extrajo con acetato de etilo (600 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (400 ml x 2), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH = 10: 1). El compuesto ter-butil 4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-1-piperidil]benzoato (92 mg, 126,04 µmol, 66 % de rendimiento) se obtuvo como un aceite incoloro.

[00795] **LC-MS:** MS (ESI^+): t_R = 0,547 min, m/z = 730,5 [M + H^+]

[00796] A una solución de 4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-1-piperidil]benzoato de ter-butilo (152 mg, 208,25 µmol, 1,0 eq) en DCM (3 ml) se le agregó TFA (237 mg, 2,08 mmol, 154,69 µl, 10,0 eq). La mezcla se agitó a 25 °C durante 15 minutos. El residuo se filtró y se concentró a presión reducida para obtener un residuo. El compuesto ácido 4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-1-piperidil]benzoico (140 mg) se obtuvo como un aceite incoloro y se utilizó directamente en el siguiente paso sin purificación adicional.

[00797] **LC-MS:** MS (ESI^+): t_R = 0,450 min, m/z = 674,5 [M + H^+]

[00798] A una solución de ácido 4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-1-piperidil]benzoico (140 mg), 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (58 mg, 213,25 µmol, 1,2 eq) en DMF (2 ml) se le agregó HATU (202,71 mg, 533,11 µmol, 3,0 eq) y DIPEA (229 mg, 1,78 mmol, 309,53 µl, 10,0 eq). La mezcla se agitó a 25 °C durante 30 min. La reacción se diluyó con agua (500 ml) y se extrajo con acetato de etilo (600 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (400 ml x 2), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH = 10: 1). El compuesto 4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (95,45 mg, 97,26 µmol, 54 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[00799] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10,0-9,7 (m, 1H), 8,1-8,2 (m, 2H), 7,92 (d, 1H, J=16,4 Hz), 7,9-7,7 (m, 2H), 7,68 (d, 2H, J=8,0 Hz), 7,6-7,4 (m, 2H), 6,91 (d, 2H, J=8,8 Hz), 6,5-6,3 (m, 2H), 6,12 (d, 1H, J=8,0 Hz), 4,69 (s, 1H), 4,51 (s, 1H), 4,3-4,2 (m, 3H),

4,2-4,1 (m, 3H), 4,1-4,0 (m, 2H), 3,92 (s, 3H), 3,9-3,8 (m, 3H), 3,57 (t, 2H, J=12,0 Hz), 3,0-2,9 (m, 1H), 2,9-2,8 (m, 3H), 2,43 (dq, 3H, J=4,4, 12,4 Hz), 2,22 (s, 2H), 2,09 (s, 2H), 2,0-1,9 (m, 3H), 1,87 (d, 2H, J=12,0 Hz), 1,5-1,4 (m, 2H), 1,25 (d, 12H, J=10,8 Hz)

[00800] **LC-MS:** MS (ESI$^+$): t_R = 2,616 min, m/z = 930,6 [M + H$^+$]

[00801] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 34.

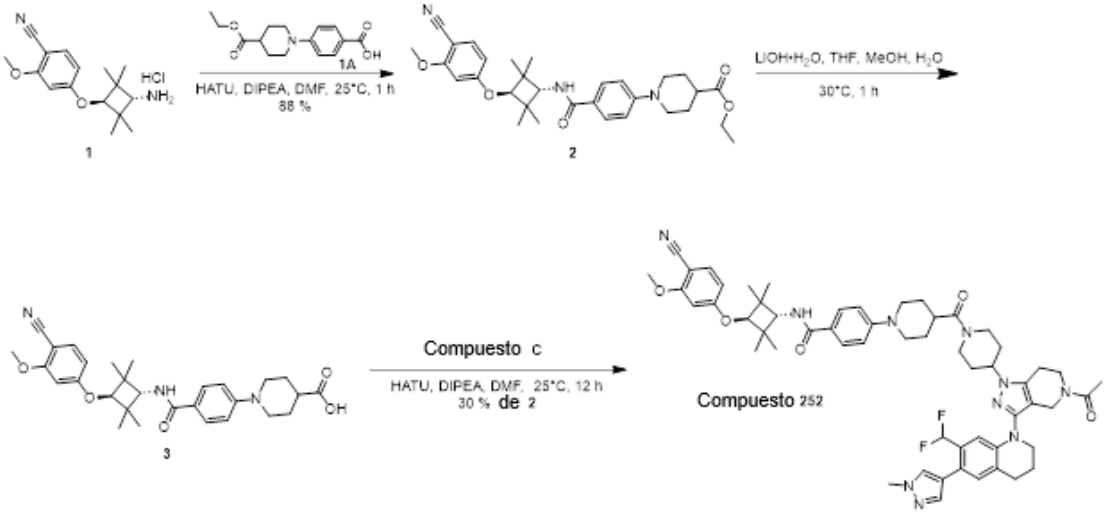
Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS (M+H)$^+$:**
249	4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]etil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,70 (d, J = 11,6 Hz, 1H), 8,14 (d, J = 5,2 Hz, 1H), 8,09 (s, 1H), 7,86 - 7,74 (m, 2H), 7,74 - 7,64 (m, 3H), 7,55 - 7,42 (m, 2H), 6,90 (d, J = 8,8 Hz, 2H), 6,47 (d, J = 2,0 Hz, 1H), 6,40 (dd, J = 2,0, 8,8 Hz, 1H), 6,12 (dd, J = 3,6, 8,0 Hz, 1H), 4,69 - 4,46 (m, 2H), 4,37 (t, J = 6,4 Hz, 2H), 4,32 - 4,22 (m, 1H), 4,20 - 4,11 (m, 3H), 4,06 - 3,98 (m, 2H), 3,92 (s, 3H), 3,84 (t, J = 6,0 Hz, 1H), 3,57 (t, J = 11,6 Hz, 2H), 3,38 - 3,25 (m, 4H), 3,05 - 2,89 (m, 3H), 2,86 (t, J = 5,6 Hz, 1H), 2,68 (s, 4H), 2,52 - 2,37 (m, 2H), 2,23 - 2,05 (m, 3H), 1,96 (d, J = 12,8 Hz, 2H), 1,25 (d, J = 9,2 Hz, 12H)	931,7
245	4-[4-[2-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]etil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,83 (d, *J* = 6,0 Hz, 1H), 9,24 (s, 1H), 8,46 - 8,29 (m, 1H), 8,10 (d, *J* = 10,8 Hz, 1H), 7,98 - 7,85 (m, 1H), 7,76 (td, *J* = 7,6, 11,7 Hz, 1H), 7,68 (d, *J* = 8,4 Hz, 2H), 7,58 (dd, *J* = 6,8, 16,2 Hz, 1H), 7,45 (d, *J* = 8,6 Hz, 1H), 7,32 (dd, *J* = 4,0, 7,8 Hz, 1H), 6,92 (d, *J* = 8,4 Hz, 2H), 6,54 - 6,34 (m, 2H), 6,12 (d, *J* = 8,0 Hz, 1H), 4,67 (s, 1H), 4,50 (s, 1H), 4,37 - 4,22 (m, 1H), 4,22 - 4,11 (m, 3H), 4,07 - 4,00 (m, 2H), 3,96 - 3,81 (m, 6H), 3,58 (t, *J* = 12,0 Hz, 2H), 2,93 (d, *J* = 6,4 Hz, 2H), 2,90 - 2,79 (m, 3H),	941,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2,52 - 2,37 (m, 2H), 2,24 - 2,06 (m, 3H), 1,97 (d, *J* = 12,0 Hz, 2H), 1,90 (d, *J* = 12,0 Hz, 2H), 1,79 (re, *J* = 7,6 Hz, 3H), 1,57 (s, 1H), 1,46 - 1,37 (m, 2H), 1,25 (re, *J* = 10,8 Hz, 12H)	
246	4-[4-[2-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]etil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,00 (s, 1H), 8,30-8,10 (m, 1H), 7,94 (s, 1H), 7,68 (d, 2H, J=8,6 Hz), 7,50-7,40 (m, 2H), 6,91 (d, 2H, J=8,8 Hz), 6,50-6,30 (m, 2H), 6,12 (d, 1H, J=8,0 Hz), 4,35 (s, 1H), 4,20-4,10 (m, 5H), 4,05 (s, 1H), 3,92 (s, 4H), 3,84 (d, 2H, J=12,8 Hz), 3,80-3,70 (m, 3H), 3,52 (t, 2H, J=12,0 Hz), 2,93 (d, 4H, J=6,4 Hz), 2,90-2,70 (m, 4H), 2,40-2,20 (m, 2H), 2,20-2,10 (m, 5H), 1,87 (d, 5H, J=8,4 Hz), 1,80-1,70 (m, 2H), 1,40-1,30 (m, 2H), 1,25 (d, 12H, J=11,2 Hz)	946,7
247	4-[4-[2-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]etil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 8,51 (d, 1H, J=1,6 Hz), 7,69 (d, 2H, J=8,8 Hz), 7,57 (dd, 1H, J=2,4, 7,8 Hz), 7,46 (d, 1H, J=8,4 Hz), 7,20-7,10 (m, 1H), 7,10-6,90 (m, 4H), 6,60-6,20 (m, 3H), 6,12 (d, 1H, J=8,0 Hz), 4,29 (s, 1H), 4,20-4,10 (m, 5H), 4,05 (s, 1H), 3,92 (s, 4H), 3,86 (d, 2H, J=12,4 Hz), 3,80-3,70 (m, 3H), 3,53 (t, 2H, J=12,0 Hz), 2,90-2,70 (m, 8H), 2,40-2,20 (m, 2H), 2,20-2,00 (m, 4H), 1,90 (t, 4H, J=9,6 Hz), 1,80-1,70 (m, 2H), 1,60-1,50 (m, 2H), 1,50-1,40 (m, 2H), 1,25 (d, 12H, J=10,4 Hz)	995,7
248	4-[4-[2-[4-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]fenil]etil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-	δ = 7,68 (s, 2H), 7,46 (d, J = 8,4 Hz, 1H), 7,26 - 7,23 (m, 3H), 7,23 (s, 1H), 7,00 (d, J = 20,4 Hz, 1H), 6,93 (d, J = 6,8 Hz, 2H), 6,90 (s, 1H), 6,65 - 6,29 (m, 3H), 6,12 (d, J = 8,0 Hz, 1H), 4,34 - 4,23 (m, 1H), 4,18 - 4,10 (m,	994,2

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	tetrametilciclobutil]benzamida	5H), 4,05 (s, 1H), 3,93 (s, 4H), 3,86 (d, J = 12,4 Hz, 2H), 3,80 - 3,70 (m, 3H), 3,53 (s, 2H), 2,94 - 2,80 (m, 5H), 2,77 (t, J = 5,6 Hz, 1H), 2,74 - 2,68 (m, 2H), 2,39 - 2,25 (m, 2H), 2,18 (s, 1H), 2,14 - 2,03 (m, 4H), 1,89 (d, J = 12,4 Hz, 4H), 1,72 - 1,49 (m, 7H), 1,46 - 1,36 (m, 2H), 1,25 (d, J = 10,8 Hz, 12H)	
250	4-[4-[2-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]etil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,84 (d, J = 6,4 Hz, 1H), 9,25 (t, J = 2,8 Hz, 1H), 8,39 (dt, J = 2,4, 7,6 Hz, 1H), 8,10 (d, J = 10,8 Hz, 1H), 7,91 (dd, J = 8,4, 14,4 Hz, 1H), 7,81 - 7,68 (m, 3H), 7,59 (dd, J = 6,8, 16,4 Hz, 1H), 7,46 (d, J = 8,4 Hz, 1H), 7,37 (dd, J = 4,4, 8,0 Hz, 1H), 6,93 (d, J = 8,8 Hz, 2H), 6,47 (d, J = 2,0 Hz, 1H), 6,40 (dd, J = 2,4, 8,8 Hz, 1H), 6,13 (d, J = 8,4 Hz, 1H), 4,67 (s, 1H), 4,51 (s, 1H), 4,35 - 4,25 (m, 1H), 4,21 - 4,13 (m, 3H), 4,06 - 4,00 (m, 2H), 3,92 (s, 3H), 3,86 (t, J = 5,6 Hz, 1H), 3,58 (t, J = 12,0 Hz, 2H), 3,37 (s, 4H), 3,20 - 3,11 (m, 2H), 2,94 (t, J = 5,6 Hz, 3H), 2,88 (t, J = 5,6 Hz, 1H), 2,77 (s, 4H), 2,46-2,45 (m, 2H), 2,22 (s, 1H), 2,09 (s, 1H), 2,01 - 1,95 (m, 2H), 1,25 (d, J = 10,8 Hz, 12H)	942,6
251	4-[4-[2-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]etil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,00 (dd, J=2,0, 5,6 Hz,1H), 8,12 (dd, J= 8,4, 12,0 Hz, 1H), 7,93 (s, 1H), 7,70 (d, J=8,4 Hz, 2H), 7,3-7,5 (m, 2H), 6,92 (d, J=8,8 Hz, 2H), 6,4-6,5 (m, 2H), 6,12 (d, J=8,0 Hz, 1H), 4,35 (s, 1H), 4,1-4,2 (m, 5H), 4,05 (s, 1H), 3,9-4,0 (m, 4H), 3,74 (qd, J=5,6, 11,6 Hz, 3H), 3,52 (t, J=12,0 Hz, 2H), 3,34 (s, 4H), 3,0-3,1	947,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		(m, 2H), 2,8-3,0 (m, 5H), 2,6-2,8 (m, 5H), 2,2-2,4 (m, 2H), 2,0-2,2 (m, 4H), 1,86 (d, J=12,4 Hz, 2H), 1,25 (d, J=10,2 Hz, 12H)	
254	4-[4-[2-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]fenil]etil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	1H NMR (500 MHz, METANOL-d10,26) δ = 9,95 (s, 1H), 8,28 - 8,14 (m, 1H), 8,06 - 7,92 (m, 1H), 7,91 - 7,75 (m, 1H), 7,69 - 7,32 (m, 1H), 7,64 - 7,33 (m, 1H), 6,97 - 6,89 (m, 1H), 6,47 - 7,11 (m, 2H), 6,38 (d, J = 8,5 Hz, 1H), 4,78 - 4,50 (m, 1H), 4,42 - 4,25 (m, 1H), 4,20 - 4,13 (m, 1H), 4,08 - 3,99 (m, 1H), 3,89 - 3,83 (m, 3H), 3,63 - 3,54 (m, 2H), 2,98 - 2,94 (m, 1H), 2,89 - 2,84 (m, 1H), 2,82 - 2,76 (m, 2H), 2,47 - 2,38 (m, 2H), 2,07 - 2,93 (m, 1H), 2,93 - 1,86 (m, 3H), 1,72 - 1,66 (m, 3H), 1,43 - 1,36 (m, 2H), 1,27 - 1,24 (m, 6H).	940,2

[00802] Ejemplo 35: Síntesis de 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 252**)



[00803] La síntesis de **1** fue reportada en WO2021/127443 A1.

[00804] La síntesis de **1A** fue reportada en WO2023/242598 A1

[00805] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-metoxibenzonitrilo (400 mg) y ácido 4-(4-etoxicarbonil-1-piperidil)benzoico (356 mg, 1,29 mmol, 1,0 *eq*) en DMF (4 ml) se añadieron HATU (587 mg, 1,54 mmol, 1,2 *eq*) y DIPEA (831 mg, 6,43 mmol, 1,1 ml, 5,0 *eq*). La mezcla resultante se agitó a 25 °C durante 1 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (50 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto 1-[4-[[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]piperidina-4-carboxilato de etilo (605 mg, 1,13 mmol, 88 % de rendimiento) se obtuvo como un aceite blanco.

[00806] **LC-MS:** MS (ESI^+): t_R = 0,896 min, m/z = 534,4 [M + H^+]

[00807] A una solución de 1-[4-[[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]piperidina-4-carboxilato de etilo (605 mg, 1,13 mmol, 1,0 *eq*) en THF (4 ml), MeOH (2 ml) y H_2O (2 ml) se agregó $LiOH·H_2O$ (142 mg, 3,40 mmol, 3,0 *eq*). La mezcla se agitó a 30 °C durante 1 h. La mezcla se concentró al vacío. El compuesto 1-[4-[[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]piperidina-4-ácido carboxílico (508 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

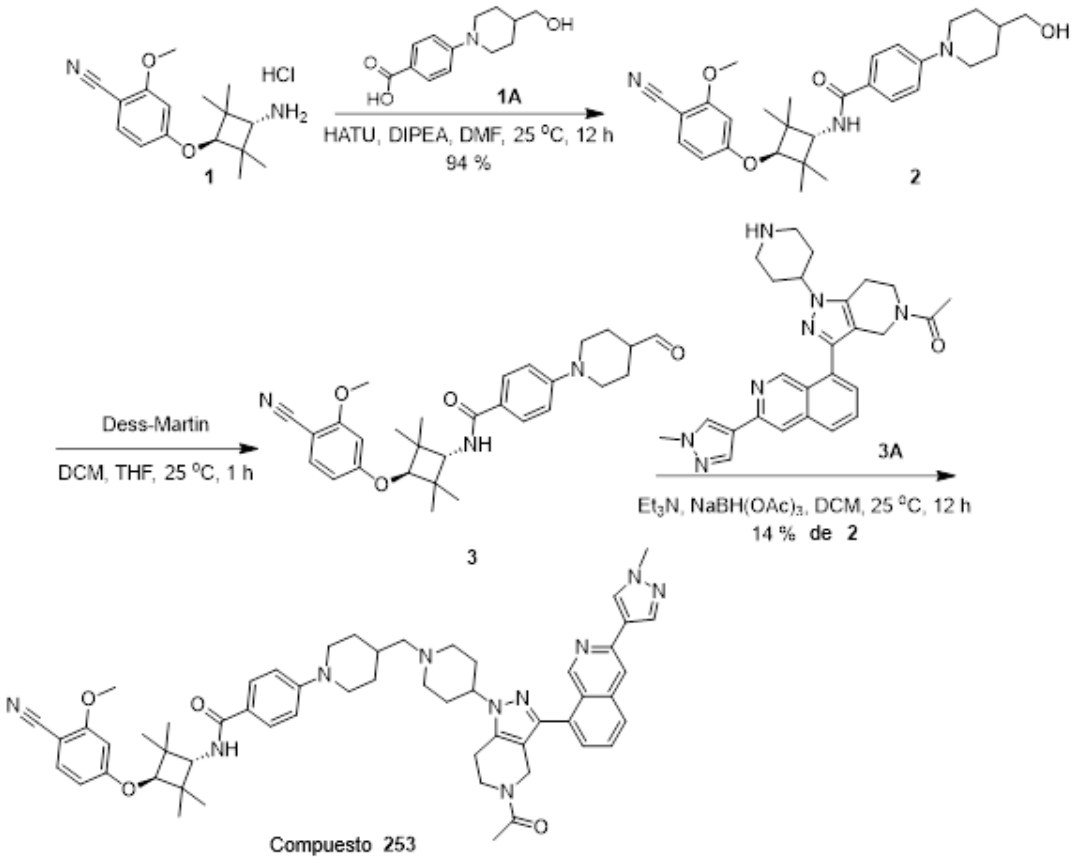
[00808] **LC-MS:** MS (ESI^+): t_R = 0,567 min, m/z = 506,3 [M + H^+]

[00809] A una solución de ácido 1-[4-[[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]carbamoil]fenil]piperidina-4-carboxílico (76 mg) y 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (70 mg, 137 µmol, 1,0 *eq*) en DMF (1,5 ml) se le agregó HATU (62 mg, 164 µmol, 1,2 *eq*) y DIPEA (88 mg, 686 µmol, 119 µl, 5,0 *eq*). La mezcla se agitó a 25 °C durante 12 h. La mezcla se filtró y concentró para obtener un residuo, el residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 55 %-85 % B durante 10 min). El compuesto 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (43,92 mg, 30 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00810] ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ = 7,80 - 7,70 (m, 1H), 7,69 - 7,78 (m, 2H), 7,78 - 7,45 (m, 2H), 7,10 - 7,54 (m, 1H), 7,02 - 6,93 (m, 1H), 6,57 - 6,48 (m, 1H), 4,58 - 4,42 (m, 1H), 4,42 - 4,31 (m, 1H), 4,26 - 5,45 (m, 3H), 4,21 - 4,08 (m, 2H), 4,08 - 4,01 (m, 1H), 3,83 - 3,79 (m, 1H), 3,78 - 3,68 (m, 3H), 3,61 - 3,55 (m, 1H), 3,28 - 3,17 (m, 3H), 2,96 - 2,71 (m, 2H), 2,71 - 2,65 (m, 1H), 2,08 (s, 3H), 2,01 - 1,86 (m, 1H), 1,79 - 1,58 (m, 1H), 1,22 - 1,14 (m, 3H)

[00811] **LC-MS:** MS (ESI$^+$): t_R = 2,611 min, m/z = 997,2 [M+H$^+$]

[00812] **Ejemplo 36**: Síntesis de 4-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 253**)



[00813] La síntesis de **1A** fue reportada en Journal of Medicinal Chemistry, 2021, vol. 64, # 17, páginas 12831 - 12854.

[00814] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-metoxibenzonitrilo (200 mg, 643 µmol, 1,0 *eq*) y ácido 4-[4-(hidroximetil)-1-piperidil]benzoico (151 mg, 643 µmol, 1,0 *eq*) en DMF (3 ml) se añadieron HATU (293 mg, 772 µmol, 1,2 *eq*) y DIPEA (415 mg, 3,22 mmol, 560 µl, 5,0 *eq*). La mezcla de reacción se agitó a 20 °C durante 12 h. La mezcla de reacción se diluyó con agua (5 ml)

y se extrajo con EtOAc (10 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (50 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 30/1 a 0/1). El compuesto N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-[4-(hidroximetil)-1-piperidil]benzamida (300 mg, 610 µmol, 94 % de rendimiento) se obtuvo como un sólido blanco.

[00815] **LC-MS:** MS (ESI^+): t_R = 0,533 min, m/z = 492,3 [M + H^+]

[00816] A una solución de N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-[4-(hidroximetil)-1-piperidil]benzamida (300 mg, 610 µmol, 1,0 *eq*) en DCM (5 ml) y THF (0,5 ml) se agregó Dess-Martin (388 mg, 915 µmol, 283 µl, 1,5 *eq*). La mezcla resultante se agitó a 25 °C durante 1 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El compuesto N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-(4-formil-1-piperidil)benzamida (298 mg) se obtuvo como un aceite rojo y se utilizó directamente en el siguiente paso sin purificación adicional .

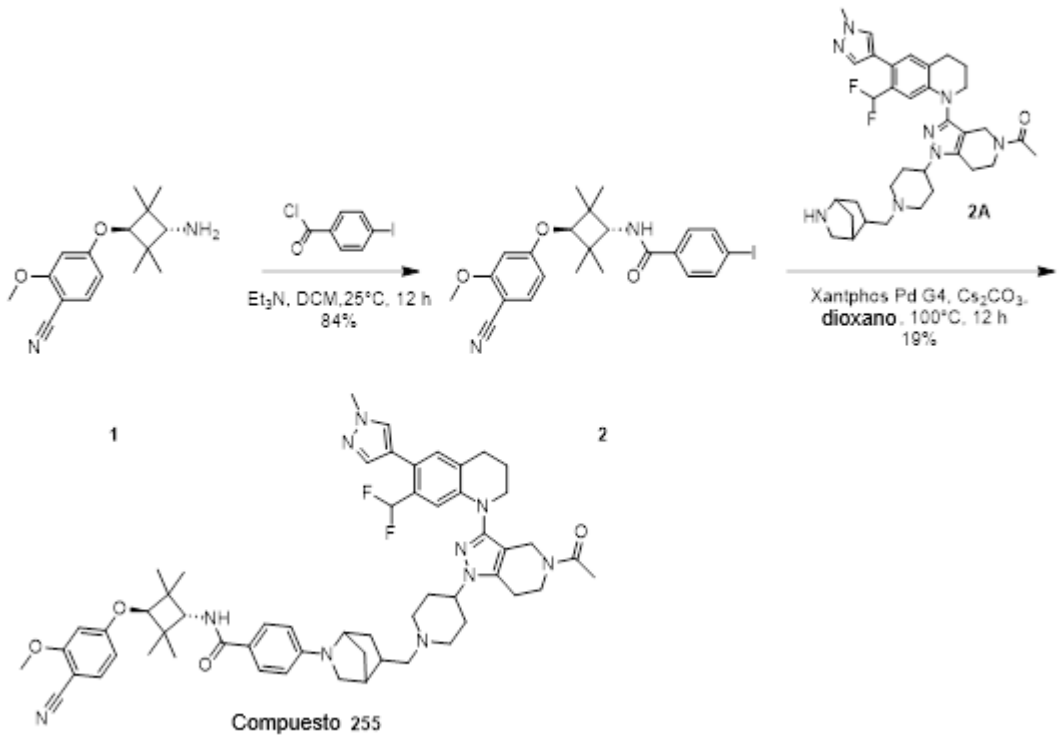
[00817] **LC-MS:** MS (ESI^+): t_R = 0,582 min, m/z = 490,3 [M + H^+]

[00818] A una solución de 1-[3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (81 mg, 177 µmol, 1,0 *eq*) y N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-(4-formil-1-piperidil)benzamida (95 mg) en DCM (2 ml) se agregó Et_3N (89 mg, 889 µmol, 123 µl, 5,0 *eq*) y $NaBH(OAc)_3$ (113 mg, 533 µmol, 3,0 *eq*). La mezcla se agitó a 25 °C durante 12 h. La mezcla se filtró y concentró para obtener un residuo, el cual se purificó mediante HPLC preparativa (columna: Waters xbridge 150*25 mm 10 µm; fase móvil: [agua (NH_4HCO_3)-ACN]; gradiente: 55 %-75 % B durante 8 min). El compuesto 4-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (25,25 mg, 14 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00819] ^{1}H NMR (400 MHz, METANOL-d**6**) δ = 9,85 (s, 1H), 8,37 (s, 1H), 8,14 - 8,03 (m, 1H), 7,92 - 7,85 (m, 2H), 7,83 - 7,76 (m, 1H), 7,75 - 7,68 (m, 1H), 7,67 - 7,61 (m, 1H), 7,60 - 7,45 (m, 1H), 7,00 - 6,90 (m, 1H), 6,67 - 6,61 (m, 1H), 6,57 - 6,47 (m, 3H), 4,57 - 4,17 (m, 2H), 4,17 - 4,09 (m, 2H), 4,09 - 4,00 (m, 1H), 3,96 - 3,89 (m, 1H), 3,88 - 3,77 (m, 2H), 3,04 - 2,92 (m, 2H), 2,90 - 2,63 (m, 3H), 2,26 - 2,18 (m, 3H), 2,18 - 2,06 (m, 1H), 2,06 - 1,88 (m, 1H), 1,85 - 1,74 (m, 1H), 1,25 - 1,10 (m, 1H).

[00820] **LC-MS:** MS (ESI$^+$): t_R = 2,042 min, m/z = 929,6 [M + H$^+$]

[00821] **Ejemplo 37**: Síntesis de 4-[5-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-2-azabiciclo[2,2,1]heptan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 255**)



[00822] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-metoxibenzonitrilo (100 mg, 322 µmol, 1,0 eq), cloruro de 4-iodobenzoílo (130 mg, 488 µmol, 1,5 eq) en DCM (1 ml) se agregó Et_3N (146 mg, 1,44 mmol, 0,2 ml, 4,5 eq). La mezcla de reacción se agitó a 25 °C durante 12 h. La mezcla se concentró hasta secarse. El residuo se purificó mediante TLC preparativa (SiO_2, éter de petróleo/acetato de etilo = 1/1) para dar N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-iodobenzamida (144 mg, 273 µmol, 84 % de rendimiento) como un sólido blanco.

[00823] **LC-MS:** MS (ESI$^+$): t_R = 0,656 min, m/z = 505,2 [M + H$^+$]

[00824] Una mezcla de N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]-4-iodo-benzamida (66 mg, 131 µmol, 1,2 eq), 1-[1-[1-(2-azabiciclo[2,2,1]heptan-5-ilmetil)-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (66 mg, 107 µmol, 1,0 eq), Xantphos Pd G4 (14 mg, 15 µmol, 0,1 eq) y Cs_2CO_3 (165 mg, 507 µmol, 4,8 eq) en dioxano (1 ml) se desgasificó y purgó con N_2 3 veces, y luego se agitó a 100 °C durante 12 h bajo

atmósfera de N_2. La mezcla se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 31 %-61 % B durante 10 min) para dar 4-[5-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-2-azabiciclo[2,2,1]heptan-2-il]-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]benzamida (20,25 mg, 21 µmol, (Rendimiento del 19 %) como un sólido rosa.

[00825] **^{1}H NMR** (400 MHz, DMSO-d6): δ = 7,75 (s, 1H), 7,70 (d, J = 8,8 Hz, 2H), 7,64 (d, J = 8,4 Hz, 1H), 7,50 (s, 1H), 7,40 - 7,32 (m, 1H), 7,10 (s, 1H), 6,93 - 6,66 (m, 2H), 6,63 (d, J = 2,0 Hz, 1H), 6,53 (t, J = 2,8, 5,6 Hz, 3H), 4,26 (s, 1H), 4,24 - 4,14 (m, 2H), 4,11 (s, 1H), 4,04 (d, J = 9,2 Hz, 1H), 4,02 - 3,95 (m, 1H), 3,90 (s, 3H), 3,86 (s, 3H), 3,75 - 3,66 (m, 2H), 3,59 (q, J = 5,6 Hz, 2H), 3,44 (d, J = 5,6 Hz, 1H), 3,04 - 2,88 (m, 2H), 2,87 - 2,80 (m, 4H), 2,18 - 2,08 (m, 2H), 2,07 (s, 3H), 2,02 - 1,93 (m, 6H), 1,91 - 1,77 (m, 4H), 1,77 - 1,70 (m, 1H), 1,69 - 1,57 (m, 2H), 1,31 (s, 1H), 1,21 (s, 6H), 1,14 (s, 6H), 1,11 - 1,01 (m, 1H).

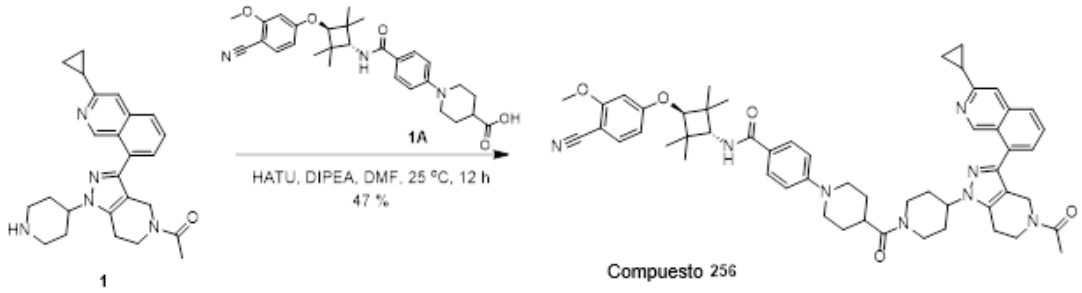
[00826] **LC-MS:** MS (ESI$^+$): t_R = 2,037 min, m/z = 995,8 [M + H$^+$]

[00827] **SFC:** t_{R1} = 1,235 min, 15 %, t_{R2} = 1,350 min, 14 %, t_{R3} = 1,877 min, 31 %, t_{R4} = 1,913 min, 40 %

[00828] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 37.

Compuesto	Nombre	^{1}H NMR (CD_3OD)	LC-MS $(M+H)^+$:
305	4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-4-metil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 8,49 (d, *J* = 8,4Hz, 1H), 7,63 (d, *J* = 8,7Hz, 2H), 7,52 (d, *J* = 8,4Hz, 2H), 7,09 (d, *J* = 8,4Hz, 1H), 7,04 (s, 1H), 3,66 (s, 2H), 6,72 (s, 1H), 6,42 (brs, 2H), 4,31-4,21 (m, 2H), 3,93-3,88 (m, 2H), 3,82 (s, 1H), 3,75-3,65 (m, 2H), 3,55-3,45 (m, 2H), 3,25-3,15 (m, 2H), 2,90-2,75 (m, 2H), 2,18--1,85 (m, 1H), 1,41-1,24 (m, 15H).	983,6

[00829] **Ejemplo 38**: Síntesis de 4-[4-[4-[5-acetil-3-(3-ciclopropil-8-isoquinolil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 256**)



[00830] A una solución de 1-[3-(3-ciclopropil-8-isoquinolil)-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il] etanona (56 mg, 134 µmol, 1,0 *eq*) y ácido 1-[4-[[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]piperidina-4-carboxílico (74 mg, 148 µmol, 1,1 *eq*) en DMF (1 ml) se le agregó HATU (61 mg, 161 µmol, 1,2 *eq*) y DIPEA (87 mg, 673 µmol, 117 µl, 5,0 *eq*). La mezcla se agitó a 25 °C durante 12 h. La mezcla se filtró y se concentró para obtener un residuo, el cual se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25 mm* 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 37 %-67 % B durante 10 min). El compuesto 4-[4-[4-[5-acetil-3-(3-ciclopropil-8-isoquinolil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (61,6 mg, 47 % de rendimiento) se obtuvo como un sólido amarillo.

[00831] ^{1}H NMR (400 MHz, DMSO-d**6**) δ = 9,73 (s, 1H), 7,95 - 7,81 (m, 1H), 7,78 - 7,69 (m, 2H), 7,68 - 7,54 (m, 2H), 7,52 - 7,28 (m, 1H), 7,28 - 6,89 (m, 2H), 6,71 - 6,60 (m, 1H), 6,56 - 6,47 (m, 1H), 4,69 - 4,42 (m, 2H), 4,31 - 4,14 (m, 1H), 4,09 - 4,00 (m, 1H), 3,95 - 3,78 (m, 1H), 3,29 - 3,23 (m, 1H), 3,01 - 2,83 (m, 1H), 2,82 - 2,71 (m, 1H), 2,32 - 2,22 (m, 1H), 2,16 - 1,97 (m, 2H), 1,92 - 1,78 (m, 1H), 1,76 - 1,56 (m, 1H), 1,28 - 1,19 (m, 1H), 1,19 - 1,11 (m, 1H), 1,09 - 0,95 (m, 1H).

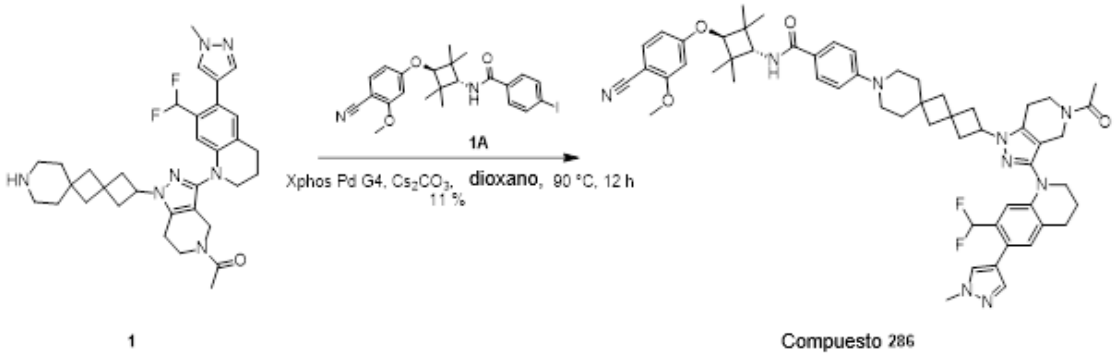
[00832] **LC-MS:** MS (ESI$^+$): t_R = 2,23 min, m/z = 903,4 [M + H$^+$]

[00833] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 38.

Compuesto	**Nombre**	**RMN ^{1}H (400 MHz, DMSO-d6):**	**LC-MS (M+H)$^+$:**
257	4-[4-[4-[5-acetil-3-[6-ciclopropil-7-(difluorometil)-1-naftil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonil]-1-piperidilo]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,99-7,88 (m, 1H), 7,79-7,70 (m, 2H), 7,69-7,61 (m, 2H), 7,61-7,28 (m, 1H), 6,91 (s, 1H), 6,66-6,62 (m, 1H), 6,51 (s, 2H), 4,61-4,40 (m, 2H), 4,14 (brs, 2H), 4,09-4,00 (m, 2H), 3,98-3,76 (m, 2H), 3,20 (s, 3H), 2,75 (s,	952,6

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS (M+H)$^+$:
		3H), 2,28-2,17 (m, 2H), 2,15-1,97 (m, 2H), 1,95-1,81 (m, 2H), 1,79-1,59 (m, 2H), 1,07-1,02 (m, 2H).	

[00834] **Ejemplo 39**: Síntesis de 4-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-9-azadiespiro[3,1,5^{6,14}]dodecan-9-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 286**)



[00835] Una mezcla de 1-[1-(9-azadiespiro[3,1,5^{6,14}]dodecan-2-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (160 mg, 227 µmol, 1,0 *eq*), N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-iodobenzamida (114 mg, 227 µmol, 1,0 *eq*), Cs_2CO_3 (222 mg, 682 µmol, 3,0 *eq*), Xphos Pd G4 (19 mg, 22 µmol, 0,1 *eq*) en dioxano (5 ml) se desgasificó y purgó con N_2 3 veces, y luego la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (15 ml) y se extrajo con EtOAc (15 ml × 2). Las capas orgánicas combinadas se lavaron con salmuera (30 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua(FA)-ACN]; gradiente: 65 %-95 % B durante 10 min). El compuesto 4-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-9-azadiespiro[3,1,5^{6,14}]dodecan-9-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (24,16 mg, 11 % de rendimiento) se obtuvo como un sólido blanco.

[00836] ^{1}H NMR (400 MHz, METANOL-d**3**) δ = 8,01 (s, 1H), 8,22 (s, 1H), 7,72 - 7,63 (m, 1H), 7,57 - 7,49 (m, 2H), 7,48 - 7,38 (m, 2H), 7,07 - 6,96 (m, 1H), 6,93 - 6,86 (m, 1H),

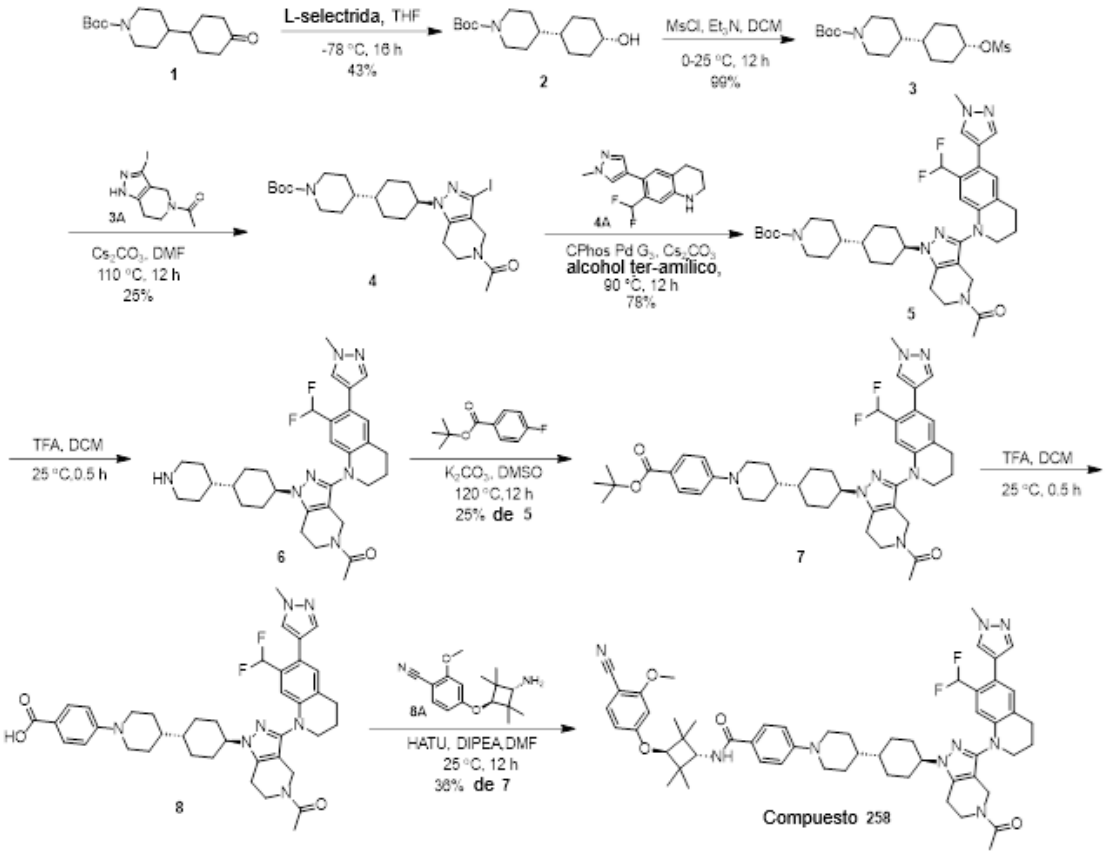
6,69 - 6,36 (m, 1H), 6,17 - 6,06 (m, 1H), 4,55 - 4,43 (m, 1H), 4,25 - 4,08 (m, 3H), 4,07 - 4,17 (m, 2H), 4,17 - 4,09 (m, 2H), 4,09 - 3,68 (m, 1H), 3,32 - 3,15 (m, 1H), 2,97 - 2,84 (m, 2H), 2,81 - 2,66 (m, 2H), 2,52 - 2,42 (m, 2H), 2,16 - 2,14 (m, 3H), 2,12 - 2,05 (m, 1H), 1,97 - 2,50 (m, 1H), 1,74 - 1,60 (m, 1H), 1,29 - 1,17 (m, 1H).

[00837] **LC-MS:** MS (ESI^+): t_R = 3,572 min, m/z = 966,7 [M + H^+]

[00838] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 39.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
287	2-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-9-azadiespiro[3,1,$5^{6,14}$]dodecan-9-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	$_1$H NMR (400 MHz, DMSO-d6) δ = 8,73 (s, 1H), 7,95 - 7,85 (m, 1H), 7,80 - 7,75 (m, 2H), 7,72 - 7,65 (m, 2H), 7,38 - 7,28 (m, 1H), 7,28 - 7,20 (m, 2H), 7,16 - 7,08 (m, 1H), 7,05 - 6,95 (m, 1H), 6,94 - 6,60 (m, 2H), 4,70 - 4,55 (m, 1H), 4,28 - 4,77 (m, 1H), 4,20 - 4,08 (m, 1H), 4,05 - 3,98 (m, 1H), 3,90 - 3,85 (m, 1H), 3,82 - 3,73 (m, 4H), 3,70 - 3,55 (m, 4H), 2,88 - 2,64 (m, 2H), 2,38 - 2,27 (m, 1H), 2,15 - 2,02 (m, 1H), 1,98 - 1,86 (m, 1H), 1,55 - 1,47 (m, 1H), 1,20 - 1,10 (m, 1H).	972,3

[00839] **Ejemplo 40**: Síntesis de 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 258**)



[00840] La síntesis de **1** fue reportada en ACS Medicinal Chemistry Letters, 2021, vol. 12, # 7, páginas 1108 - 1115.

[00841] A una solución de 4-bromo-4-cloro-1-fluoropiridina (6 g, 21,32 mmol, 1 eq) en THF (60 ml) se agregó NaOMe (1 M, 25,59 ml, 1 eq). La mezcla se agitó a -78 °C durante 16 h en atmósfera de N_2. La mezcla se agitó a 0 °C durante 30 min. La reacción se diluyó con agua (50 ml) y se extrajo con acetato de etilo (100 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (80 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. La mezcla se purificó mediante HPLC preparativa (columna: Welch Ultimate XB-SiOH 250*50*10um; fase móvil: [Hexano-EtOH]; B%: 5 %, modo de elución isocrática). El compuesto 4-(4-hidroxiciclohexil)piperidina-1-carboxilato de ter-butilo (2,8 g, 9,19 mmol, 43 % de rendimiento) se obtuvo como un aceite incoloro.

[00842] *^{1}H NMR (400 MHz, $CDCl_3$) δ 4,13 – 4,03 (m, 2H), 4,03 (s, 2H), 2,64 (t, J = 12,1 Hz, 2H), 1,80 (s, 2H), 1,68 (d, J = 12,8 Hz, 2H), 1,58 – 1,51 (m, 2H), 1,51 – 1,47 (m, 3H), 1,46 – 1,44 (m, 1H), 1,42 – 1,37 (m, 1H), 1,32 – 1,22 (m, 1H).*

[00843] **LC-MS:** MS (ESI$^+$): t_R = 0,585 min, m/z = 228,0 [M - 55]

[00844] A una solución de ter-butil 4-(4-hidroxiciclohexil)piperidina-1-carboxilato (1,3 g,

4,59 mmol, 1 *eq*) ter-butil 4-(4-hidroxiciclohexil)piperidina-1-carboxilato (1,3 g, 4,59 mmol, 1 *eq*) en DCM (15 ml) se le agregó Et_3N (2,32 g, 22,94 mmol, 3,19 ml, 5 *eq*) y MsCl (1,18 g, 10,30 mmol, 797,30 µl, 2,25 *eq*) a 0 °C. La mezcla se agitó a 25 °C durante 12 h. La mezcla se diluyó con agua helada (80 ml) y se extrajo con diclorometano (100 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (100 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 20 g, eluyente de gradiente de éter de petróleo/éter de acetato de etilo al 0-16 % a 80 ml/min). El compuesto ter-butil 4-(4-metilsulfoniloxiciclohexil)piperidina-1-carboxilato (1,65 g, 4,56 mmol, 99 % de rendimiento) se obtuvo como un aceite incoloro.

[00845] ^{1}H NMR (400 MHz, $CDCl_3$): **δ** 4,98 (s, 3H), 3,01 (s, 3H), 2,64 - 2,65 (m, 2H), 2,15 - 2,06 (m, 3H), 1,71 - 1,54 (m, 2H), 1,46 - 1,38 (m, 2H), 1,21 - 1,09 (m, 2H).

[00846] A una solución de 4-(4-metilsulfoniloxiciclohexil)piperidina-1-carboxilato de ter-butilo (1,61 g, 4,47 mmol, 1,3 *eq*) y 1-(3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridin-5-il)etanona (1 g, 3,44 mmol, 1 *eq*) en DMF (10 ml) se agregó Cs_2CO_3 (3,36 g, 10,31 mmol, 3 *eq*). La mezcla se agitó a 110 °C durante 30 min. La reacción se diluyó con agua (80 ml) y se extrajo con acetato de etilo (100 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (100 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. La mezcla se purificó mediante HPLC preparativa (columna: Welch Ultimate XB-CN 250*50*10um; fase móvil: [Hexano-EtOH]; gradiente: 1 %-35 % B durante 15 min). El compuesto ter-butil 4-[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]piperidina-1-carboxilato (480 mg, 862,57 µmol, 25 % de rendimiento) se obtuvo como un sólido blanco.

[00847] **LC-MS:** MS (ESI$^+$): t_R = 0,583 min, m/z = 557,1 [M + H$^+$]

[00848] A una solución de 4-[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]piperidina-1-carboxilato de ter-butilo (429 mg, 771,32 µmol, 1 *eq*) y 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (243 mg, 925,58 µmol, 1,2 *eq*) en alcohol terc-amílico (10 ml) se agregó CPHOS PD G_3 (62 mg, 77,13 µmol, 0,1 *eq*) y Cs_2CO_3 (753 mg, 2,31 mmol, 3 *eq*). La mezcla de reacción se agitó a 90 °C durante 12 h en N_2. La reacción se diluyó con agua (50 ml) y se extrajo con diclorometano (60 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 20 g, eluyente de gradiente de acetato de etilo/éter de

petróleo de 0~100 % a 100 ml/min).

[00849] El compuesto ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]piperidina-1-carboxilato (420 mg, 607,07 µmol, 78 % de rendimiento) se obtuvo como un sólido amarillo.

[00850] **LC-MS:** MS (ESI^+): t_R = 0,620 min, m/z = 692,4 [M + H^+]

[00851] A una solución de ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]piperidina-1-carboxilato (350 mg, 505,89 µmol, 1 eq) en DCM (2 ml) se le agregó TFA (3,07 g, 26,93 mmol, 2 ml, 53,22 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[4-(4-piperidil)ciclohexil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (299 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00852] **LC-MS:** MS (ESI^+): t_R = 0,435 min, m/z = 592,3 [M + H^+]

[00853] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[4-(4-piperidil)ciclohexil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (299 mg, 505,29 µmol, 1 eq) en DMSO (5 ml) se agregó K_2CO_3 (698 mg, 5,05 mmol, 10 eq), 4-fluorobenzoato de ter-butilo (198 mg, 1,01 mmol, 2 eq). La mezcla se agitó a 120 °C durante 30 min. La reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH = 20:1). El compuesto ter-butil 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-1-piperidil]benzoato (100 mg, 130,22 µmol, rendimiento del 25 % en dos pasos) se obtuvo como un sólido amarillo.

[00854] **LC-MS:** MS (ESI^+): t_R = 0,625 min, m/z = 768,2 [M + H^+]

[00855] A una solución de ter-butil 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-1-piperidil]benzoato (100 mg, 130,22 µmol, 1 eq) en DCM (2 ml) se le agregó TFA (3,07 g, 26,93 mmol, 2 ml, 206,77 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto ácido 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-1-piperidil]benzoico (92 mg) se obtuvo como un

aceite azul y se utilizó directamente en el siguiente paso sin purificación adicional.

[00856] **LC-MS:** MS (ESI^+): t_R = 0,523 min, m/z = 712,3 [M + H^+]

[00857] A una solución de ácido 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-1-piperidil]benzoico (90 mg, 126,43 µmol, 1 eq) en DMF (3 ml) se le agregó DIPEA (326 mg, 2,53 mmol, 440,44 µl, 20 eq), 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (34 mg, 126,43 µmol, 1 eq) y HATU (144 mg, 379,30 µmol, 3 eq). La mezcla se agitó a 25 °C durante 30 min. La reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó mediante HPLC preparativa (columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua(FA)-ACN]; gradiente: 65 %-95 % B durante 2 min). El compuesto 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (44,47 mg, 45,93 µmol, 36 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00858] **1H NMR** (400 MHz, $CDCl_3$) δ = 7,69 (d, *J* = 8,8 Hz, 2H), 7,53 (d, *J* = 5,3 Hz, 1H), 7,46 (d, *J* = 8,6 Hz, 1H), 7,42 - 7,38 (m, 1H), 7,05 - 6,86 (m, 4H), 6,68 - 6,38 (m, 3H), 6,12 (d, *J* = 8,1 Hz, 1H), 4,26 (s, 1H), 4,17 - 4,12 (m, 2H), 4,05 (s, 1H), 3,96 (d, *J* = 2,3 Hz, 3H), 3,94 - 3,86 (m, 7H), 3,77 - 3,67 (m, 3H), 2,91 - 2,72 (m, 6H), 2,17 (s, 1H), 2,12 - 2,04 (m, 4H), 2,03 - 1,94 (m, 6H), 1,82 (br d, *J* = 12,4 Hz, 2H), 1,42 (br s, 4H), 1,25 (d, *J* = 10,1 Hz, 12H), 1,22 - 1,12 (m, 2H)

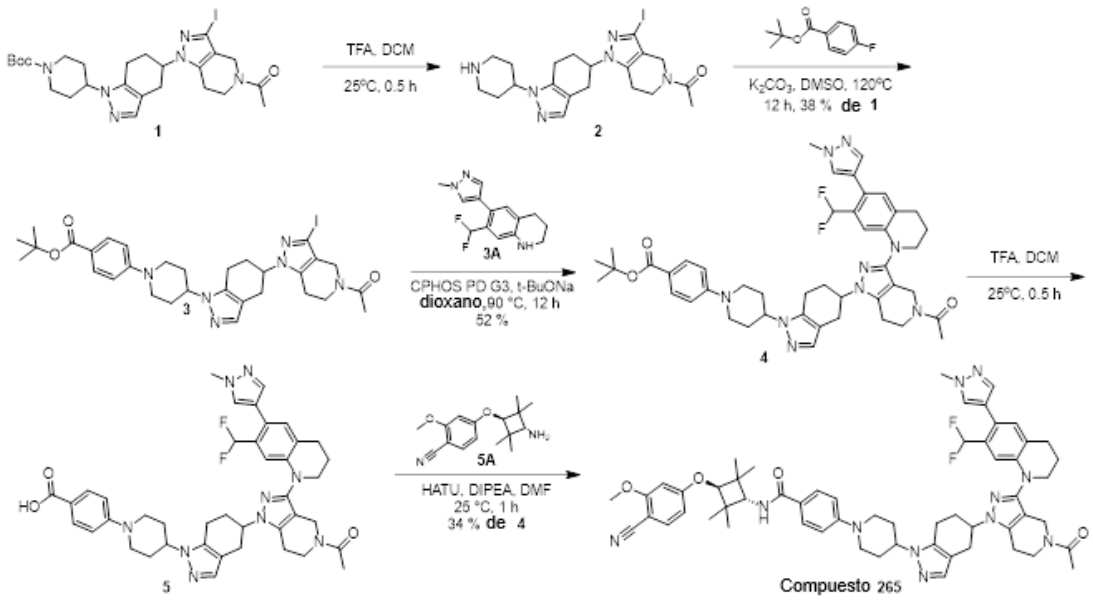
[00859] **LC-MS:** MS (ESI^+): t_R = 3,557 min, m/z = 968,7 [M + H^+]

[00860] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 40.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
259	4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,68 (d, *J* = 8,6 Hz, 1H), 7,53 (d, *J* = 5,0 Hz, 1H), 7,46 (d, *J* = 8,5 Hz, 1H), 7,40 (d, *J* = 8,6 Hz, 1H), 6,68 (d, *J* = 8,1 Hz, 1H), 4,30 (d, *J* = 8,8 Hz, 1H), 4,07 (d, *J* = 2,6 Hz, 2H), 3,94 - 3,90 (m, 4H), 3,90 (br s, 2H), 3,77 - 3,68 (m, 1H), 2,92 - 2,77 (m, 3H), 2,74 - 2,18 (m, 3H), 2,15 - 2,04 (m, 3H), 2,02 - 1,90 (m, 2H), 1,81 - 1,69 (m, 4H),	968,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		1,53 - 1,29 (m, 1H), 1,25 (d, *J* = 9,9 Hz, 3H).	
304	4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-3-metil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,65 (d, J = 8,4Hz, 1H), 7,46 (d, J = 8,7Hz, 2H), 6,87 (d, J = 8,4Hz, 2H), 6,53 (d, J = 8,4Hz, 1H), 4,27 (s, 1H), 4,10 (s, 2H), 4,05 (s, 1H), 3,81 (brs, 2H), 3,80-3,65 (m, 2H), 3,62-3,55 (m, 2H), 3,35 (s, 3H), 3,20-3,02 (m, 2H), 2,97-2,68 (m, 2H), 2,26-1,81 (m, 2H), 1,25-1,21 (m, 2H), 1,18-1,12 (m, 1H), 1,10-0,86 (m, 3H).	983,7

[00861] Ejemplo 41: Síntesis de 4-[4-[5-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 265**)



[00862] A una solución de ter-butil 4-[5-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-4,5,6,7-tetrahidroindazol-1-il]piperidina-1-carboxilato (270 mg, 454,17 µmol, 1 eq) en DCM (5 ml) se le agregó TFA (259 mg, 2,27 mmol, 168,68 µl, 5 eq). La mezcla de reacción se agitó a 25 °C durante 0,5 h. La mezcla se concentró hasta secarse. El compuesto 1-[3-iodo-1-[1-(4-piperidil)-4,5,6,7-tetrahidroindazol-5-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (230 mg, crudo) se obtuvo como un aceite

amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00863] **LC-MS:** MS (ESI^+): t_R = 0,396 min, m/z = 495,0 [M + H^+]

[00864] A una solución de 1-[3-iodo-1-[1-(4-piperidil)-4,5,6,7-tetrahidroindazol-5-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (230 mg, 465,24 µmol, 1 eq) y K_2CO_3 (643 mg, 4,65 mmol, 10 eq) en DMSO (5 ml) se agregó 4-fluorobenzoato de ter-butilo (456 mg, 2,33 mmol, 5 eq). La mezcla de reacción se agitó a 120 °C durante 12 h. La mezcla de reacción se neutralizó añadiendo agua (10 ml) a 0 °C, y luego se diluyó con agua (30 ml) y se extrajo con acetato de etilo (50 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía preparativa en capa fina (sílice, DCM: MeOH = 20: 1). El compuesto ter-butil 4-[4-[5-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]benzoato (120 mg, 178,95 µmol, 38 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo claro.

[00865] **LC-MS:** MS (ESI^+): t_R = 0,578 min, m/z = 671,1 [M + H^+]

[00866] A una solución de ter-butil 4-[4-[5-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]benzoato (110 mg, 164,04 µmol, 1 eq) y 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (65 mg, 246,05 µmol, 1,5 eq) en dioxano (10 ml) se agregó CPHOS PD G_3 (13 mg, 16,40 µmol, 0,1 eq) y t-BuONa (2 M, 246,05 µl, 3 eq). La mezcla de reacción se agitó a 90 °C durante 12 h en N_2. La mezcla se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía preparativa en capa fina (sílice, DCM: MeOH = 20: 1). El compuesto ter-butil 4-[4-[5-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]benzoato (70 mg, 86,85 µmol, 52 % de rendimiento) se obtuvo como un aceite amarillo.

[00867] **LC-MS:** MS (ESI^+): t_R = 0,597 min, m/z = 806,3 [M + H^+]

[00868] A una solución de ter-butil 4-[4-[5-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]benzoato (70 mg, 86,85 µmol, 1 eq) en DCM (3 ml) se le agregó TFA (50 mg, 434,27 µmol, 32,26 µl, 5 eq). La mezcla de reacción se agitó a 25 °C durante 0,5 h. La mezcla se concentró hasta secarse. El compuesto ácido 4-[4-[5-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]benzoico (65 mg) se obtuvo como un aceite amarillo y se utilizó directamente

en el siguiente paso sin purificación adicional.

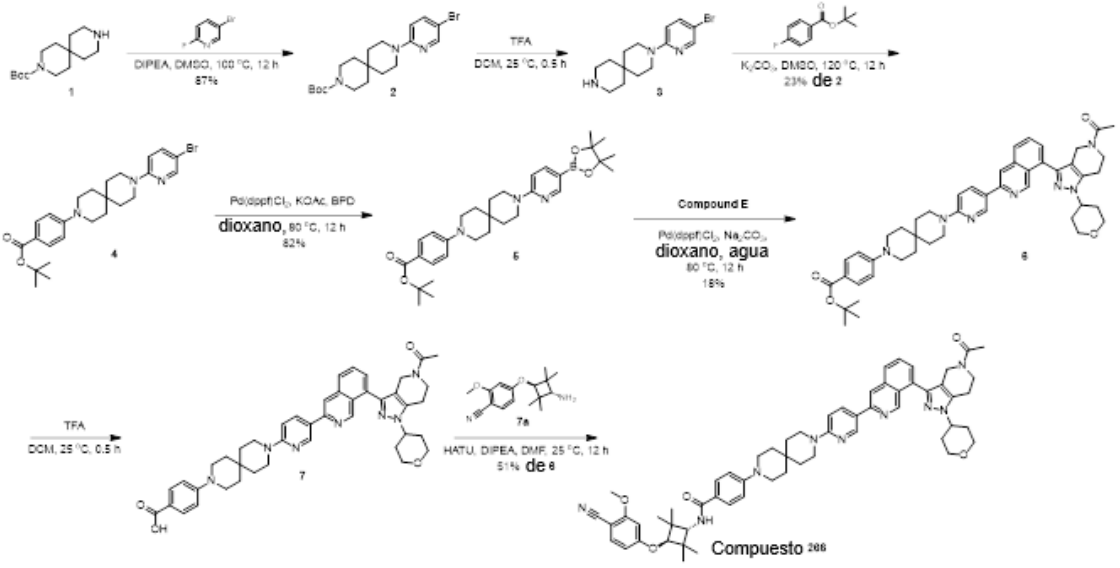
[00869] **LC-MS:** MS (ESI^+): t_R = 0,509 min, m/z = 750,4 [M + H^+]

[00870] A una solución de ácido 4-[4-[5-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]benzoico (65 mg) y DIPEA (111 mg, 861,17 µmol, 0,15 ml, 9,93 eq) en DMF (3 ml) se le agregó 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (24 mg, 86,68 µmol, 1 eq) y HATU (66 mg, 173,37 µmol, 2 eq). La mezcla de reacción se agitó a 25 °C durante 1 h. La mezcla de reacción se neutralizó añadiendo agua (10 ml) a 25 °C, y luego se diluyó con agua (20 ml) y se extrajo con acetato de etilo (30 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía preparativa en capa fina (sílice, DCM: MeOH = 20: 1). El residuo se purificó mediante HPLC preparativa (condiciones de FA: columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua(FA)-ACN]; gradiente: 55 %-85 % B durante 10 min). El compuesto 4-[4-[5-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-4,5,6,7-tetrahidroindazol-1-il]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (30,66 mg, 30,23 µmol, rendimiento del 34 % en dos pasos) se obtuvo como un sólido blanco.

[00871] ^{1}H NMR (400 MHz, DMSO-d_3) δ = 7,70 (s, 1H), 7,46 (d, **J** = 4,8 Hz, 2H), 7,41 (d, J = 4,8 Hz, 1H), 7,33 - 7,29 (m, 3H), 7,08 - 6,99 (m, 2H), 6,92 - 6,87 (m, 1H), 6,70 - 6,45 (m, 1H), 6,41 - 2,0 (m, 1H), 4,37 - 4,21 (m, 1H), 4,19 – 4,12 (m, 1H), 4,07 - 3,99 (m, 1H), 3,96 - 4,27 (m, 3H), 3,94 - 3,83 (m, 4H), 3,81 - 3,66 (m, 1H), 3,17 - 3,08 (m, 1H), 3,02 - 2,38 (m, 2H), 2,96 – 2,73 (m, 1H), 2,58 - 2,46 (m, 2H), 2,43 - 2,26 (m, 2H), 2,18 - 1,98 (m, 1H).

[00872] **LC-MS:** MS (ESI^+): t_R = 3,476 min, m/z = 1006,7 [M + H^+]

[00873] **Ejemplo 42**: Síntesis de 4-[3-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 266**)



[00874] A una solución de 3,9-diazaespiro[5,5]undecano-3-carboxilato de ter-butilo (3,00 g, 11,79 mmol, 1 eq) en DMSO (30 ml) se le añadieron DIPEA (4,57 g, 35,38 mmol, 6,16 ml, 3 eq) y 5-bromo-2-fluoropiridina (2,08 g, 11,79 mmol, 1,21 ml, 1 eq). La mezcla se agitó a 100 °C durante 30 min. La reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (100 ml x 3). La capa orgánica combinada se lavó con salmuera (100 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 50/1 a 10/1). El compuesto ter-butil 9-(5-bromo-2-piridil)-3,9-diazaespiro[5,5]undecano-3-carboxilato (4,20 g, 10,24 mmol, 87 % de rendimiento) se obtuvo como un sólido amarillo.

[00875] A una solución de 9-((5-fluoro-2-(trifluorometil)bencil)oxi)5,5-metilazetidin-3-carboxilato de ter-butilo (4,50 g, 10,97 mmol) en DCM (40 ml) se le agregó TFA (832 mg, 38,30 µL, 7,29 mmol). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto 3-(5-bromo-2-piridil)-3,9-diazaespiro[5,5]undecano (4,50 g) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00876] A una solución de 3-(5-bromo-2-piridil)-3,9-diazaespiro[5,5]undecano (4,50 g) en DMSO (60 ml) se le añadieron K_2CO_3 (14,60 g, 106 mmol, 10 eq) y 4-fluorobenzoato de ter-butilo (2,08 g, 10,61 mmol, 1 eq). La mezcla resultante se agitó a 120 °C durante 12 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). La capa orgánica combinada se lavó con salmuera (100 ml×6), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó por cromatografía en columna

(SiO_2, éter de petróleo/acetato de etilo = 50/1 a 3/1). El compuesto ter-butil 4-[3-(5-bromo-2-piridil)-3,9-diazaespiro[5,5]undecan-9-il]benzoato (1,20 g, 2,47 mmol, 23 % de rendimiento) se obtuvo como un sólido amarillo.

[00877] **LC-MS:** MS (ESI+): t_R = 0,587 min, m/z = 488,2 [M + H^+]

[00878] A una solución de 4-[3-(5-bromo-2-piridil)-3,9-diazaespiro[5,5]undecan-9-il]benzoato de ter-butilo (900 mg, 1,85 mmol, 1 eq) y BPD (563 mg, 2,22 mmol, 1,2 eq) en dioxano (15 ml) se añadieron KOAc (363 mg, 3,70 mmol, 2 eq) y $Pd(dppf)Cl_2$ (67 mg, 92 µmol, 0,05 eq). La mezcla se agitó a 80 °C durante 12 horas en una atmósfera de nitrógeno. La mezcla se filtró, se lavó con etanol (100 ml) y se concentró. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 50/1 a 0/1). El compuesto ter-butil 4-[3-[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]benzoato (800 mg, 1,50 mmol, 81 % de rendimiento) se obtuvo como un sólido amarillo.

[00879] A una solución de 4-[3-[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]benzoato de ter-butilo (300 mg, 562 µmol, 1 eq) y [8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil] trifluorometanosulfonato (97 mg, 185 µmol, 0,33 eq) en dioxano (5 ml) y agua (0,5 ml) se agregó Na_2CO_3 (119 mg, 1,12 mmol, 2 eq) y $Pd(dppf)Cl_2$ (20 mg, 28 µmol, 0,05 eq). La mezcla se agitó a 80 °C durante 12 horas en una atmósfera de nitrógeno. La mezcla se vertió en agua (50 ml) y se extrajo con EtOAc (50 ml dos veces). La capa orgánica combinada se lavó con salmuera (100 ml×2), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 15/1 a 10/1). El compuesto ter-butil 4-[3-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]benzoato (80 mg, 102 µmol, 18 % de rendimiento) se obtuvo como un sólido amarillo.

[00880] **LC-MS:** MS (ESI+): t_R = 0,520 min, m/z = 782,4 [M + H^+]

[00881] A una solución de 4-[3-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]benzoato de ter-butilo (80 mg, 102 µmol, 1 eq) en DCM (1 ml) se le agregó TFA (1,54 g, 13,46 mmol, 1 ml, 131,59 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto ácido 4-[3-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]benzoico (75 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00882] A una solución de ácido 4-[3-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]benzoico (75 mg) y DIPEA (34 mg, 267 µmol, 46 µl, 3 eq) en DMF (1 ml) se le agregó 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (24 mg, 89 µmol, 1 eq) y HATU (67 mg, 178 µmol, 2 eq). La mezcla resultante se agitó a 25 °C durante 12 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). La capa orgánica combinada se lavó con salmuera (100 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante TLC preparativa (SiO_2, diclorometano/metanol=15/1) y mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 35 %-65 % B durante 9 min). El compuesto 4-[3-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-3,9-diazaespiro[5,5]undecan-9-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (47,5 mg, 45 µmol, 51 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[00883] **^{1}H NMR** (400 MHz, CLOROFORMO-*d*) δ = 9,76 (d, *J*=15,2 Hz, 1 H) 8,93 (dd, *J*=6,0, 2,0 Hz, 1 H) 8,33 (s, 1 H) 8,00 (d, *J*=9,2 Hz, 1 H) 7,91-7,81 (m, 1 H) 7,76-7,72 (m, 1 H) 7,72-7,67 (m, 2 H) 7,57-7,48 (m, 1 H) 7,46 (d, *J*=8,4 Hz, 1 H) 6,94 (d, *J*=8,8 Hz, 2 H) 6,83 (d, *J*=9,2 Hz, 1 H) 6,47 (d, *J*=2,0 Hz, 1 H) 6,41 (dd, *J*=8,8, 2,0 Hz, 1 H) 6,13 (d, *J*=8,0 Hz, 1 H) 4,66 (s, 1 H) 4,49 (s, 1 H) 4,34-4,24 (m, 1 H) 4,21-4,12 (m, 3 H) 4,07-3,99 (m, 2 H) 3,85 (t, *J*=5,6 Hz, 1 H) 3,70 (s, 4 H) 3,63-3,52 (m, 2 H) 3,43-3,30 (m, 4 H) 2,98-2,90 (m, 1 H) 2,87 (t, *J*=5,6 Hz, 1 H) 2,53-2,38 (m, 2 H) 2,22 (s, 1 H) 2,08 (s, 2 H) 1,98 (d, *J*=13,2 Hz, 4 H) 1,72 (dt, *J*=14,8, 5,6 Hz, 8 H) 1,27 (s, 6 H) 1,24 (s, 6 H).

[00884] **LC-MS:** MS (ESI+): t_R = 2,744 min, m/z = 982,6 [M + H^+]

[00885] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 42.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
267	4-[4-[1-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-4-piperidil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,73 (d, J = 14,0 Hz, 1H), 8,90 (dd, J = 2,4, 6,0 Hz, 1H), 8,27 (ddd, J = 2,4, 6,4, 8,8 Hz, 1H), 7,96 (d, J = 8,8 Hz, 1H), 7,89 - 7,79 (m, 1H), 7,75 - 7,64 (m, 3H), 7,57 - 7,42 (m, 2H), 6,92 (d, J = 9,2 Hz, 2H), 6,81 (br d, J = 8,8 Hz, 1H), 6,47 (d, J = 2,0 Hz, 1H), 6,40 (dd, J = 2,0, 8,4 Hz, 1H), 6,12 (d, J = 8,0 Hz, 1H), 4,65 (s, 1H), 4,52 -	996,6

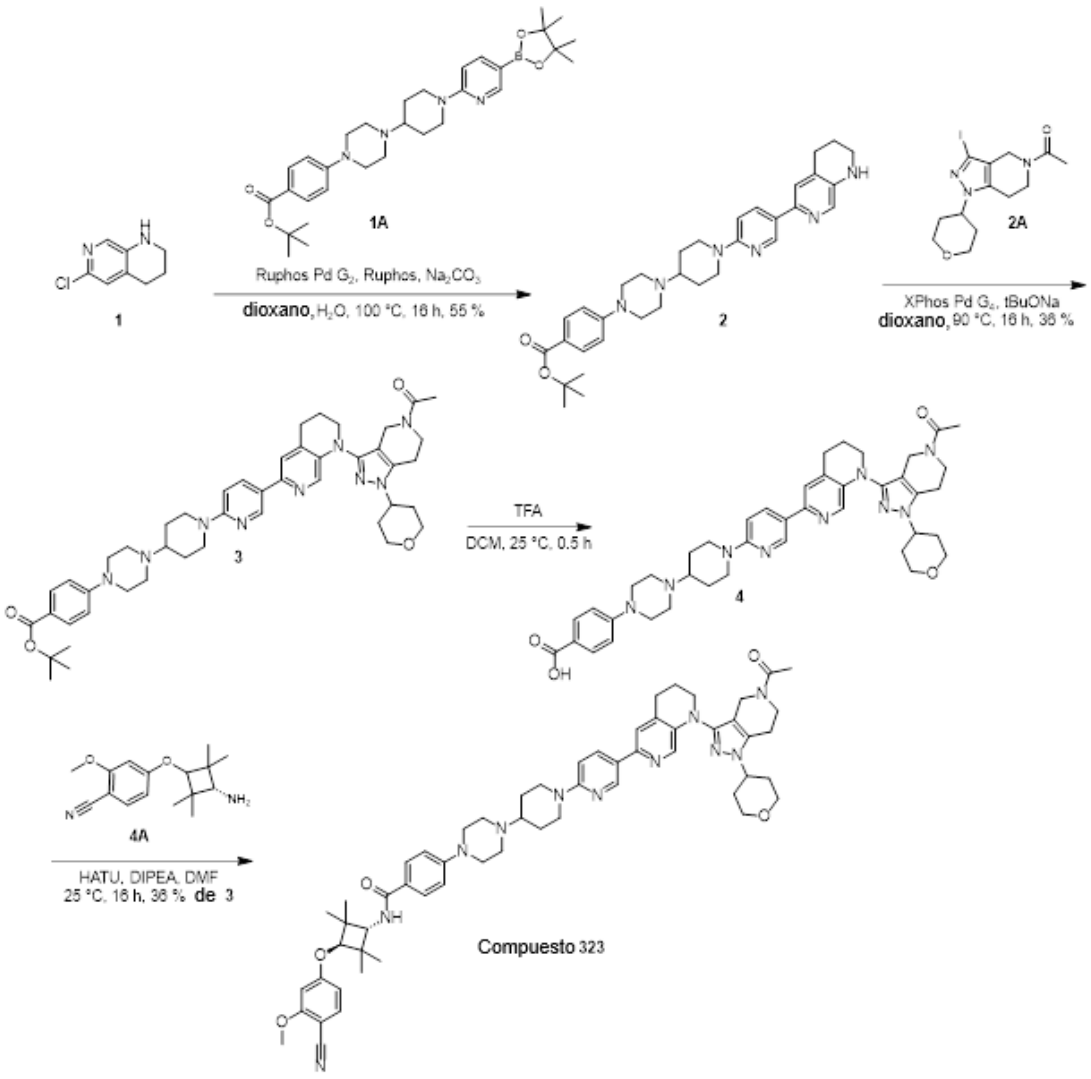
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		4,42 (m, 3H), 4,28 (dt, J = 3,6, 12,0 Hz, 1H), 4,21 - 4,11 (m, 3H), 4,06 - 3,99 (m, 2H), 3,96 - 3,81 (m, 6H), 3,57 (br t, J = 12,0 Hz, 2H), 2,96 - 2,73 (m, 6H), 2,52 - 2,39 (m, 2H), 2,22 - 2,06 (m, 3H), 1,97 (br d, J = 12,4 Hz, 2H), 1,86 (br d, J = 11,6 Hz, 4H), 1,45 - 1,33 (m, 6H), 1,25 (d, J = 10,4 Hz, 12H)	
268	4-[4-[1-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]azetidin-3-il]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,74 (d, *J* = 13,2 Hz, 1H), 8,94 - 8,80 (m, 1H), 8,27 (dd, *J* = 6,4, 8,6 Hz, 1H), 7,95 (d, *J* = 9,6 Hz, 1H), 7,90 - 7,79 (m, 1H), 7,76 - 7,67 (m, 3H), 7,54 - 7,44 (m, 2H), 6,93 (d, *J* = 8,8 Hz, 2H), 6,47 (d, *J* = 2,0 Hz, 1H), 6,45 - 6,37 (m, 2H), 6,12 (d, *J* = 8,0 Hz, 1H), 4,65 (s, 1H), 4,48 (s, 1H), 4,34 - 4,25 (m, 1H), 4,24 - 4,14 (m, 5H), 4,05 (s, 1H), 4,02 (br t, *J* = 6,0 Hz, 1H), 3,92 (s, 3H), 3,90 - 3,83 (m, 4H), 3,57 (br t, *J* = 12,0 Hz, 2H), 2,95 - 2,82 (m, 4H), 2,63 - 2,54 (m, 1H), 2,51 - 2,40 (m, 2H), 2,21 (s, 1H), 2,08 (s, 2H), 1,97 (d, *J* = 12,4 Hz, 2H), 1,85 (d, *J* = 13,2 Hz, 3H), 1,44 - 1,30 (m, 3H), 1,25 (d, *J* = 10,4 Hz, 12H)	968,7
269	4-[9-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]-3-azaespiro[5,5]undecan-3-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,71 (d, J = 12,4 Hz, 1H), 8,15 (d, J = 4,4 Hz, 1H), 8,08 (d, J = 2,0 Hz, 1H), 7,87 - 7,76 (m, 2H), 7,74 - 7,65 (m, 3H), 7,54 - 7,43 (m, 2H), 6,93 (d, J = 8,8 Hz, 2H), 6,47 (d, J = 2,0 Hz, 1H), 6,40 (dd, J = 2,4, 7,6 Hz, 1H), 6,13 (d, J = 8,4 Hz, 1H), 4,66 (s, 1H), 4,49 (s, 1H), 4,33 - 4,12 (m, 5H), 4,07 - 3,99 (m, 2H), 3,92 (s, 3H), 3,85 (t, J = 5,6 Hz, 1H), 3,57 (t, J = 12,0 Hz, 2H),	970,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		3,33 (q, J = 5,2 Hz, 4H), 2,97 - 2,82 (m, 2H), 2,52 - 2,37 (m, 2H), 2,22 - 2,04 (m, 7H), 1,95 (t, J = 12,8 Hz, 4H), 1,84 (d, J = 5,6 Hz, 2H), 1,64 - 1,57 (m, 2H), 1,44 - 1,36 (m, 2H), 1,25 (d, J = 11,2 Hz, 12H)	
270	4-[4-[4-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]-1-piperidil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,92-9,68 (m, 1H), 8,23-8,03 (m, 2H), 7,90-7,65 (m, 2H), 7,57-7,42 (m, 1H), 6,80 (s, 1H), 6,56-6,37 (m, 1H), 6,17 (s, 2H), 4,78-4,49 (m, 2H), 4,21 (brs, 2H), 4,21-4,10 (m, 2H), 4,09-3,96 (m, 2H), 3,92 (s, 3H), 3,81 (s, 3H), 3,63-3,51 (m, 2H), 3,50-3,29 (m, 2H), 2,99-2,82 (m, 2H), 2,57-2,37 (m, 2H), 2,35-2,23 (m, 2H).	985,6
271	4-[4-[4-[4-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]pirazol-1-il]ciclohexil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,68 (d, J = 11,2 Hz, 1H), 8,17 - 7,99 (m, 2H), 7,88 - 7,76 (m, 2H), 7,73 - 7,63 (m, 3H), 7,51 - 7,42 (m, 2H), 6,93 (d, J = 8,8 Hz, 2H), 6,49 - 6,38 (m, 2H), 6,13 (d, J = 8,0 Hz, 1H), 4,79 (s, 8H), 4,66 - 4,47 (m, 2H), 4,32 - 4,24 (m, 1H), 4,20 - 4,11 (m, 4H), 4,05 (s, 1H), 4,01 (t, J = 5,6 Hz, 1H), 3,95 - 3,90 (m, 4H), 3,89 - 3,81 (m, 2H), 3,57 (t, J = 12,0 Hz, 2H), 2,93 (t, J = 5,6 Hz, 1H), 2,86 (t, J = 5,6 Hz, 1H), 2,84 - 2,75 (m, 2H), 2,51 - 2,38 (m, 2H), 2,33 (d, J = 10,4 Hz, 2H), 2,21 (s, 1H), 2,07 (s, 2H), 1,98 (s, 2H), 1,86 - 1,83 (m, 2H), 1,45 - 1,39 (m, 2H), 1,25 (d, J = 10,4 Hz, 12H).	984,8
272	4-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-3-azaespiro[5,5]undecan-3-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-	7,69 (d, J = 5,2 Hz, 1H), 7,46 (d, J = 8,4 Hz, 1H), 7,38 (br s, 1H), 6,92 (d, J = 10,0 Hz, 1H), 6,12 (d, J = 8,4 Hz, 1H), 4,31 (br s, 1H), 4,05 (s, 1H), 3,96 (s, 1H), 3,94 - 3,86 (m, 5H), 3,80 - 3,66 (m, 3H), 2,92 - 2,85	954,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	tetrametilciclobutil]benzamida	(m, 2H), 2,84 - 2,71 (m, 3H), 2,24 - 2,14 (m, 3H), 2,13 - 2,03 (m, 1H), 1,92 (s, 3H), 1,87 - 1,78 (m, 1H), 1,58 - 1,33 (m, 1H), 1,25 (d, J = 10,0 Hz, 3H).	
321	4-[4-[1-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]-4-piperidil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,73 (d, *J* = 12,0 Hz, 1H), 8,91 (dd, *J* = 2,4, 4,6 Hz, 1H), 8,33 - 8,22 (m, 1H), 7,97 (d, *J* = 9,6 Hz, 1H), 7,89 - 7,80 (m, 1H), 7,76 - 7,66 (m, 3H), 7,55 - 7,42 (m, 2H), 6,93 (d, *J* = 8,8 Hz, 2H), 6,82 (dd, *J* = 2,4, 8,9 Hz, 1H), 6,47 (d, *J* = 2,0 Hz, 1H), 6,40 (dd, *J* = 2,4, 8,6 Hz, 1H), 6,13 (d, *J* = 8,0 Hz, 1H), 4,65 (s, 1H), 4,53 - 4,45 (m, 3H), 4,34 - 4,24 (m, 1H), 4,20 - 4,12 (m, 3H), 4,06 - 4,00 (m, 2H), 3,92 (s, 3H), 3,85 (t, *J* = 5,6 Hz, 1H), 3,57 (t, *J* = 12,0 Hz, 2H), 3,39 - 3,28 (m, 4H), 3,04 - 2,89 (m, 3H), 2,87 (t, *J* = 5,4 Hz, 1H), 2,82 - 2,73 (m, 4H), 2,67 - 2,58 (m, 1H), 2,51 - 2,39 (m, 2H), 2,21 (s, 1H), 2,11 - 1,93 (m, 6H), 1,68 - 1,62 (m, 2H), 1,25 (d, *J* = 9,6 Hz, 12H)	997,6
322	4-[4-[1-[5-[8-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3-isoquinolil]-2-piridil]azetidin-3-il]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,74 (d, J = 12,8 Hz, 1H), 8,88 (dd, J = 5,8, 2,3 Hz, 1H), 8,33-8,23 (m, 1H), 7,96 (d, J = 9,8 Hz, 1H), 7,90-7,79 (m, 1H), 7,75-7,68 (m, 3H), 7,56-7,44 (m, 2H), 6,94 (d, J = 8,9 Hz, 2H), 6,49-6,43 (m, 2H), 6,40 (dd, J = 8,6, 2,1 Hz, 1H), 6,13 (d, J = 8,1 Hz, 1H), 4,65 (s, 1H), 4,48 (s, 1H), 4,36-4,26 (m, 1H), 4,24 (t, J = 7,5 Hz, 2H), 4,20-4,14 (m, 3H), 4,07-4,00 (m, 4H), 3,92 (s, 3H), 3,85 (t, J = 5,6 Hz, 1H), 3,57 (t, J = 12,0 Hz, 2H), 3,48-3,42 (m, 1H), 3,40-3,33 (m, 4H), 2,94 (t, J	969,6

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		= 5,8 Hz, 1H), 2,87 (t, J = 5,4 Hz, 1H), 2,68-2,58 (m, 4H), 2,51-2,40 (m, 2H), 2,21 (s, 1H), 2,08 (s, 2H), 1,97 (d, J = 12,5 Hz, 2H), 1,25 (d, J = 9,9 Hz, 12H)	

[00886] Ejemplo 43: Síntesis de 4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]-4-piperidil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 323**)



[00887] La síntesis del **compuesto 1** fue reportada en WO2022/20342 A1.

[00888] A una solución de 6-cloro-1,2,3,4-tetrahidro-1,7-naftiridina (100 mg, 593,04

µmol, 1,0 eq) y 4-[4-[1-[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-piridil]-4-piperidil]piperazin-1-il]benzoato de ter-butilo (400 mg, 729,23 µmol, 1,23 eq) en dioxano (10 ml) y H_2O (2 ml) se agregó carbonato de sodio (189 mg, 1,78 mmol, 3,0 eq), RuPhos (28 mg, 59,30 µmol, 0,1 eq) y Ruphos Pd G_2 (46 mg, 59,30 µmol, 0,1 eq). La mezcla de reacción se agitó a 45 oC durante 16 h. La mezcla de reacción se inactivó con agua (50 ml) y se extrajo con acetato de etilo (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 25/1 a 10/1). El compuesto ter-butil 4-[4-[1-[5-(1,2,3,4-tetrahidro-1,7-naftiridin-6-il)-2-piridil]-4-piperidil]piperazin-1-il]benzoato (180 mg, 324,49 µmol, 55 % de rendimiento) se obtuvo como un sólido amarillo.

[00889] LC-MS: MS (ESI^+): t_R = 0,465 min, m/z = 555,4 [M + H^+]

[00890] A una solución de 4-[4-[1-[5-(1,2,3,4-tetrahidro-1,7-naftiridin-6-il)-2-piridil]-4-piperidil]piperazin-1-il]benzoato de ter-butilo (190 mg, 342,51 µmol, 1,0 eq) y 1-(3-iodo-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il)etanona (193 mg, 513,77 µmol, 1,5 eq) en dioxano (10 ml) se le agregó t-BuONa (2 M, 513,77 µl, 3,0 eq) y metanosulfonato(2-diciclohexilfosfino-2,4, 6-tri-i-propil-1,1-bifenil)(2-metilamino-1,1-bifenil-2-il)paladio(II) (30 mg, 34,25 µmol, 0,1 eq). La mezcla de reacción se agitó a 45 oC durante 16 h. La mezcla de reacción se inactivó con agua (50 ml) y se extrajo con acetato de etilo (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 15/1 a 10/1). El compuesto ter-butil 4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]-4-piperidil]piperazin-1-il]benzoato (100 mg, 124,69 µmol, 36 % de rendimiento) se obtuvo como un aceite amarillo.

[00891] LC-MS: MS (ESI^+): t_R = 0,429 min, m/z = 802,4[M + H^+]

[00892] A una solución de ter-butil 4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]-4-piperidil]piperazin-1-il]benzoato (100 mg, 124,69 µmol, 1,0 eq) en diclorometano (3 ml) se le agregó ácido trifluoroacético (4,61 g, 40,39 mmol, 3 ml, 323,91 eq). La mezcla de reacción se agitó a 25 °C durante 0,5 h. La mezcla se concentró hasta secarse. El producto crudo se usó directamente en la próxima etapa. El compuesto ácido 4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-

2H-1,7-naftiridin-6-il]-2-piridil]-4-piperidil]piperazin-1-il]benzoico (100 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00893] **LC-MS:** MS (ESI^+): t_R = 0,390 min, m/z = 746,3 [M + 1]

[00894] A una solución de ácido 4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]-4-piperidil]piperazin-1-il]benzoico (100 mg) y 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (73 mg, 232,58 µmol, 2,0 eq, HCl) en N,N-dimetilformamida (5 ml) se le agregó hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (133 mg, 348,86 µmol, 3,0 eq) y N,N-diisopropiletilamina (45 mg, 348,86 µmol, 60,77 µl, 3,0 eq). La mezcla de reacción se agitó a 45 oC durante 16 h. La mezcla de reacción se inactivó con agua (50 ml) y se extrajo con acetato de etilo (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua(FA)-ACN]; gradiente: 15 %-45 % B durante 10 min). El compuesto 4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]-4-piperidil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (43,59 mg, 41,78 µmol, 36 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino).

[00895] **^{1}H** (400 MHz, CLOROFORMO-d) δ = 8,65 (dd, *J* = 2,4, 7,3 Hz, 1H), 8,50 (s, 1H), 8,03 (ddd, *J* = 2,4, 8,8, 10,8 Hz, 1H), 7,88 (s, 1H), 7,70 (d, *J* = 8,8 Hz, 2H), 7,45 (d, *J* = 8,8 Hz, 1H), 7,35 - 7,27 (m, 1H), 6,92 (d, *J* = 8,8 Hz, 2H), 6,73 (dd, *J* = 4,8, 9,0 Hz, 1H), 6,47 (d, *J* = 2,0 Hz, 1H), 6,40 (dd, *J* = 2,4, 8,6 Hz, 1H), 6,12 (d, *J* = 8,0 Hz, 1H), 4,43 (d, *J* = 13,2 Hz, 2H), 4,34 (s, 1H), 4,20 - 4,09 (m, 5H), 4,05 (s, 1H), 3,92 (s, 4H), 3,79 - 3,65 (m, 3H), 3,52 (t, *J* = 12,4 Hz, 2H), 3,36 - 3,27 (m, 4H), 2,95 - 2,86 (m, 4H), 2,82 (t, *J* = 5,6 Hz, 1H), 2,79 - 2,72 (m, 5H), 2,63 - 2,53 (m, 1H), 2,37 - 2,25 (m, 2H), 2,18 - 2,05 (m, 5H), 1,97 (d, *J* = 12,4 Hz, 2H), 1,86 (d, *J* = 13,2 Hz, 2H), 1,67 - 1,56 (m, 2H), 1,25 (d, *J* = 9,6 Hz, 12H)

[00896] **LC-MS:** MS (ESI^+): t_R = 2,583 min, m/z = 1002,8 [$M + H^+$]

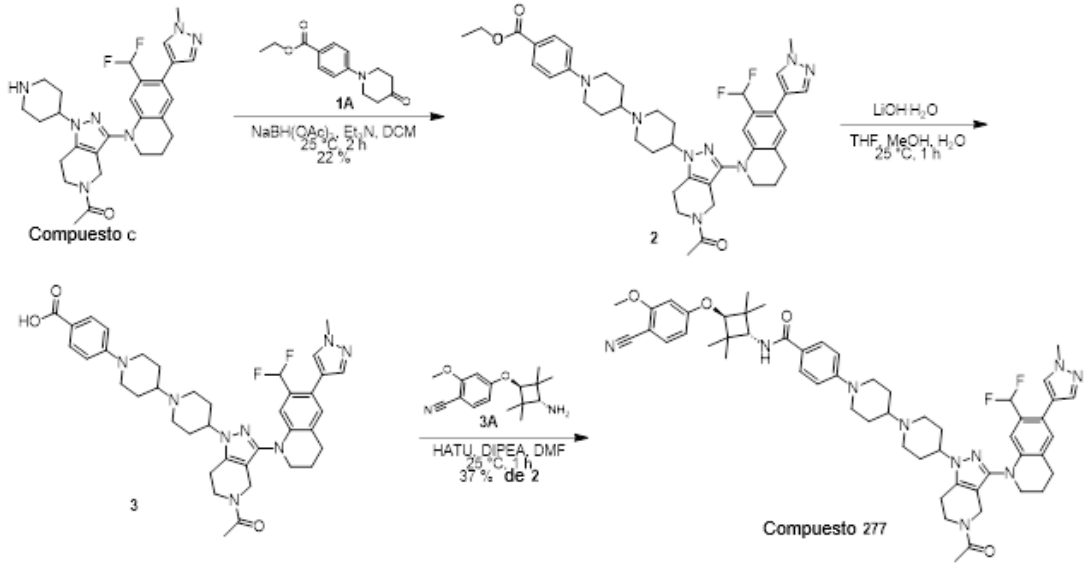
[00897] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 43.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
324	4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-	δ = 8,61 (dd, J = 7,8, 2,1 Hz, 1H), 8,19 (s, 1H), 8,11-	974,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	dihidro-4H-pirazolo[4,3-c]piridin-3-il)-3,4-dihidro-2H-1,7-naftiridin-6-il]-2-piridil]azetidin-3-il]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,96 (m, 1H), 7,88 (s, 1H), 7,71 (d, J = 8,8 Hz, 2H), 7,45 (d, J = 8,6 Hz, 1H), 7,28 (s, 1H), 7,25 (s, 1H), 6,93 (d, J = 9,0 Hz, 2H), 6,47 (d, J = 2,1 Hz, 1H), 6,44-6,33 (m, 2H), 6,13 (d, J = 8,1 Hz, 1H), 4,34 (s, 1H), 4,22-4,15 (m, 4H), 4,15-4,09 (m, 3H), 4,05 (s, 1H), 3,99 (dd, J = 7,9, 5,4 Hz, 2H), 3,92 (s, 4H), 3,78-3,66 (m, 3H), 3,52 (t, J = 12,0 Hz, 2H), 3,41 (t, J = 6,3 Hz, 1H), 3,39-3,32 (m, 4H), 2,95-2,85 (m, 2H), 2,82 (t, J = 5,4 Hz, 1H), 2,75 (t, J = 5,4 Hz, 1H), 2,67-2,56 (m, 4H), 2,36-2,24 (m, 2H), 2,17 (s, 1H), 2,15-2,03 (m, 4H), 1,84 (s, 1H), 1,25 (d, J = 9,6 Hz, 12H)	
325	4-[4-[1-[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]-4-piperidil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	*1*H NMR (400 MHz, DMSO-d_6) δ = 8,04 (s, 1H), 8,26 - 7,86 (m, 1H), 7,81 - 7,73 (m, 2H), 7,68 - 7,62 (m, 2H), 7,60 - 7,28 (m, 1H), 7,28 - 6,90 (m, 2H), 6,89 - 6,82 (m, 1H), 6,80 - 6,48 (m, 1H), 4,58 - 4,39 (m, 2H), 4,34 - 4,26 (m, 1H), 4,22 - 4,13 (m, 1H), 4,11 - 4,02 (m, 1H), 4,02 - 3,82 (m, 1H), 3,79 - 3,58 (m, 1H), 3,54 - 3,39 (m, 4H), 3,27 - 3,02 (m, 4H), 2,93 - 2,72 (m, 2H), 2,21 - 1,91 (m, 1H), 1,90 - 1,76 (m, 1H), 1,69 - 1,42 (m, 1H), 1,22 - 1,80 (m, 1H), 1,15 - 1,07 (m, 1H).	1051,8
326	4-(4-(1-(5-(1-(5-acetil-1-(tetrahidro-2H-piran-4-il)-4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-1,2,3,4-tetrahidroquinolin-6-il)piridin-2-il)azetidin-3-il)piperazin-1-il)-N-((1r,3r)-3-(4-ciano-3-	δ = 7,99 (d, J = 2,0 Hz, 1H), 7,81 - 7,73 (m, 2H), 7,68 - 7,61 (m, 1H), 7,53 (d, J = 9,2 Hz, 1H), 7,50 - 7,43 (m, 1H), 7,05 - 6,94 (m, 3H), 6,89 - 6,81 (m, 1H), 6,78 - 6,49 (m, 3H), 6,48 - 6,44 (m, 1H), 4,35 - 4,25 (m,	1023,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	metoxifenoxi)-2,2,4,4-tetrametilciclobutil)benzamida	2H), 4,21 - 4,12 (m, 2H), 4,10 - 4,02 (m, 3H), 3,95 (d, J = 10,8 Hz, 2H), 3,90 (s, 3H), 3,84 (d, J = 5,2, 7,6 Hz, 2H), 3,77 - 3,68 (m, 2H), 3,63 - 3,58 (m, 2H), 3,49 - 3,42 (m, 3H), 3,30 (d, J = 3,2 Hz, 8H), 2,87 (d, J = 6,4 Hz, 3H), 2,76 (d, J = 5,2 Hz, 1H), 2,08 (s, 2H), 2,04 - 1,93 (m, 5H), 1,87 - 1,77 (m, 2H), 1,22 (s, 6H), 1,14 (s, 6H)	

[00898] **Ejemplo 44**: Síntesis de 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 277**)



[00899] La síntesis de **1A** fue reportada en European Journal of Medicinal Chemistry, 2013, vol. 66, páginas 32-45.

[00900] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (180 mg, 353 µmol, 1,0 eq), 4-(4-oxo-1-piperidil)benzoato de etilo (530 µmol, 1,5 eq) en DCM (5 ml) se agregó Et_3N (107 mg, 1,0 mmol, 0,1 ml, 3,0 eq) y $NaBH(OAc)_3$ (370 mg, 1,77 mmol, 5,0 eq). La mezcla se agitó a 25 °C durante 2 h. La reacción se detuvo añadiendo $NaHCO_3$ saturado (20 ml) a 0 °C y, a continuación, se extrajo con acetato de etilo (30

ml × 3). Las capas orgánicas combinadas se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante *prep*-HPLC (columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua(FA)-ACN]; gradiente: 20 %-50 % B durante 10 min). El compuesto 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]benzoato de etilo (60 mg, 80,0 µmol, 22 % en dos pasos) se obtuvo como un sólido blanco.

[00901] **LC-MS:** MS (ESI^+): t_R = 0,513 min, m/z = 741,4 [M + H^+]

[00902] A una solución de 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]benzoato de etilo (50 mg, 67,4 µmol, 1,0 eq) en THF (0,5 ml) y MeOH (0,5 ml) se agregó la solución de $LiOH·H_2O$ (14 mg, 5,0 eq) en H_2O (0,5 ml). La mezcla se agitó a 25 °C durante 1 h. La reacción se acidificó con HCl acuoso 1 M hasta alcanzar un pH de 5, y luego se extrajo con DCM (10 ml × 3). Las capas orgánicas combinadas se secaron y se concentraron a presión reducida. El compuesto ácido 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]benzoico (45 mg) se obtuvo como un sólido blanco.

[00903] **LC-MS:** MS (ESI^+): t_R = 0,476 min, m/z = 713,4 [M + H^+]

[00904] A una solución de ácido 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]benzoico (40 mg) en DMF (2 ml) se le agregó DIPEA (36 mg, 281 µmol, 49 µl, 5,0 eq), HATU (43 mg, 112,23 µmol, 2,0 eq) y 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (19 mg, 61,73 µmol, 1,1 eq, sal de HCl). La mezcla se agitó a 25 °C durante 1 hora. La mezcla de reacción se concentró a presión reducida para obtener el producto crudo. El residuo se purificó mediante *prep*-HPLC (columna: Welch Xtimate C18 150*25mm*5um; fase móvil: [agua(FA)-ACN]; gradiente: 28 %-58 % B durante 10 min). El compuesto 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (20,36 mg, 20,17 µmol, 37 % en dos pasos) se obtuvo como un sólido amarillo.

[00905] ^1H NMR (400 MHz, CD-$\mathbf{d_3}$) δ = 7,76 - 7,64 (m, 1H), 7,55 - 7,44 (m, 1H), 7,13 (t, *J* = 8,4 Hz, 1H), 7,03 (br d, *J* = 7,3 Hz, 1H), 6,68 - 6,51 (m, 2H), 4,53 - 4,35 (m, 1H), 4,28 - 4,22 (m, 1H), 4,16 (d, *J* = 7,3 Hz, 1H), 4,11 - 4,08 (m, 1H), 4,08 - 4,05 (m, 1H), 3,93 - 3,92 (m, 1H), 3,91 - 3,88 (m, 1H), 3,87 - 3,81 (m, 1H), 3,79 - 3,63 (m, 1H), 3,26 -

3,14 (m, 1H), 2,96 - 2,82 (m, 2H), 2,44 - 2,32 (m, 2H), 2,31 - 2,23 (m, 2H), 2,19 (br s, 3H), 2,12 - 2,05 (m, 2H), 2,05 - 1,98 (m, 1H), 1,92 - 1,74 (m, 1H).

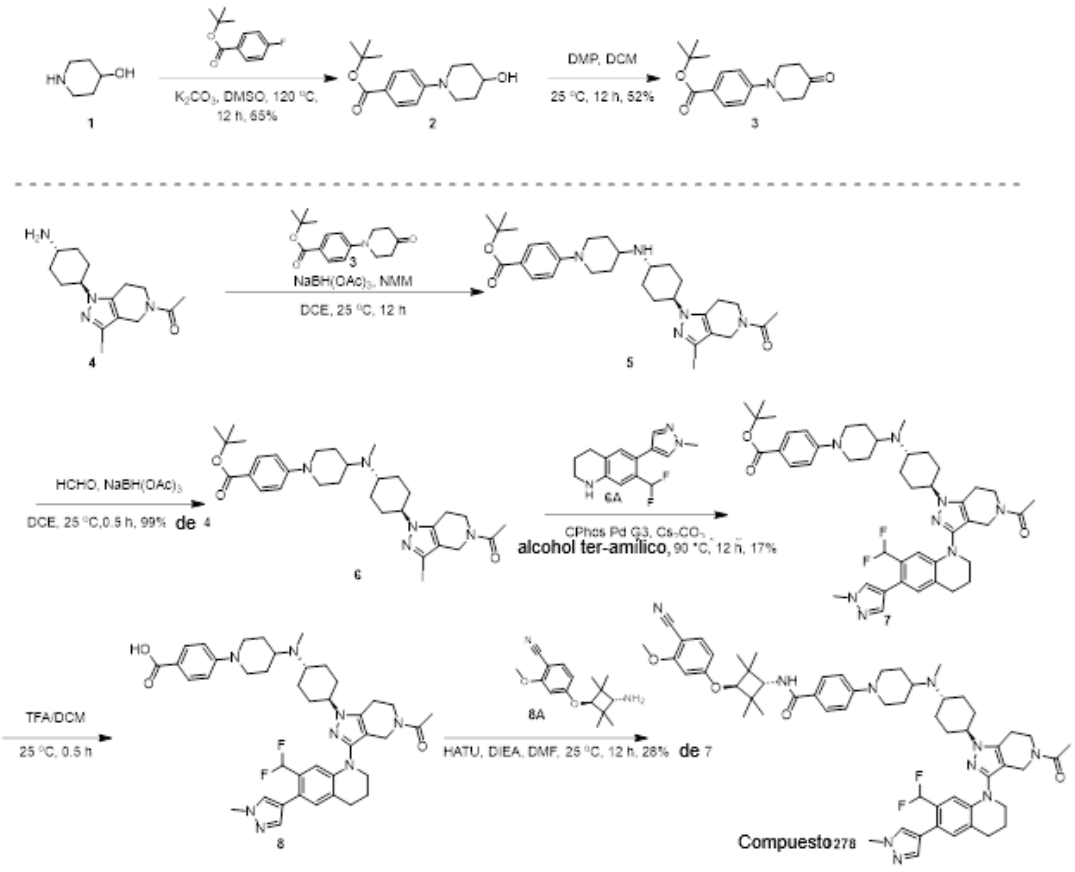
[00906] **LC-MS:** MS (ESI^+): t_R = 2,303 min, m/z = 969,6 [M + H^+]

[00907] Los compuestos que se muestran a continuación se prepararon de forma similar a como se describe en el Ejemplo 44.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
370	4-[3-[7-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,5]nonan-2-il]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,66 (d, J = 8,8 Hz, 1H), 7,06-6,85 (m, 2H), 6,69-6,38 (m, 2H), 6,09 (d, J = 8,1 Hz, 1H), 4,10 (s, 1H), 4,05 (s, 1H), 3,80 (s, 1H), 3,19 (s, 2H), 3,09 (brs, 2H), 2,78 (t, J = 7,2 Hz, 2H), 2,72 (t, J = 7,2 Hz, 2H), 2,13 (s, 1H), 2,10-2,03 (m, 2H), 2,02-1,93 (m, 2H) 1,93-1,86 (m, 2H).	981,7
371	2-[4-[7-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,5]nonan-2-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	8,71 (d, J = 8,6 Hz, 1H), 7,41 (d, J = 8,1 Hz, 1H), 7,08 (br s, 1H), 6,78 (d, J = 8,7 Hz, 1H), 6,00 (d, J = 8,1 Hz, 1H), 4,76 (br s, 1H), 4,26 (s, 1H), 3,96 (s, 1H), 3,92 - 3,81 (m, 2H), 3,78 - 3,65 (m, 3H), 3,47 - 3,21 (m, 3H), 3,16 - 3,04 (m, 3H), 2,94 - 2,84 (m, 2H), 2,81 - 2,67 (m, 1H), 2,16 (s, 3H), 2,11 - 2,03 (m, 1H), 1,95 - 1,81 (m, 1H), 1,24 (d, J = 17,2 Hz, 3H).	1015,7
372	4-[4-[7-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[3,5]nonan-2-il]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	1H NMR (500 MHz, DMSO-d6) δ = 8,87 - 8,67 (m, 1H), 7,67 - 7,57 (m, 2H), 7,54 - 7,70 (m, 1H), 7,70 - 7,40 (m, 1H), 7,08 - 6,99 (m, 1H), 6,94 - 6,82 (m, 1H), 6,60 - 6,28 (m, 1H), 4,30 - 4,20 (m, 1H), 4,17 - 4,04 (m, 1H), 4,02 - 3,81 (m, 3H), 3,76 - 3,61 (m, 1H), 4,51 - 3,31 (m, 2H), 4,09 - 4,00 (m, 1H), 2,93 - 2,62 (m, 1H), 2,37 - 2,25 (m, 3H), 2,18 - 2,00 (m, 1H), 1,98 - 1,82 (m, 1H), 1,78 (d, J = 3,4 Hz, 3H), 1,23 (d, J = 16,8 Hz, 3H), 1,99 - 1,93 (m, 1H).	1009,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
373	2-[4-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-7-azaespiro[3,5]nonan-7-il]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2 H) 7,57 (d, *J*=8,8 Hz, 1 H) 7,53 (d, *J*=5,2 Hz, 1 H) 7,41 (d, *J*=6,4 Hz, 1 H) 7,07-7,00 (m, 1 H) 6,99-6,94 (m, 2 H) 6,81 (dd, *J*=8,8, 2,4 Hz, 1 H) 6,69-6,37 (m, 1 H) 5,96 (d, *J*=8,0 Hz, 1 H) 4,97 (d, *J*=13,2 Hz, 2 Alto) 4,62-4,50 (m, 1H) 4,25 (s, 1 H) 4,15-4,10 (m, 2 H) 4,05 (s, 1 H) 3,96 (d, *J*=2,4 Hz, 3 H) 3,91-3,86 (m, 1 H) 3,73 (d, *J*=5,6 Hz, 2 H) 3,00-2,92 (m, 2 H) 2,92-2,85 (m, 3 H) 2,75 (d, *J*=4,8 Hz, 3 H) 2,70-2,61 (m, 3 H) 2,55-2,42 (m, 3 H) 2,32 (d, *J*=10,4 Hz, 3 H) 2,15 (s, 1 H) 2,11-2,05 (m, 3 H) 2,04 (s, 2 H) 1,88 (d, *J*=5,2 Hz, 4 H) 1,58 (qd, *J*=12,0, 3,6 Hz, 2 H) 1,26 (s, 6 H) 1,22 (s, 6 H)	1015,7
374	4-[4-[2-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-7-azaespiro[3,5]nonan-7-il]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,67 (d, J = 8,7 Hz, 1H), 7,53 (d, J = 8,1 Hz, 1H), 7,47 (d, J = 2,2 Hz, 1H), 7,07 (d, J = 8,6 Hz, 1H), 6,97 (dd, J = 6,84, 8,6 Hz, 1H), 6,40 (d, J = 8,1 Hz, 1H), 6,28 (d, J = 8,7 Hz, 1H), 4,23 (dd, J = 4,06, 11,9 Hz, 1H), 3,76 - 3,66 (m, 3H), 3,58 - 3,30 (m, 1H), 3,09 - 2,79 (m, 3H), 2,78 - 2,71 (m, 3H), 2,69 - 2,64 (m, 1H), 2,61 - 2,33 (m, 4H), 2,30 - 2,12 (m, 2H), 2,12 - 2,02 (m, 2H), 1,90 - 1,80 (m, 1H), 1,24 (d, J = 15,3 Hz, 3H).	1009,7

[00908] Ejemplo 45: Síntesis de 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]benzamida (**Compuesto 278**)



[00909] A una solución de 4-fluorobenzoato de ter-butilo (10,00 g, 50,96 mmol, 1,0 eq) en DMSO (50 ml) se le añadieron K_2CO_3 (17,61 g, 127,41 mmol, 2,5 eq) y piperidin-4-ol (5,15 g, 50,96 mmol, 1,0 eq). La mezcla se agitó a 120 °C durante 12 horas. La reacción se diluyó con agua (200 ml) y se extrajo con acetato de etilo (80 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (300 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto 4-(4-hidroxi-1-piperidil)benzoato de ter-butilo (9,24 g, 33,31 mmol, 65 % de rendimiento) se obtuvo como un sólido blanco.

[00910] ^{1}H NMR (400 MHz, CDCl**3**): δ 7,30 - 7,77 (m, 1H), 6,87 (dd, *J* = 10,0, 9,0 Hz, 1H), 3,97 - 3,85 (m, 1H), 3,80 (t, *J* = 5,2 Hz, 1H), 3,07 (d, J = 5,2 Hz, 2H), 13,0 - 3,76 (m, 2H), 2,07 - 1,91 (m, 2H), 1,69 - 1,56 (m, 12H).

[00911] A una solución de 4-(4-hidroxi-1-piperidil)benzoato de ter-butilo (5,24 g, 18,89 mmol, 1,0 eq) en diclorometano (50 ml) se le agregó Dess-Martin (10,42 g, 24,56 mmol, 7,61 ml, 1,3 eq). La mezcla se agitó a 25 °C durante 30 min. La reacción se diluyó con agua (200 ml) y se extrajo con acetato de etilo (80 ml x 3). Las capas orgánicas

combinadas se lavaron con salmuera (300 ml x 3), se secaron en sulfato de sodio, se filtraron y se concentraron hasta secarse. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto 4-(4-oxo-1-piperidil)benzoato de ter-butilo (2,73 g, 9,91 mmol, 52 % de rendimiento) se obtuvo como un sólido amarillo.

[00912] ^{1}H NMR (400 MHz, DMSO-d**3**) δ = 7,92 (d, J = 9,0 Hz, 1H), 6,90 (d, $_J$ = 9,0 Hz, 1H), 3,74 (t, J = 6,1 Hz, 1H), 2,56 (d, J = 6,1 Hz, 4H), 1,59 (s, 9H).

[00913] **LC-MS:** MS (ESI$^+$): t_R = 0,533 min, m/z = 276,0 [M + H$^+$]

[00914] A una solución de 1-[1-(4-aminociclohexil)-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (357 mg, 919,52 µmol, 1,0 eq) en DCE (5 ml) se le añadieron NMM (930 mg, 9,20 mmol, 1,01 ml, 10,0 eq) y 4-(4-oxo-1-piperidil)benzoato de ter-butilo (379 mg, 1,38 mmol, 1,5 eq). La mezcla se agitó a 25 °C durante 10 min. Se agregó $NaBH(OAc)_3$ (584 mg, 2,76 mmol, 3,0 eq) y la mezcla se agitó a 25 °C durante 12 h. La mezcla se vertió en agua (50 ml). La fase acuosa se extrajo con acetato de etilo (20 ml x 3). La capa orgánica combinada se lavó con salmuera (100 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El compuesto ter-butil 4-[4-[[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]amino]-1-piperidil]benzoato (595 mg, 918,79 µmol, 99 % de rendimiento) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso.

[00915] **LC-MS:** MS (ESI$^+$): t_R = 0,488 min, m/z = 648,3 [M + H$^+$]

[00916] A una solución de 4-[4-[[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]amino]-1-piperidil]benzoato de ter-butilo (595 mg, 918,79 µmol, 1,0 eq) en DCE (8 ml) se añadieron HCHO (137 mg, 4,59 mmol, 126,57 µl, 5,0 eq) y $NaBH(OAc)_3$ (584 mg, 2,76 mmol, 3,0 eq). La mezcla se agitó a 25 °C durante 0,5 h y luego se vertió en agua (50 ml). La fase acuosa se extrajo con acetato de etilo (30 ml x 2). La capa orgánica combinada se lavó con salmuera (80 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (0 % - 10 % de metanol en diclorometano). El compuesto ter-butil 4-[4-[[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]-metil-amino]-1-piperidil]benzoato (600 mg, 906,87 µmol, 98 % de rendimiento) se obtuvo como un sólido blanco.

[00917] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7,87 (d, J = 1,6 Hz, 1H), 6,86 (d, **J** = 1,6 Hz, 1H), 3,95-3,86 (m, 1H), 2,90-2,62 (m, 1H), 2,30-2,16 (m, 1H), 2,13-1,94 (m, 1H), 1,87-1,65 (m, 1H), 1,58 (s, 9H).

[00918] **LC-MS:** MS (ESI$^+$): t_R = 0,497 min, m/z = 662,3 [M + H$^+$]

[00919] A una solución de 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (178 mg, 676,07 µmol, 1,0 eq), 4-[4-[[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]-metil-amino]-1-piperidil]benzoato de ter-butilo (447 mg, 676,07 µmol, 1,0 eq) en alcohol terc-amílico (8 ml) se le agregó Cs_2CO_3 (660 mg, 2,03 mmol, 3,0 eq) y Cphos Pd G3 (54 mg, 67,61 µmol, 0,1 eq). La mezcla se agitó a 90 °C durante 12 h en N_2. El residuo se vertió en agua (50 ml). La fase acuosa se extrajo con acetato de etilo (30 ml x 2). La capa orgánica combinada se lavó con salmuera (50 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 10/1 a 10/1). El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 20 %-50 % B durante 10 min) para obtener el compuesto deseado. Luego fue liofilizado. El compuesto ter-butil 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]benzoato (96 mg, 120,45 µmol, 17 % de rendimiento) se obtuvo como un sólido blanco.

[00920] **LC-MS:** MS (ESI^+): t_R = 0,505 min, m/z = 797,3 [M + H^+]

[00921] A una solución de ter-butil 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]benzoato (96 mg, 120,45 µmol, 1,0 eq) en diclorometano (3 ml) se le agregó ácido trifluoroacético (4,61 g, 40,39 mmol, 3 ml, 335,30 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El compuesto ácido 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]benzoico (89 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00922] **LC-MS:** MS (ESI^+): t_R = 0,455 min, m/z = 741,4 [M + H^+]

[00923] A una solución de ácido 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]benzoico (89 mg) en DMF (3 ml) se le agregó DIPEA (310 mg, 2,40 mmol, 418,47 µl, 20,0 eq), 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (37 mg, 120,13 µmol, 1,0 eq) y la mezcla se agitó a 25 °C durante 10 min. Se agregó hexafluorofosfato azabenzotriazol tetrametil uronio (91 mg, 240,25 µmol, 2,0 eq) y la mezcla se agitó a 25 °C durante 12 h. La mezcla se vertió en agua (50 ml). La fase acuosa se extrajo con acetato de etilo (30 ml x 2). La capa orgánica combinada se

lavó con salmuera (50 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 15/1 a 10/1). El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 23 %-53 % B durante 10 min) para obtener el compuesto deseado. Luego fue liofilizado. Se obtuvo el compuesto 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]benzamida (35,07 mg, 34,82 μmol, 28 % de rendimiento) como un sólido blanco.

[00924] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8,48 (s, 1H), 7,69 (d, J = 8,8 Hz, 2H), 7,54 (d, J = 5,4 Hz, 1H), 7,46 (d, J = 8,6 Hz, 1H), 7,41 (d, J = 6,5 Hz, 1H), 7,05 (s, 1H), 6,92 (d, J = 8,9 Hz, 2H), 6,87 (d, J = 5,4 Hz, 1H), 6,68-6,37 (m, 3H), 6,12 (d, J = 8,4 Hz, 1H), 4,30-4,10 (m, 3H), 4,05 (s, 1H), 4,00-3,84 (m, 10H), 3,80-3,62 (m, 3H), 2,92-2,79 (m, 6H), 2,79-2,70 (m, 2H), 2,40-2,27 (m, 3H), 2,17 (s, 1H), 2,13-1,97 (m, 10H), 1,91 (d, J = 12,5 Hz, 2H), 1,70-1,49 (m, 4H), 1,25 (d, J = 10,5 Hz, 12H)

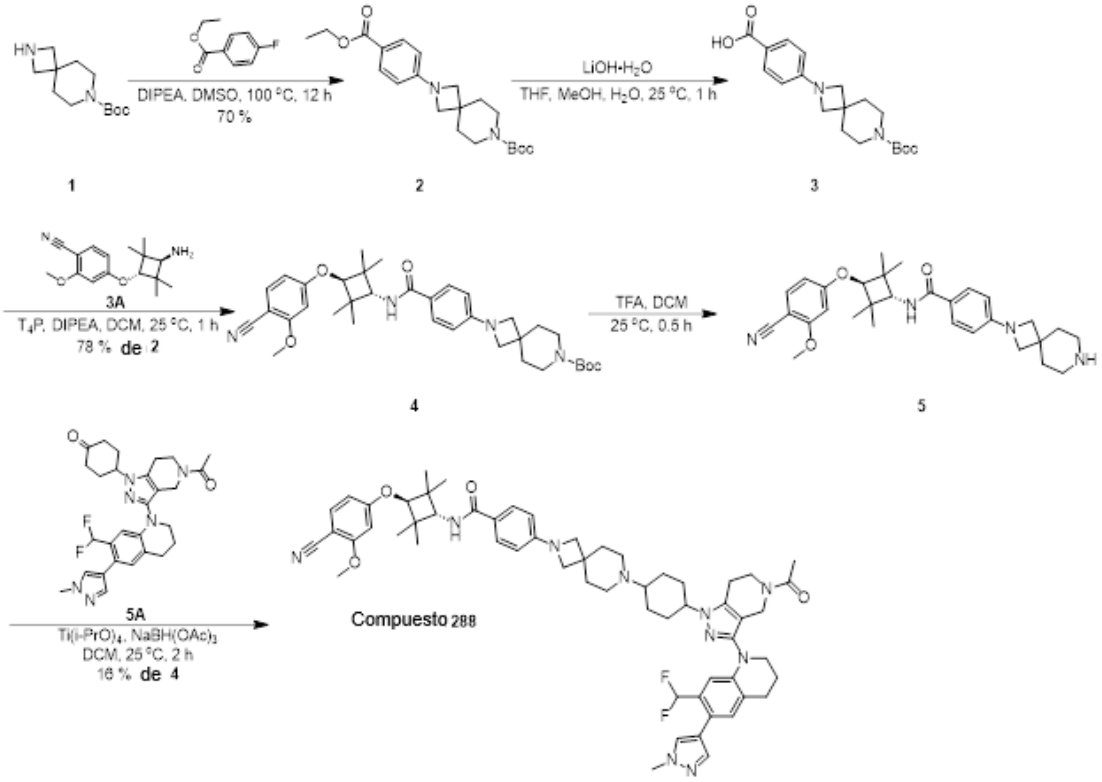
[00925] **LC-MS:** MS (ESI^+): t_R = 3,034 min, m/z = 997,8 [$M + H^+$]

[00926] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 45.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
280	4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]benzamida	1H NMR (400 MHz, METANOL-d4) δ = 8,63 (s, 1H), 7,87 (d, J = 8,0 Hz, 1H), 7,79 – 7,62 (m, 1H), 7,60 - 7,44 (m, 1H), 7,06 - 6,94 (m, 2H), 6,85 - 7,48 (m, 1H), 7,35 - 4,66 (m, 1H), 4,69 - 4,60 (m, 1H), 4,55 (d, J = 5,3 Hz, 1H), 4,38 - 4,27 (m, 1H), 4,11 - 3,96 (m, 1H), 3,83 (br t, J = 5,6 Hz, 1H), 3,09 - 2,98 (m, 1H), 2,97 - 2,79 (m, 1H), 2,71 - 3,93 (m, 1H), 2,34 (br d, J = 13,7 Hz, 1H), 2,25 - 2,97 (m, 2H), 2,97 - 1,92 (m, 1H), 1,76 - 1,61 (m, 1H), 1,53 - 1,39 (m, 1H), 1,32 - 1,17 (m, 2H).	997,7
282	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-	δ 8,75-8,32 (m, 1H), 7,95-7,84 (m, 2H), 7,76-7,67 (m, 2H), 7,24-7,17 (m, 1H), 7,09 (s, 1H), 7,04-6,96 (m, 1H),	1003,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	6,94 (s, 2H), 4,80-4,67 (m, 2H), 4,28 (brs, 2H), 4,20-4,08 (m, 2H), 4,07-3,97 (m, 2H), 3,86 (s, 3H), 3,54 (s, 3H), 3,08-2,93 (m, 2H), 2,83-2,59 (m, 2H), 2,19-2,07 (m, 2H), 2,00-1,87 (m, 2H), 1,56-1,34 (m, 2H).	
284	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-metil-amino]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	7,57 (d, J = 8,7 Hz, 1H), 7,53 (d, J = 8,1 Hz, 1H), 7,41 (d, J = 6,4 Hz, 1H), 6,90 (d, J = 8,6 Hz, 1H), 6,81 (dd, J = 2,4, 8,6 Hz, 1H), 5,98 (d, J = 8,1 Hz, 1H), 4,94 (d, J = 8,7 Hz, 1H), 4,28 (dd, J = 4,10, 11,9 Hz, 1H), 3,96 - 3,90 (m, 3H), 3,81 - 3,66 (m, 1H), 3,15 - 3,02 (m, 3H), 2,97 - 2,83 (m, 3H), 2,82 - 2,71 (m, 2H), 2,32 - 2,22 (m, 6H), 2,13 - 1,99 (m, 2H), 1,89 - 1,79 (m, 2H), 1,70 - 1,55 (m, 1H), 1,24 (d, J = 15,2 Hz, 3H).	1003,6

[00927] Ejemplo 46: Síntesis de 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2,7-diazaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 288**)



[00928] La síntesis de **5A** fue reportada en Journal of Medicinal Chemistry, 2024, vol. 67, # 7, páginas 5275 - 5304.

[00929] Una mezcla de 2,7-diazaespiro[3,5]nonano-7-carboxilato de ter-butilo (5,00 g, 22,1 mmol, 1,0 eq), 4-fluorobenzoato de etilo (3,72 g, 22,1 mmol, 3,2 ml, 1,0 eq), DIPEA (8,57 g, 66,3 mmol, 11,5 ml, 3,0 eq) en DMSO (50 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 100 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (500 ml) y se extrajo con EtOAc (200 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 3/0). El compuesto ter-butil 2-(4-etoxicarbonilfenil)-2, 7-diazaespiro [3,5] nonano-7-carboxilato (5,87 g, 15,7 mmol, 70 % de rendimiento) se obtuvo como un aceite amarillo.

[00930] **LC-MS:** MS (ESI^+): t_R = 0,706 min, m/z = 375,1 [M + H^+]

[00931] A una solución de 2-(4-etoxicarbonilfenil)-2,7-diazaespiro[3,5]nonano-7-carboxilato de ter-butilo (3,00 g, 8,01 mmol, 1,0 eq) en THF (20 ml), MeOH (20 ml) y H_2O (10 ml) se agregó LiOH•H_2O (3,36 g, 80,1 mmol, 10,0 eq). La mezcla se agitó a 25 °C durante 1 h. El pH de la mezcla de reacción se ajustó a aproximadamente 3 con HCl

(1 M) y luego se extrajo con EtOAc (100 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El compuesto ácido 4-(7-tert-butoxicarbonil-2, 7-diazaespiro [3,5] nonan-2-il) benzoico (2,78 g) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[00932] **LC-MS:** MS (ESI^+): t_R = 0,535 min, m/z = 247,0 [M - 99]

[00933] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-metoxibenzonitrilo (350 mg, 1,28 mmol, 1,0 eq) en DCM (10 ml) se le añadieron DIPEA (449 mg, 3,48 mmol, 606 µl, 3,0 eq) y T_4P (1,67 g, 2,32 mmol, 50 % de pureza, 2,0 eq). Luego se agregó ácido 4-(7-tert-butoxicarbonil-2,7-diazaespiro[3,5]nonan-2-il)benzoico (401 mg). La mezcla resultante se agitó a 25 °C durante 1 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 2/1 a 0/1). El compuesto ter-butil 2-[4-[[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]carbamoil]fenil]-2,7-diazaespiro[3,5]nonano-7-carboxilato (550 mg, 912 µmol, 78 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[00934] **LC-MS:** MS (ESI^+): t_R = 0,624 min, m/z = 603,4 [M + H^+]

[00935] A una solución de 2-[4-[[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]-2,7-diazaespiro[3,5]nonano-7-carboxilato de ter-butilo (150 mg, 248 µmol, 1,0 eq) en DCM (2 ml) se le agregó TFA (2 ml). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El compuesto N-[3-(4-ciano-3-metoxifenoxi)-2, 2, 4, 4-tetrametilciclobutil]-4-(2, 7-diazaespiro[3,5]nonan-2-il)benzamida (110 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[00936] **LC-MS:** MS (ESI^+): t_R = 0,521 min, m/z = 503,3 [M + H^+]

[00937] A una solución de 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexanona (50 mg, 95 µmol, 1,0 eq) y N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-(2,7-diazaespiro[3,5]nonan-2-il)benzamida (57 mg) en DCM (4 ml) se agregó $Ti(i\text{-}PrO)_4$ (54 mg, 191 µmol, 56 µl, 2,0 eq) a 25 °C durante 1 h, luego Se agregó $NaBH(OAc)_3$ (101 mg, 478 µmol, 5,0 eq). La mezcla resultante se agitó a 60 °C durante 1 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y

se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex Luna C18 150*25mm*10um; fase móvil: [H_2O (0,225 % FA)-ACN]; gradiente: 30 %-60 % B durante 15,0 min). El compuesto 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2,7-diazaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (16,10 mg, 15,95 μmol, 16 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

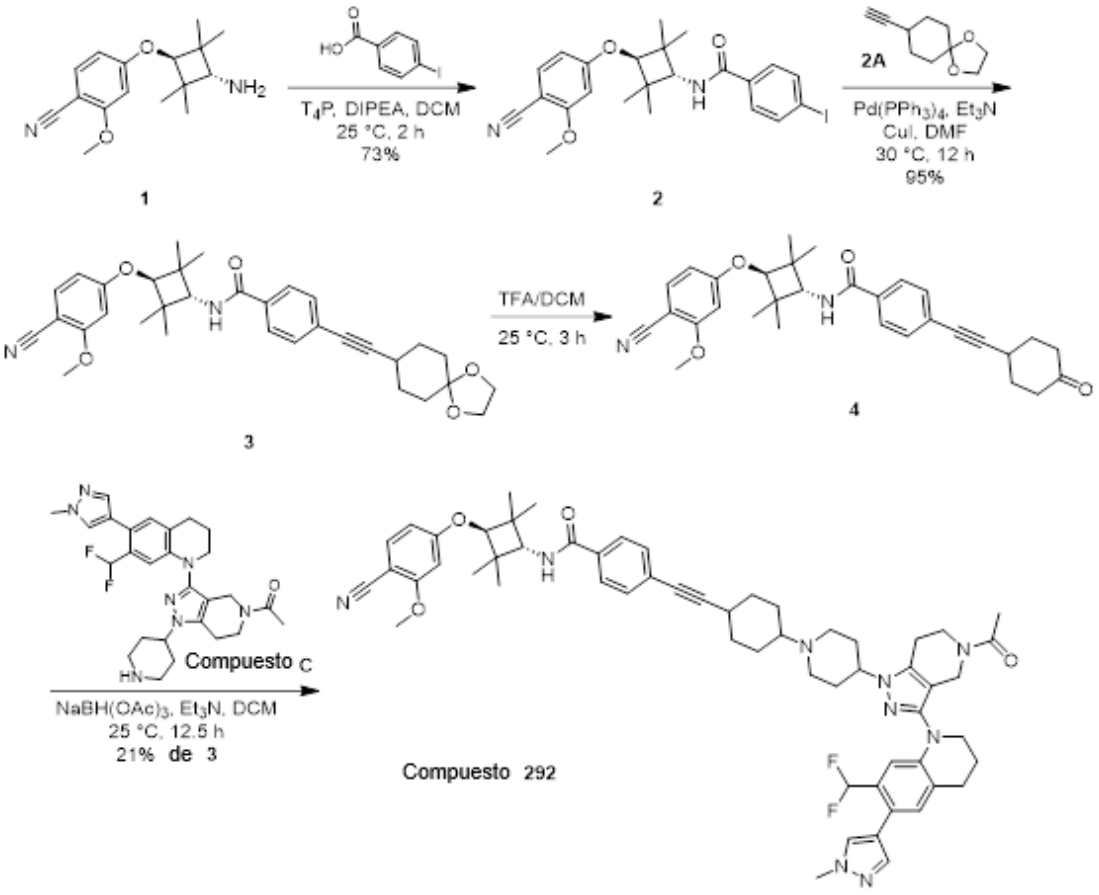
[00938] ^{1}H NMR (400 MHz, DMSO-$\mathbf{d}_6$) δ = 8,13 (s, 1H), 7,78 - 7,71 (m, 2H), 7,64 - 7,49 (m, 2H), 7,43 - 7,11 (m, 2H), 6,82 - 6,61 (m, 1H), 6,53 (d, J = 8,4 Hz, 1H), 6,41 (d, *J* = 8,4 Hz, 1H), 4,45 - 4,31 (m, 2H), 4,27 - 4,11 (m, 1H), 4,04 - 4,85 (m, 1H), 3,90 - 3,84 (m, 1H), 3,75 - 3,58 (m, 2H), 3,35 - 2,85 (m, 2H), 2,73 (s, 3H), 2,23 (s, 2H), 2,08 (s, 3H), 2,03 (s, J = 1,5 Hz, 3H), 1,21 (s, 1H), 1,14 (s, 3H).

[00939] **LC-MS:** MS (ESI$^+$): t_R = 2,515 min, m/z = 1009,8 [M + H$^+$]

[00940] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 46.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
391	2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,71 (s, 2H), 7,66 - 7,50 (m, 2H), 7,45 - 7,37 (m, 1H), 7,11 - 7,00 (m, 1H), 6,98 (d, J = 2,4 Hz, 1H), 6,95 - 6,88 (m, 1H), 6,86 - 6,78 (m, 1H), 6,73 - 6,36 (m, 1H), 5,97 (d, J = 8,0 Hz, 1H), 4,31 - 4,08 (m, 4H), 4,06 (s, 1H), 4,01 - 3,89 (m, 8H), 3,80 - 3,69 (m, 3H), 3,01 - 2,75 (m, 4H), 2,63 (s, 4H), 2,45 - 2,16 (m, 6H), 2,14 - 2,05 (m, 4H), 1,77 (s, 2H), 1,60 (t, J = 12,0 Hz, 2H), 1,25 (d, J = 14,0 Hz, 12H).	975,6

[00941] **Ejemplo 47**: Síntesis de 4-[2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclohexil]etinil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 292**)



[00942] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-metoxibenzonitrilo (1,40 g, 5,10 mmol, 1,0 eq) y ácido 4-yodobenzoico (1,52 g, 6,12 mmol, 1,2 eq) en DCM (28 ml) se añadieron DIPEA (3,32 g, 25,7 mmol, 5,0 eq) y T_4P (3,71 g, 10,3 mmol, 2,0 eq). La mezcla se agitó a 25 °C durante 2 h en atmósfera de N_2. La mezcla de reacción se diluyó con agua (40 ml) y se extrajo con acetato de etilo (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 3/1). El producto crudo se trituró con éter de petróleo/acetato de etilo = 3/1 (12 ml) a 25 °C durante 60 min. El compuesto deseado N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-iodobenzamida (1,89 g, 3,75 mmol, 73 % de rendimiento) se obtuvo como un sólido blanco.

[00943] **LC-MS:** MS (ESI^+): t_R = 0,961 min, m/z = 505,1 [M + H^+]

[00944] A una solución de N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-iodobenzamida (200 mg, 397 µmol, 1,0 eq), 8-etinil-1,4-dioxaespiro[4,5]decano (198 mg,

1,19 mmol, 3,0 eq), Et_3N (120 mg, 1,19 mmol, 3,0 eq), CuI (15 mg, 79 µmol, 0,2 eq) y $Pd(PPh_3)_4$ (92 mg, 79 µmol, 0,2 eq) en DMF (4 ml). La mezcla se agitó a 30 °C durante 12 h en atmósfera de N_2. La mezcla de reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 2/1). El compuesto deseado N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-[2-(1,4-dioxaespiro[4,5]decan-8-il)etinil]benzamida (204 mg, 376 µmol, 95 % de rendimiento) se obtuvo como un aceite marrón.

[00945] **LC-MS:** MS (ESI^+): t_R = 1,054 min, m/z = 543,4 [$M + H^+$]

[00946] A una solución de N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-[2-(1,4-dioxaespiro[4,5]decan-8-il)etinil]benzamida (96 mg, 177 µmol, 1,0 eq) en DCM (2 ml) se le agregó TFA (1,54 g, 13,5 mmol, 76,1 eq). La mezcla se agitó a 25 °C durante 3 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El compuesto N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-[2-(4-oxociclohexil)etinil]benzamida (88 mg) se obtuvo como un aceite marrón y se utilizó directamente en el siguiente paso sin purificación adicional.

[00947] **LC-MS:** MS (ESI^+): t_R = 0,642 min, m/z = 499,4 [$M + H^+$]

[00948] A una solución de N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-[2-(4-oxociclohexil)etinil]benzamida (88 mg), 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (90 mg, 177 µmol, 1,0 eq) en DCM (2 ml) se agregó Et_3N (179 mg, 1,76 mmol, 10,0 eq). La mezcla se agitó a 25 °C durante 0,5 h. Y luego se agregó $NaBH(OAc)_3$ (187 mg, 883 µmol, 5,0 eq). La mezcla de reacción se agitó a 25 °C durante 12 h. A continuación la mezcla de reacción se diluyó con EtOAc (150 ml) y agua (30 ml). Los extractos orgánicos combinados se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener un residuo crudo. El residuo se purificó mediante HPLC preparativa (condición FA; columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 33 %-63 % B durante 10 min). El compuesto deseado 4-[2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclohexil]etinil]-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]benzamida (37,71 mg, 37,57 µmol, 21 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[00949] ^1H NMR (400 MHz, CLOROFORMO-**d**) δ = 9,86 (d, *J* = 2,9 Hz, 1H), 7,89 - 7,76

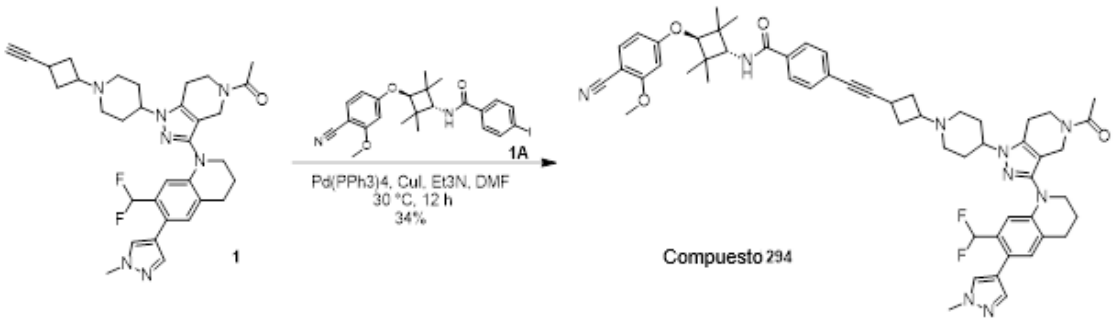
(m, 1H), 7,73 - 7,69 (m, 2H), 7,57 - 7,06 (m, 2H), 7,54 - 7,43 (m, 2H), 6,96 (br t, *J* = 2,4 Hz, 1H), 6,81 - 6,78 (m, 1H), 5,94 - 5,90 (m, 1H), 4,70 - 4,45 (m, 2H), 4,35 - 4,23 (m, 2H), 4,22 - 4,13 (m, 3H), 4,12 - 4,06 (m, 2H), 4,05 - 3,99 (m, 3H), 3,83 - 3,57 (m, 2H), 2,97 - 2,81 (m, 2H), 2,51 - 2,34 (m, 2H), 2,27 - 2,19 (m, 2H), 2,14 - 2,01 (m, 2H), 1,98 - 1,85 (m, 2H).

[00950] LC-MS: MS (ESI^+): t_R = 2,461 min, m/z = 992,6 [M + H^+]

[00951] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 47.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
293	2-[2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclohexil]etinil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 9,14 - 9,02 (m, 2H), 8,66 (s, 1H), 7,58 (d, *J* = 8,8 Hz, 1H), 7,53 (d, *J* = 6,0 Hz, 1H), 7,42 - 7,39 (m, 1H), 7,02 (s, 1H), 6,97 (s, 1H), 6,88 - 6,78 (m, 2H), 6,70 - 6,26 (m, 2H), 5,49 - 4,44 (m, 1H), 4,39 - 4,22 (m, 1H), 4,20 - 4,08 (m, 3H), 4,00 - 3,93 (m, 4H), 3,91 - 3,88 (m, 1H), 3,76 - 3,65 (m, 3H), 3,21 - 2,96 (m, 2H), 2,93 - 2,80 (m, 3H), 2,76 - 2,57 (m, 2H), 2,54 - 2,45 (m, 3H), 2,21 (s, 2H), 2,18 - 2,16 (m, 2H), 2,09 - 2,04 (m, 4H), 2,00 (d, *J* = 10,0 Hz, 4H), 1,71 - 1,50 (m, 2H), 1,45 - 1,35 (m, 2H), 1,33 - 1,29 (m, 6H), 1,24 (s, 6H)	998,4

[00952] Ejemplo 48: Síntesis de 4-[2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutil]etinil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 294**)



[00953] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(3-etinilciclobutil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (80 mg, 136 µmol, 1,0 eq) y N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-iodobenzamida (69 mg, 136 µmol, 1,0 eq) en DMF (2 ml) se le agregó Et_3N (41 mg, 408 µmol, 3,0 eq) y CuI (5 mg, 27,2 µmol, 0,2 eq) y $Pd(PPh_3)_4$ (31 mg, 27,2 µmol, 0,2 eq) a 25 °C. La mezcla se agitó a 30 °C durante 12 h bajo N_2. La mezcla de reacción se vertió en agua fría (20 ml). La fase acuosa se extrajo con acetato de etilo (20 ml x 3). La capa orgánica recolectada se secó en Na_2SO_4 anhidro y se concentró al vacío. El residuo se purificó mediante HPLC semipreparativa de fase inversa (columna: Phenomenex Luna C18 150 × 25mm × 10um; fase móvil: [agua (FA)-ACN]; gradiente: 31 %-61 % B durante 10 min). El compuesto 4-[2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutil]etinil]-N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]benzamida (44,60 mg, 46,2 µmol, 34 % de rendimiento) se obtuvo como un sólido blanquecino.

[00954] **^{1}H NMR** (400 MHz, CLOROFORMO-d) δ = 7,69 (d, J = 8,0 Hz, 2H), 7,53 (d, J = 5,6 Hz, 1H), 7,46 (d, J = 8,4 Hz, 3H), 7,43 - 7,37 (m, 1H), 7,08 - 6,97 (m, 1H), 6,87 (d, J = 5,6 Hz, 1H), 6,71 - 6,35 (m, 3H), 6,20 (d, J = 8,0 Hz, 1H), 4,74 (d, J = 2,4 Hz, 1H), 4,24 (s, 1H), 4,17 - 4,09 (m, 2H), 4,06 (s, 1H), 4,00 - 3,86 (m, 8H), 3,80 - 3,64 (m, 3H), 3,13 - 2,99 (m, 2H), 2,97 - 2,70 (m, 6H), 2,55 (d, J = 7,2 Hz, 2H), 2,29 - 2,19 (m, 3H), 2,18 - 2,13 (m, 2H), 2,11 - 2,03 (m, 5H), 2,02 - 1,95 (m, 2H), 1,27 (s, 6H), 1,25 (s, 6H)

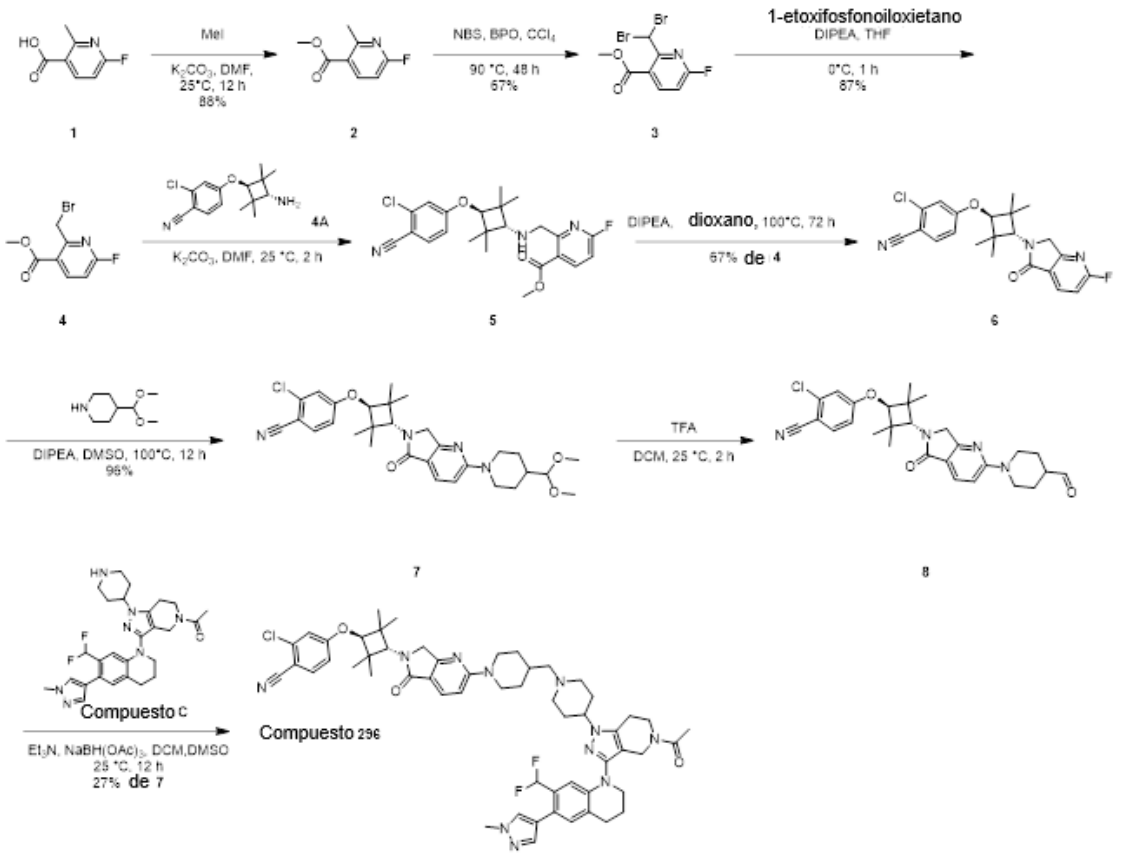
[00955] **LC-MS:** MS (ESI^+): t_R = 2,099 min, m/z =964,2 [M + H^+]

[00956] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 48.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
295	2-[2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-	δ = 9,03 (s, 2H), 7,63 - 7,49 (m, 2H), 7,41 (d, *J* = 6,8 Hz, 1H), 7,09 - 6,94 (m, 2H),	970,3

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutil]etinil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	6,93 - 6,76 (m, 2H), 6,76 - 6,24 (m, 2H), 4,28 - 4,14 (m, 2H), 4,10 (d, *J* = 12,4 Hz, 2H), 3,96 (s, 3H), 3,89 (t, *J* = 5,6 Hz, 1H), 3,78 - 3,64 (m, 3H), 3,49 (s, 4H), 3,19 - 3,04 (m, 2H), 3,02 - 2,96 (m, 1H), 2,91 - 2,81 (m, 3H), 2,77 - 2,71 (m, 1H), 2,63 - 2,53 (m, 2H), 2,41 (s, 1H), 2,30 - 2,23 (m, 2H), 2,16 (s, 2H), 2,11 - 2,02 (m, 6H), 1,29 (s, 6H), 1,24 (s, 6H)	

[00957] Ejemplo 49: Síntesis de 4-[3-[2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametil-ciclobutoxi]-2-cloro-benzonitrilo (**Compuesto 296**)



[00958] A una solución de ácido 6-fluoro-2-metil-piridina-3-carboxílico (2,00 g, 12,89 mmol, 1,0 eq) en DMF (20 ml) se le añadieron K_2CO_3 (4,00 g, 28,94 mmol, 2,24 eq) y

MeI (2,50 g, 17,61 mmol, 1,10 ml, 1,37 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla se neutralizó con agua (100 ml) y la fase acuosa se extrajo con acetato de etilo (150 ml × 2). Las capas orgánicas combinadas se lavaron con salmuera (120 ml), se secaron sobre Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 6/1) para obtener el compuesto 6 (1,91 g, 88 % de rendimiento) como un sólido amarillo.

[00959] LC-MS: MS (ESI^+): t_R = 0,508 min, m/z = 170,1 [$M+H^+$]

[00960] A una solución de 6-fluoro-2-metil-piridina-3-carboxilato de metilo (1,91 g, 11,29 mmol, 1,0 eq) en CCl_4 (20 ml) se le añadieron BPO (1,4 g, 5,78 mmol, 0,5 eq) y NBS (6,00 g, 33,71 mmol, 3,0 eq). La mezcla se agitó a 90 °C durante 48 h. La mezcla se concentró al vacío. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 20/1 a 10/1) para obtener el compuesto 2 (2,45 g, 67 % de rendimiento) como un sólido amarillo.

[00961] LC-MS: MS (ESI^+): t_R = 0,574 min, m/z = 327,9 [$M+H^+$]

[00962] A una solución de 2-(dibromometil)-6-fluoro-piridina-3-carboxilato de metilo (2,45 g, 7,49 mmol, 1,0 eq) en THF (30 ml) se le añadieron DIPEA (4,08 g, 31,58 mol, 5,5 ml, 4,2 eq) y 1-etoxifosfonoiloxietano (3,22 g, 23,29 mmol, 3 ml, 3,1 eq). La mezcla se agitó a 0 °C durante 1 h. La reacción se detuvo añadiendo 250 ml de agua a 0 °C, y luego se diluyó con acetato de etilo (100 ml) y se extrajo con acetato de etilo (100 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 50/1 a 10/1) para obtener el compuesto 2 (1,6 g, 87 % de rendimiento) como un sólido amarillo.

[00963] LC-MS: MS (ESI^+): t_R = 0,551 min, m/z = 248,0 [$M+H^+$]

[00964] A una solución de 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-cloro-benzonitrilo (650 mg, 2,06 mmol, 1,02 eq) y K_2CO_3 (700 mg, 5,06 mmol, 1,0 ml, 2,51 eq) en DMF (2 ml) se agregó gota a gota una solución de 2-(bromometil)-6-fluoro-piridina-3-carboxilato de metilo (0,5 g, 2,02 mmol, 1,0 eq) en DMF (1 ml) a 25 °C y se agitó a 25 °C durante 2 h bajo N_2. La mezcla de reacción se neutralizó añadiendo 20 ml de agua a 0 °C, y luego se diluyó con 20 ml de acetato de etilo y se extrajo con acetato de etilo (20 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml × 2), se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener 2-[[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]amino]metil]-6-fluoropiridina-3-

carboxilato de metilo (0,89 g) como una goma amarilla y se utilizó en el siguiente paso sin purificación adicional.

[00965] **LC-MS:** MS (ESI$^+$): t_R = 0,547 min, m/z = 446,2 [M+H$^+$]

[00966] A una solución de 2-[[[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]amino]metil]-6-fluoropiridina-3-carboxilato de metilo (1,78 g, 3,99 mmol, 1,0 eq) en dioxano (20 ml) se agregó DIPEA (1,48 g, 11,48 mmol, 2,0 ml, 2,9 eq), la mezcla se agitó a 100 °C durante 72 h bajo N_2. La mezcla de reacción se neutralizó añadiendo 250 ml de agua a 0 °C, y luego se diluyó con 100 ml de acetato de etilo y se extrajo con acetato de etilo (100 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol=100/1 a 50/1) para obtener 2-cloro-4-[3-(2-fluoro-5-oxo-7H-pirrolo[3,4-b]piridin-6-il)-2,2,4,4-tetrametilciclobutoxi]benzonitrilo (1,10 g, 2,66 mmol, 67 % de rendimiento en dos pasos) como un sólido blanco.

[00967] **LC-MS:** MS (ESI$^+$): t_R = 0,640 min, m/z = 414,2 [M+H$^+$]

[00968] A una solución de 2-cloro-4-[3-(2-fluoro-5-oxo-7H-pirrolo[3,4-b]piridin-6-il)-2,2,4,4-tetrametil-ciclobutoxi]benzonitrilo (300 mg, 725 µmol, 1,0 eq), 4-(dimetoximetil)piperidina (127 mg, 798 µmol, 1,1 eq) en DMSO (4 ml) se le agregó DIPEA (297 mg, 2,30 mmol, 0,4 ml, 3,2 eq). La mezcla se agitó a 100 °C durante 30 min. La reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (100 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/0 a 1/1) para obtener 2-cloro-4-[3-[2-[4-(dimetoximetil)-1-piperidil]-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametilciclobutoxi]benzonitrilo (383 mg, 693 µmol, 96 % de rendimiento) como un sólido blanco.

[00969] **LC-MS:** MS (ESI$^+$): t_R = 0,961 min, m/z = 553,3 [M+H$^+$]

[00970] A una solución de 2-cloro-4-[3-[2-[4-(dimetoximetil)-1-piperidil]-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametil-ciclobutoxi]benzonitrilo (190 mg, 344 µmol, 1,0 eq) en DCM (2 ml) se le agregó TFA (1 ml). La mezcla se agitó a 25 °C durante 2 h. La mezcla de reacción se concentró para dar 2-cloro-4-[3-[2-(4-formil-1-piperidil)-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametil-ciclobutoxi]benzonitrilo (174 mg) como un sólido blanco y se utilizó en el siguiente paso sin purificación adicional.

[00971] **LC-MS:** MS (ESI$^+$): t_R = 0,681 min, m/z = 507,2 [M+H$^+$]

[00972] A una solución de 2-cloro-4-[3-[2-(4-formil-1-piperidil)-5-oxo-7H-pirrolo[3,4-

b]piridin-6-il]-2,2,4,4-tetrametil-ciclobutoxi]benzonitrilo (174 mg), 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (175 mg, 344 µmol, 1,0 eq) en DCM (1 ml) y DMSO (1 ml) se agregó Et_3N (182 mg, 1,80 mmol, 0,25 ml, 5,2 eq) a 25 °C durante un período de 0,5 h bajo N_2. Luego se agregó $NaBH(OAc)_3$ (220 mg, 1,04 mmol, 3,0 eq). La mezcla se agitó a 25 °C durante 30 min. La reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (100 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-60 % B durante 10 min) para dar 4-[3-[2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-1-piperidil]-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametil-ciclobutoxi]-2-cloro-benzonitrilo (92,46 mg, 91 µmol, 27 % de rendimiento en dos pasos) como un sólido blanco.

[00973] **^{1}H NMR** (400 MHz, DMSO-d6): δ = 7,89 (d, J = 8,8 Hz, 1H), 7,75 (s, 1H), 7,69 (d, J = 8,8 Hz, 1H), 7,50 (s, 1H), 7,27 (d, J = 2,4 Hz, 1H), 7,10 (s, 1H), 7,05 (d, J = 2,4, 8,8 Hz, 1H), 6,96 - 6,63 (m, 3H), 4,59 (s, 2H), 4,50 (s, 1H), 4,43 (d, J = 12,0 Hz, 2H), 4,29 (s, 1H), 4,19 - 4,10 (m, 2H), 4,05 - 3,99 (m, 1H), 3,86 (s, 3H), 3,73 (d, J = 5,2 Hz, 1H), 3,68 (d, J = 5,2 Hz, 2H), 3,59 (d, J = 5,2 Hz, 2H), 3,17 (s, 1H), 2,98 - 2,89 (m, 4H), 2,85 (d, J = 5,6 Hz, 3H), 2,73 (s, 1H), 2,18 (d, J = 6,0 Hz, 2H), 2,08 - 2,02 (m, 4H), 2,02 - 1,93 (m, 4H), 1,87 - 1,78 (m, 4H), 1,37 (s, 6H), 1,18 - 0,99 (m, 8H).

[00974] **LC-MS:** MS (ESI$^+$): t_R = 1,974 min, m/z = 1000,6 [M + H$^+$]

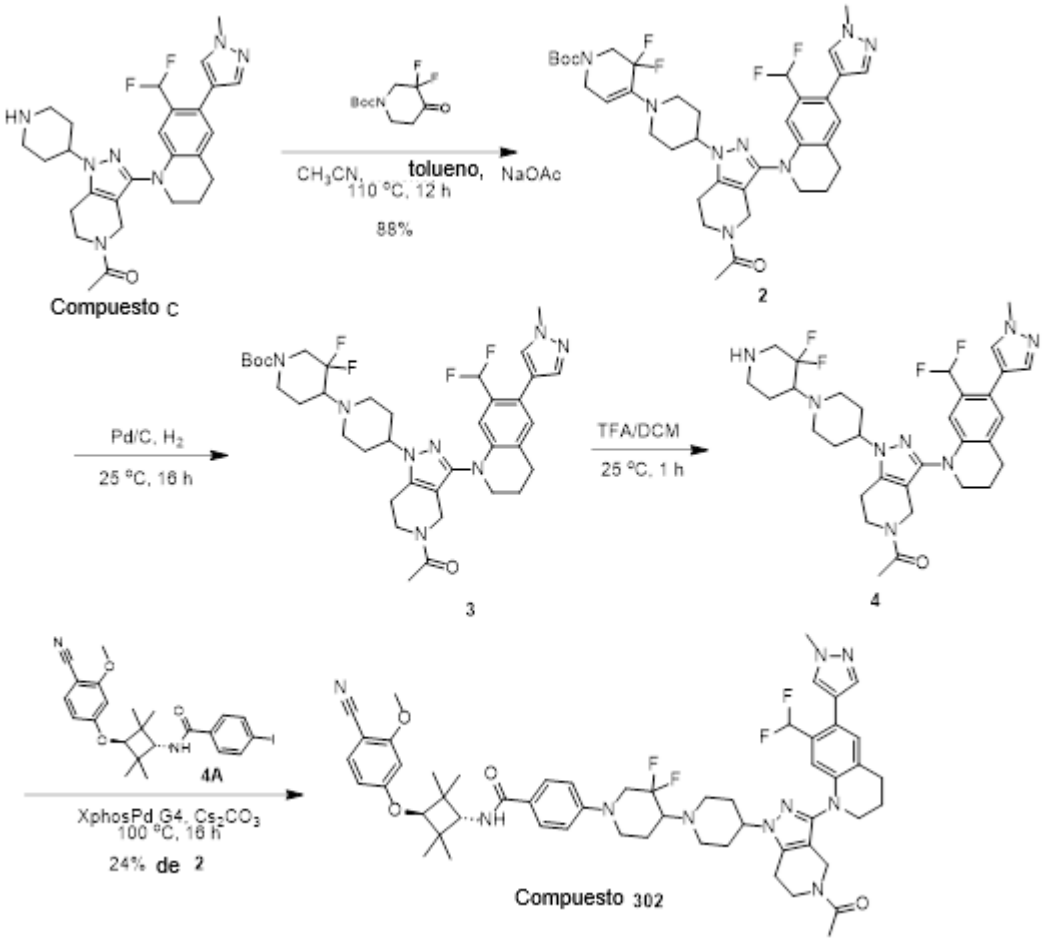
[00975] **SFC**: t_{R1} = 1,260 min, 99 %.

[00976] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 49.

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS (M+H)$^+$:
297	4-[3-[2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametil-ciclobutoxi]-2-cloro-benzonitrilo	δ = 7,89 (d, *J* = 8,8 Hz, 1H), 7,77 - 7,68 (m, 2H), 7,49 (s, 1H), 7,32 - 7,23 (m, 1H), 7,10 (s, 1H), 7,08 - 7,03 (m, 1H), 6,94 - 6,63 (m, 3H), 4,60 (s, 2H), 4,52 - 4,45 (m, 3H), 4,29 (s, 1H), 4,19 - 3,97 (m, 9H), 3,88 - 3,84 (m, 3H), 3,76 - 3,65 (m, 3H), 3,60 - 3,55 (m, 3H), 3,02 - 2,88 (m, 5H), 2,84 (d, *J* = 4,8 Hz, 3H), 2,71 - 2,60 (m, 2H), 2,34 - 2,27 (m, 2H), 2,09 - 2,05 (m, 4H), 2,02 - 1,93 (m,	986,6

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
		5H), 1,88 - 1,80 (m, 4H), 1,52 - 1,40 (m, 3H), 1,37 (s, 5H), 1,30 - 1,16 (m, 2H), 1,13 (s, 5H), 1,09 - 1,02 (m, 1H), 0,91 - 0,78 (m, 1H)	
298	4-[3-[2-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-3-azaespiro[5,5]undecan-3-il]-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametilciclobutoxi]-2-clorobenzonitrilo	δ = 7,89 (d, J = 8,8 Hz, 1H), 7,75 (s, 1H), 7,69 (d, J = 8,8 Hz, 1H), 7,50 (s, 1H), 7,27 (d, J = 2,4 Hz, 1H), 7,10 (s ancho, 1H), 7,07 - 7,02 (m, 1H), 6,96 - 6,62 (m, 3H), 4,59 (s, 2H), 4,50 (s, 1H), 4,29 (s, 1H), 4,22 - 4,12 (m, 2H), 4,10 - 4,00 (m, 1H), 3,87 (s, 3H), 3,74 (d ancho, J = 5,2 Hz, 1H), 3,67 (br s, 5H), 3,62 - 3,55 (m, 2H), 2,91 - 2,71 (m, 4H), 2,13 - 1,97 (m, 7H), 1,85 (br d, J = 10,4 Hz, 2H), 1,74 (br d, J = 8,8 Hz, 2H), 1,62 (br s, 2H), 1,43 - 1,28 (m, 9H), 1,25 - 1,19 (m, 1H), 1,13 (s, 6H)	971,6
299	4-[3-[2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carbonilo]-1-piperidilo]-5-oxo-7H-pirrolo[3,4-b]piridin-6-il]-2,2,4,4-tetrametil-ciclobutoxi]-2-cloro-benzonitrilo	*δ* = 7,89 (d, J = 8,8 Hz, 1H), 7,77 - 7,73 (m, 1H), 7,71 (d, J = 8,8 Hz, 1H), 7,50 (s, 1H), 7,27 (d, J = 2,4 Hz, 1H), 7,10 (s, 1H), 7,05 (dd, J = 2,4, 8,8 Hz, 1H), 6,93 - 6,66 (m, 3H), 4,60 (s, 2H), 4,51 - 4,41 (m, 4H), 4,39 - 4,33 (m, 1H), 4,29 (s, 1H), 4,16 (br d, J = 18,4 Hz, 3H), 3,86 (s, 3H), 3,78 - 3,67 (m, 2H), 3,61 - 3,55 (m, 2H), 3,22 - 3,14 (m, 1H), 3,06 (br t, J = 11,6 Hz, 3H), 2,88 (br d, J = 6,0 Hz, 1H), 2,84 (br s, 2H), 2,78 - 2,64 (m, 2H), 2,08 (s, 2H), 2,01 - 1,88 (m, 6H), 1,71 (br d, J = 11,2 Hz, 3H), 1,61 - 1,49 (m, 2H), 1,37 (s, 6H), 1,13 (s, 6H)	1014,6

[00977] Ejemplo 50: Síntesis de 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-3,3-difluoro-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 302**)



[00978] Una mezcla de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (300 mg, 549 µmol, 1,0 *eq*, sal de HCl), 3,3-difluoro-4-oxo-piperidina-1-carboxilato de ter-butilo (388 mg, 1,65 mmol, 3,0 *eq*), NaOAc (180 mg, 2,20 mmol, 4,0 *eq*), HOAc (99 mg, 1,65 mmol, 94 µl, 3,0 *eq*) y 4A MS (2 g) en CH_3CN (12 ml) y Tol. La mezcla se desgasificó y se purgó con N_2, y a continuación se agitó la mezcla a 110 °C durante 12 h en atmósfera de N_2. La solución de mezcla se filtró y la torta de filtro se lavó con agua (100 l). La solución se lavó con $NaHCO_{33}$ saturado (20 ml), salmuera (20 ml), se secó, se filtró y se concentró para obtener un residuo. El residuo se purificó mediante *prep*-TLC (EA) para obtener el producto deseado ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-3,3-difluoro-2,6-dihidropiridina-1-carboxilato (350 mg, 482 µmol, 88 % de rendimiento) como un sólido amarillo.

[00979] **LC-MS:** MS (ESI^+): t_R = 0,611 min, m/z = 727,3 [M + H^+]

[00980] Pd/C (500 mg) se agregó a un matraz de fondo redondo de un solo cuello de 100 ml bajo N_2, y luego se agregó THF (20 ml) a 25 °C bajo N_2. Después de la adición,

se agregó ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-3,3-difluoro-2,6-dihidropiridina-1-carboxilato (350 mg, 482 µmol, 1,0 *eq*) bajo N_2. La suspensión se desgasificó y se purgó con H_2 3 veces. La mezcla se agitó bajo H_2 (15 psi) a 25 °C durante 16 h. La mezcla de reacción se filtró y el filtro se concentró para obtener el producto. El producto crudo se usó en la siguiente etapa sin purificación adicional. El compuesto ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-3,3-difluoro-piperidina-1-carboxilato (180 mg) se obtuvo como un sólido amarillo.

[00981] **LC-MS:** MS (ESI^+): t_R = 0,507 min, m/z = 729,4 [M + H^+]

[00982] A una solución de ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-3,3-difluoro-piperidina-1-carboxilato (180 mg) en DCM (5 ml) se le agregó TFA (1 ml). La mezclar se agitó a 25 °C durante 1 h. Se agregó solución acuosa saturada de $NaHCO_3$ a la mezcla de reacción hasta alcanzar un pH de 7-8. Luego, la mezcla se extrajo con EtOAc (20 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(3,3-difluoro-4-piperidil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (155 mg) se obtuvo como un sólido amarillo.

[00983] LC-MS (ESI, m/z): 629,3 [M+H]

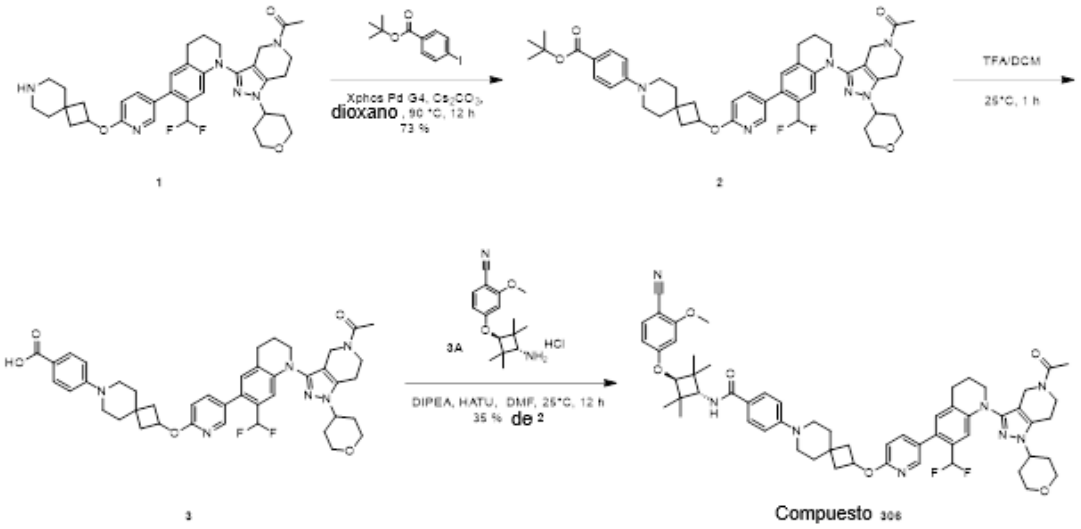
[00984] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-(3,3-difluoro-4-piperidil)-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (75 mg) y N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-iodobenzamida (72 mg, 143 µmol, 1,2 eq) en dioxano (2 ml) se le agregó Xphos Pd G4 (21 mg, 24 µmol, 0,2 eq) y Cs_2CO_3 (117 mg, 358 µmol, 3,0 eq). La mezcla se agitó a 100 °C durante 16 h en atmósfera de N_2. La mezcla de reacción se concentró para proporcionar un residuo. El residuo se purificó mediante *prep*-HPLC (columna: Waters xbridge 150*25mm 10um; fase móvil: [agua (hidróxido de amonio v/v)-ACN]; gradiente: 46 %-76 % B durante 9 min). El compuesto 4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-3,3-difluoro-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (57,16 mg, 55,81 µmol, 24 % de rendimiento en tres pasos) se obtuvo como un sólido blanquecino.

[00985] Compuesto **68**: 1H NMR (400 MHz, CD_3OD) δ 7,76 (d, *J* = 5,6 Hz, 1H), 7,64 (s,

1H), 7,53 (s, 1H), 7,51 (d, *J* = 8,8 Hz, 1H), 7,09 (d, *J* = 5,6 Hz, 1H), 7,03 (d, *J* = 9,2 Hz, 2H), 6,72 - 6,55 (m, 1H), 6,55 - 6,42 (m, 2H), 4,26 - 4,21 (m, 2H), 4,13 - 4,04 (m, 1H), 3,93 - 3,81 (m, 1H), 3,75 - 3,67 (m, 2H), 3,25 - 2,93 (m, 2H), 2,91 - 2,82 (m, 2H), 2,18 - 1,93 (m, 2H), 1,41 - 1,15 (m, 2H).

[00986] **LC-MS:** MS (ESI$^+$): t_R = 2,028 min, m/z = 1005,4 [M + H$^+$]

[00987] **Ejemplo 51**: Síntesis de 4-[2-[[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]oxi]-7-azaespiro[3,5]nonan-7-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 306**)



[00988] A una mezcla de 1-[3-[6-[6-(7-azaespiro[3,5]nonan-2-iloxi)-3-piridil]-7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (150 mg, 231 µmol, 1,0 *eq*) y 4-yodobenzoato de ter-butilo (105 mg, 347 µmol, 1,5 *eq*) en dioxano (3 ml) se agregó Cs_2CO_3 (226 mg, 695 µmol, 3,0 *eq*) y Xphos Pd G4 (19 mg, 23 µmol, 0,1 *eq*) bajo N_2. La mezcla se agitó a 90 °C durante 12 h. La mezcla se filtró y se concentró para obtener el compuesto 295j (85,0 mg) como un aceite amarillo. El residuo se purificó mediante TLC preparativa (SiO_2, DCM/MeOH = 10/1). El compuesto ter-butil 4-[2-[[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]oxi]-7-azaespiro[3,5]nonan-7-il]benzoato (142 mg, 170 µmol, 73 % de rendimiento) se obtuvo como un sólido blanco.

[00989] **LC-MS:** MS (ESI$^+$): t_R = 0,998 min, m/z = 823,3 [M + H$^+$]

[00990] A una mezcla de 4-[2-[[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]oxi]-7-

azaespiro[3,5]nonan-7-il]benzoato de ter-butilo (142 mg, 172 µmol, 1,0 *eq*) en DCM (3 ml) se agregó TFA (1,54 g, 13,4 mmol, 1 ml, 78,0 *eq*). La mezcla se agitó a 25 °C durante 1 h. La mezcla se concentró al vacío. El compuesto ácido 4-[2-[[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]oxi]-7-azaespiro[3,5]nonan-7-il]benzoico (132 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[00991] **LC-MS:** MS (ESI^+): t_R = 0,872 min, m/z = 767,3 [M + H^+]

[00992] A una mezcla de ácido 4-[2-[[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]oxi]-7-azaespiro[3,5]nonan-7-il]benzoico (132 mg) y 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (53 mg, 172 µmol, 1,0 *eq*) en DMF (2 ml) se agregó DIPEA (111 mg, 860 µmol, 149 µl, 5,0 *eq*) y HATU (78 mg, 206 µmol, 1,2 *eq*). La mezcla se agitó a 25 °C durante 12 h. La mezcla se filtró y se concentró para obtener el compuesto 295j (85,0 mg) como un aceite amarillo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 65 %-95 % B durante 10 min). El compuesto 4-[2-[[5-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-il]-2-piridil]oxi]-7-azaespiro[3,5]nonan-7-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (62,61 mg, 60,41 µmol, 35 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[00993] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8,10 (s, 1H), 7,81 - 7,70 (m, 1H), 7,68 - 7,57 (m, 2H), 7,56 - 7,43 (m, 2H), 7,08 - 7,28 (m, 1H), 7,28 - 6,82 (m, 2H), 6,81 - 6,50 (m, 1H), 5,32 - 5,15 (m, 1H), 4,37 - 4,25 (m, 2H), 4,23 - 4,13 (m, 1H), 4,09 - 4,02 (m, 1H), 3,99 - 3,88 (m, 1H), 3,80 - 3,68 (m, 1H), 3,65 - 3,57 (m, 1H), 3,51 - 3,43 (m, 2H), 3,31 - 3,27 (m, 2H), 3,25 - 3,17 (m, 2H), 2,91 - 2,74 (m, 1H), 2,48 - 2,39 (m, 1H), 2,03 - 1,94 (m, 1H), 1,93 - 1,79 (m, 1H), 1,76 - 1,63 (m, 1H).

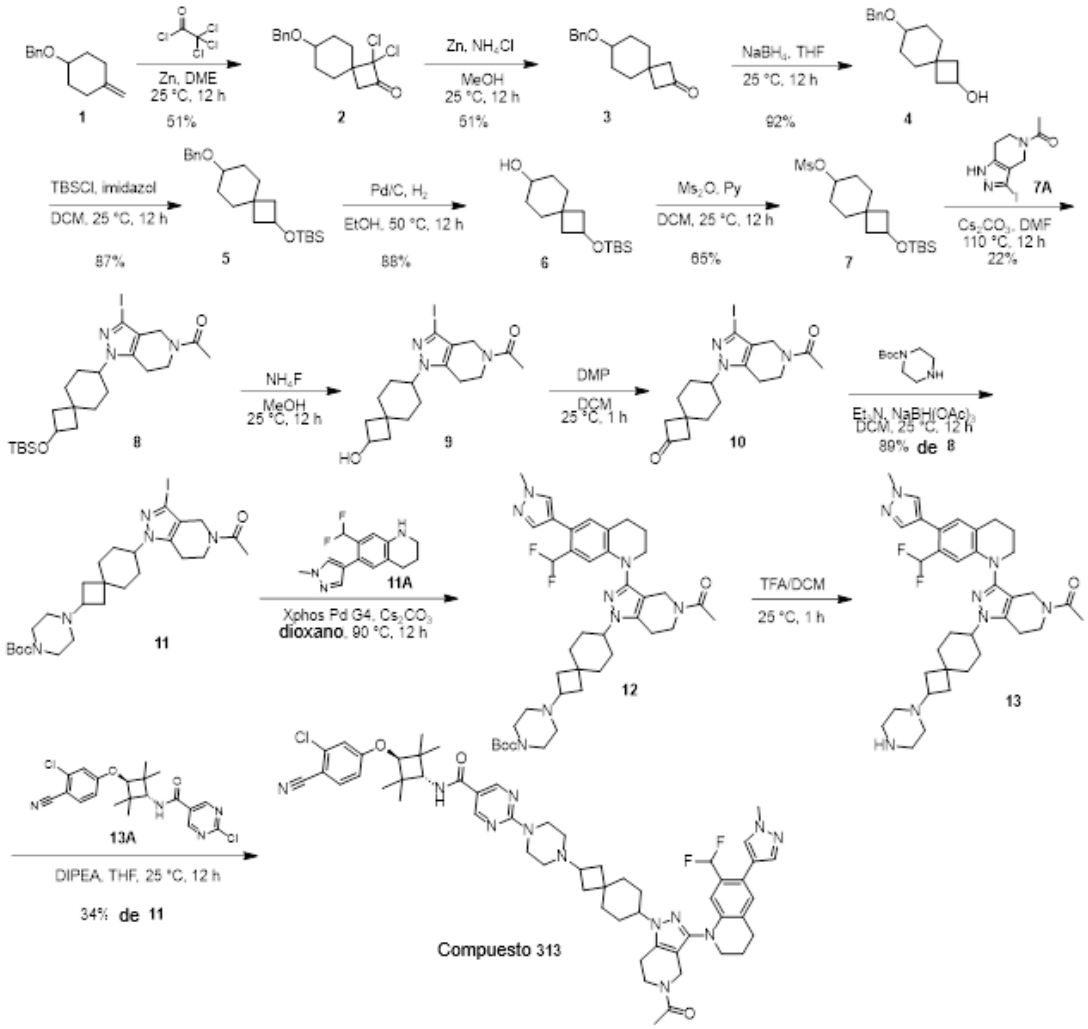
[00994] **LC-MS:** MS (ESI^+): t_R = 2,917 min, m/z = 1023,6 [M + H^+]

[00995] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 51.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS $(M+H)^+$:**
307	4-[2-[4-[1-(5-acetil-1-tetrahidropiran-4-il-6,7-dihidro-4H-pirazolo[4,3-c]piridin-3-il)-7-(difluorometil)-3,4-dihidro-2H-quinolin-6-	δ = 7,69 (d, *J*=8,8 Hz, 2 H) 7,46 (d, *J*=8,8 Hz, 1 H) 7,22 (d, *J*=8,4 Hz, 2 H) 7,02 – 6,91 (m, 3 H) 6,90 - 6,80 (m, 3 H) 6,61 - 6,27 (m, 3	1022,4

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	il]fenoxi]-7-azaespiro[3,5]nonan-7-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	H) 6,12 (d, *J*=8,4 Hz, 1 H) 4,83 - 4,69 (m, 1 H) 4,28 (s, 1 H) 4,21 - 4,09 (m, 5 H) 4,05 (s, 1 H) 3,92 (s, 4 H) 3,80 - 3,68 (m, 3 H) 3,53 (m, 2 H) 3,37 - 3,22 (m, 4 H) 2,95 - 2,80 (m, 3 H) 2,76 (m, 1 H) 2,55 - 2,44 (m, 2 H) 2,39 - 2,24 (m, 2 H) 2,17 (s, 1 H) 2,14 – 1,99 (m, 6 H) 1,88 (m, 2 H) 1,83 - 1,77 (m, 4 H) 1,25 (d, *J*=10,0 Hz, 12 H)	

[00996] Ejemplo 52: Síntesis de 2-[4-[7-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]espiro[3,5]nonan-2-il]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 313**)



[00997] La síntesis de **1** fue reportada en Bioorganic and Medicinal Chemistry Letters, 2019, vol. 29, # 16, páginas 2100 - 2106.

[00998] La síntesis de **7A** fue reportada en Journal of Medicinal Chemistry, 2024, vol. 67, # 7, páginas 5275 - 5304.

[00999] La síntesis de **11A** fue reportada en Journal of Medicinal Chemistry, 2017, vol. 60, # 22, páginas 9162 - 9183

[001000] La síntesis de **13A** fue reportada en Journal of Medicinal Chemistry, 2023, vol. 66, # 7, páginas 4784 - 4801.

[001001] A una solución de (4-metilenciclohexoxi)metilbenceno (23,00 g, 113,7 mmol, 1,0 *eq*), Zn (29,93 g, 457,7 mmol, 4,0 *eq*) en dioxano (230 ml) se agregó gota a gota la solución de 1,2-dimetoxietano (20,49 g, 227,4 mmol, 23,6 ml, 2,0 *eq*) y cloruro de 2,2,2-tricloroacetilo (31,01 g, 170,6 mmol, 190 ml, 1,5 *eq*) en dioxano (100 ml) bajo N_2. La mezcla se agitó a 25 °C durante 12 h en atmósfera de N_2. La mezcla de reacción se ajustó con una solución acuosa saturada de $NaHCO_3$ (150 ml) a pH = 7~8 y luego se

extrajo con EA (200 ml × 3). Las capas orgánicas combinadas se secaron y se concentraron a presión reducida. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/0 a 5/1) para obtener el producto 7-benciloxi-3,3-dicloro-espiro[3,5]nonan-2-ona (18,00 g, 57,47 mmol, 51 % de rendimiento) como una goma de color amarillo claro.

[001002] LC-MS: MS (ESI^+): t_R = 0,662 min, m/z = 335,1 [M + Na^+]

[001003] Una mezcla de 7-benciloxi-3,3-dicloro-espiro[3,5]nonan-2-ona (18,00 g, 57,47 mmol, 1,0 *eq*), Zn (18,58 g, 284,1 mmol, 4,9 *eq*), NH_4Cl (18,44 g, 344,8 mmol, 6,0 *eq*) en MeOH (180 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 25 °C durante 12 h bajo atmósfera de N2. La mezcla de reacción se ajustó con una solución acuosa saturada de $NaHCO_3$ (150 ml) a pH = 7~8 y luego se extrajo con EA (200 ml x 3). Las capas orgánicas combinadas se secaron y se concentraron a presión reducida. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/0 a 3/1) para obtener el producto 7-benciloxispiro[3,5]nonan-2-ona (7,20 g, 29,47 mmol, 51 % de rendimiento) como un aceite incoloro.

[001004] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7,36 - 7,30 (m, 4H), 7,29 - 7,28 (m, 2H), 4,58 (d, *J* = 2,0 Hz, 1H), 3,50 - 3,48 (m, 1H), 2,81 - 2,78(m, 1H), 4,69 - 4,57 (m, 1H), 1,89 (s, 2H), 1,87 - 3,83(m, 1H), 1,63 - 1,55 (m, 1H).

[001005] A una solución de 7-benciloxispiro[3,5]nonan-2-ona (7,20 g, 29,47 mmol, 1,0 *eq*) en THF (75 ml) se agregó $NaBH_4$ (2,23 g, 58,94 mmol, 2,0 *eq*) a 0 °C bajo N_2. La mezcla se agitó a 25 °C durante 12 h bajo N_2. La mezcla se neutralizó mediante la adición de NH_4Cl saturado (50 ml), se diluyó con agua (50 ml) y se extrajo con EtOAc (100 ml × 3). Los extractos orgánicos combinados se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener un residuo crudo. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 50/1 a 5/1) para obtener el compuesto 7 (6,70 g, 92 % de rendimiento) como un sólido amarillo.

[001006] ^{1}H NMR (400 MHz, CDCl3) δ 7,35 (m, 4H), 7,28-4,54 (m, 12H), 4,23-4,18 (m, 12H), 3,39 (s, 8H), 2,26-2,15 (m, 1H), 2,14-1,97(m, 1H), 1,83-1,81(m, 8H), 1,71-1,62 (m, 4H), 1,40-1,28 (m, 12H).

[001007] Una mezcla de 7-benciloxiespiro[3,5]nonan-2-ol (6,70 g, 27,20 mmol, 1,0 *eq*), imidazol (5,55 g, 81,59 mmol, 3,0 *eq*) y ter-butil-cloro-dimetil-silano (6,15 g, 40,80 mmol, 5,0 ml, 1,5 *eq*) en DCM (60 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 25 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (30 ml) y se extrajo con DCM (100 ml × 3). Los extractos orgánicos

combinados se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener un residuo crudo. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 50/1 a 5/1) para obtener el producto (7-benciloxiespiro[3,5]nonan-2-il)oxi-ter-butil-dimetilsilano (8,50 g, 23,57 mmol, 87 % de rendimiento) como un aceite amarillo claro.

[001008] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7,29 (s, 1H), 7,27 - 7,25 (m, 2H), 4,29 - 4,26 (m, 1H), 3,38 - 3,35 (m, 1H), 2,23 - 2,11 (m, 1H), 1,68 - 1,61 (m, 1H), 1,39 (s, 4H), 0,88 (s, 3H), 0,05 (s, 3H)**.**

[001009] A una solución de (7-benciloxiespiro[3,5]nonan-2-il)oxi-ter-butil-dimetilsilano (8,50 g, 23,57 mmol, 1,0 *eq*) en EtOH (100 ml) se agregó Pd/C (2,5 g) bajo atmósfera de N_2. La suspensión se desgasificó y se purgó con H_2 3 veces. La mezcla se agitó bajo H_2 a 50 °C durante 12 h. La mezcla de reacción se filtró y se concentró a presión reducida para obtener un residuo. El producto crudo se usó en la siguiente etapa sin purificación adicional. Compuesto 2-[ter-butil(dimetil)silil]oxispiro[3,5]nonan-7-ol (5,60 g, 20,70 mmol, 88 % de rendimiento) como goma amarilla.

[001010] ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 4,25 – 4,22 (m, 1H), 3,47 – 3,45 (m, 2H), 2,20 – 2,05 (m, 4H), 1,68 1,56 (m, 2H), 1,31 – 1,28 (m, 4H), 0,86 (s, 9H).

[001011] A una solución de 2-[ter-butil(dimetil)silil]oxiespiro[3,5]nonan-7-ol (5,60 g, 20,70 mmol, 1,0 *eq*) en DCM (60 ml) se le agregó Py (8,19 g, 103,52 mmol, 8,4 ml, 5,0 *eq*) y la solución de metanosulfonato de metilsulfonilo (10,82 g, 62,11 mmol, 3,0 *eq*) en DCM (15 ml) a 0 °C bajo N_2. La mezcla se agitó a 25 °C durante 12 h en N_2. La mezcla de reacción se diluyó con DCM (150 ml), se lavó con NaCl saturado (50 ml × 3), se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/0 a 5/1) para obtener el producto [2-[ter-butil(dimetil)silil]oxiespiro[3,5]nonan-7-il] metanosulfonato (4,70 g, 13,48 mmol, 65 % de rendimiento) como un sólido amarillo claro.

[001012] ^{1}H NMR (400 MHz, $CDCl_3$) δ **4,71-4,66 (m, 2H), 4,25-4,20 (m, 2H), 2,22-2,21 (m, 1H), 2,12-1,87 (m, 1H), 1,72-1,64 (m, 3H), 1,46-1,41 (m, 3H), 0,92 (s, 3H).**

[001013] Una mezcla de 1-(3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridin-5-il)etanona (3,92 g, 13,48 mmol, 1,0 *eq*), [2-[ter-butil(dimetil)silil]oxispiro[3,5]nonan-7-il] metanosulfonato (4,70 g, 13,48 mmol, 1 *eq*) y Cs_2CO_3 (13,18 g, 40,45 mmol, 3,0 *eq*) en DMF (40 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 110 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (20 ml) y se extrajo con EA (100 ml × 3). Las capas orgánicas combinadas se lavaron

con salmuera (20 ml x 3), se secaron en $Na2SO_4$, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante *prep*-HPLC (columna: Phenomenex luna C18 (250*70 mm, 10 µm); fase móvil: [agua(FA)-ACN]; gradiente: 60 %-90 % B durante 30 min) para obtener el producto 1-[1-[2-[ter-butil(dimetil)silil]oxiespiro[3,5]nonan-7-il]-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (1,60 g, 2,94 mmol, 22 % de rendimiento) como un sólido blanco.

[001014] LC-MS: MS (ESI^+): t_R = 0,739 min, m/z = 544,2 [M + H^+]

[001015] A una solución de 1-[1-[2-[ter-butil(dimetil)silil]oxiespiro[3,5]nonan-7-il]-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (300 mg, 552 µmol, 1,0 *eq*) en MeOH (10 ml) se agregó NH_4F (204 mg, 5,52 mmol, 10,0 *eq*). La mezcla resultante se agitó a 25 °C durante 12 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener el producto 1-[1-(2-hidroxiespiro[3,5]nonan-7-il)-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (240 mg) como un sólido blanco. El producto crudo se usó en la siguiente etapa sin purificación adicional.

[001016] LC-MS: MS (ESI^+): t_R = 0,465 min, m/z = 430,1 [M + H^+]

[001017] A una solución de 1-[1-(2-hidroxiespiro[3,5]nonan-7-il)-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (240 mg) en DCM (5 ml) se agregó DMP (474 mg, 1,12 mmol, 346 µl, 2,0 *eq*) a 0 °C. La mezcla se agitó a 25 °C durante 1 h bajo N_2. La reacción se inactivó por la adición por goteo de solución saturada de $NaHCO_3$ (15 ml). La solución se extrajo con EtOAc (70 ml × 3). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida para dar el producto 7-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)espiro[3,5]nonan-2-ona (238 mg) como goma amarilla. El producto crudo se usó en la siguiente etapa sin purificación adicional.

[001018] LC-MS: MS (ESI^+): t_R = 0,485 min, m/z = 428,1 [M + H^+]

[001019] A una solución de 7-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)espiro[3,5]nonan-2-ona (238 mg), ter-butil piperazina-1-carboxilato (124 mg, 668 µmol, 1,2 *eq*) en DCM (5 ml) se agregó Et_3N (113 mg, 1,11 mmol, 155 µl, 2,0 *eq*) y $NaBH(OAc)_3$ (590 mg, 2,79 mmol, 5,0 *eq*).La mezcla se agitó a 25 °C durante 12 h bajo N_2. La reacción se inactivó por la adición por goteo de solución saturada de $NaHCO_3$ (15 ml). La solución se extrajo con EtOAc (50 ml × 3). Los extractos orgánicos combinados se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener un residuo crudo. El residuo se purificó mediante cromatografía en columna (SiO_2, éter de

petróleo/acetato de etilo = 10/1 a diclorometano/metanol = 10/1) para dar el producto ter-butil 4-[7-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)espiro[3,5]nonan-2-il]piperazina-1-carboxilato (295 mg, 494 µmol, 89 % de rendimiento en tres pasos) como un sólido blanco.

[001020] LC-MS: MS (ESI^+): t_R = 0,468 min, m/z = 598,3 [M + H^+]

[001021] A una solución de ter-butil 4-[7-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)espiro[3,5]nonan-2-il]piperazina-1-carboxilato (155 mg, 259 µmol, 1,0 *eq*), 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (68 mg, 259 µmol, 1,0 *eq*) en dioxano (2 ml) se agregó Xphos Pd G4 (22 mg, 25,94 µmol, 0,1 *eq*) y Cs_2CO_3 (254 mg, 778,20 µmol, 3,0 *eq*). La mezcla se agitó a 90 °C durante 12 h en N_2. La mezcla se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante *prep*-TLC (diclorometano : metanol = 10 :1) para obtener el producto ter-butil 4-[7-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]espiro[3,5]nonan-2-il]piperazina-1-carboxilato (50 mg) como un sólido amarillo claro.

[001022] LC-MS: MS (ESI^+): t_R = 0,504 min, m/z = 733,5 [M + H^+]

[001023] A una solución de ter-butil 4-[7-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]espiro[3,5]nonan-2-il]piperazina-1-carboxilato (50 mg) en DCM (1 ml) se le agregó TFA (0,5 ml). La mezcla se agitó a 25 °C durante 1 h y se inactivó mediante la adición de $NaHCO_3$ (70,0 mg, 0,83 mmol). La solución se extrajo con EtOAc (20 ml × 3). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener el producto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(2-piperazin-1-ilespiro[3,5]nonan-7-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (43 mg) como un sólido amarillo. El producto crudo se usó en la siguiente etapa sin purificación adicional.

[001024] LC-MS: MS (ESI^+): t_R = 0,481 min, m/z = 633,4 [M + H^+]

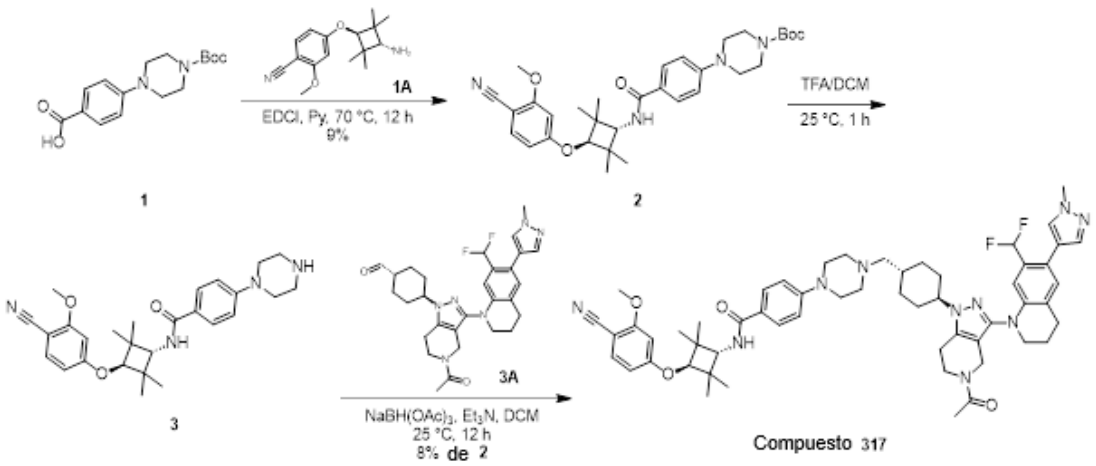
[001025] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(2-piperazin-1-ilespiro[3,5]nonan-7-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (43 mg), 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (28 mg, 68 µmol, 1,0 *eq*) en THF (1 ml) se agregó DIPEA (26 mg, 204 µmol, 35 µl, 3,0 *eq*). La mezcla se agitó a 25 °C durante 12 h en N_2. La mezcla se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante *prep*-HPLC (columna: Phenomenex luna C18 150*25mm* 10um;fase móvil: [agua(FA)-ACN];gradiente:26 %-56 % B durante 10 min) para dar el

producto 2-[4-[7-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]espiro[3,5]nonan-2-il]piperazin-1-il]-N-[3-(3-cloro-4-ciano-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (24,52 mg, 23,31 µmol, 34 % de rendimiento en tres pasos) como un sólido blanco.

[001026] **^{1}H NMR** (400 MHz, CD_3OD) δ = 8,75 (s, 2H), 7,73 - 7,71 (d, *J* = 8,8 Hz, 1H), 7,64 (s, 1H), 7,51 (s, 1H), 7,13 - 7,09 (m, 2H), 6,99 - 6,97 (m, 1H), 6,73 - 6,42 (m, 2H), 4,59 (s, 2H), 4,27 (m, 1H), 4,23 - 4,21 (m, 2H), 4,13 (m, 1H), 3,96 (m, 3H), 3,93 (m, 3H), 3,92 (m, 1H), 3,81 (m, 1H), 3,65 (m, 2H), 2,90 - 2,89 (m, 3H), 2,81 (m, 2H), 2,49 (m, 4H), 2,25 (m, 1H), 2,18 (m, 2H), 2,08 (m, 2H), 2,03 (m, 3H), 1,81 (m, 3H), 1,78 (m, 3H), 1,61 (m, 3H), 1,28 (s, 6H), 1,21 (s, 6H).

[001027] LC-MS: MS (ESI$^+$): t_R = 3,132 min, m/z = 1015,7 [M + H$^+$]

[001028] Ejemplo 53: Síntesis de 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]metil]piperazin-1-il]-N-[(1R)-3-(4-ciano-3-metoxifenoxi)-1-isopropil-2,2-dimetilpropil]benzamida (**Compuesto 317**)



[001029] A una solución de ácido 4-(4-tert-butoxicarbonilpiperazin-1-il)benzoico (150 mg, 490 µmol, 1,0 eq) en piridina (5 ml) se le añadieron 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (161 mg, 588 µmol, 1,2 eq) y EDCI (94 mg, 490 µmol, 1,0 eq). La mezcla de reacción se agitó a 70 °C durante 12 h. A continuación la mezcla de reacción se diluyó con EtOAc (100 ml) y agua (20 ml). Los extractos orgánicos combinados se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener un residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 0/1). El compuesto deseado ter-butil 4-[4-[[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]piperazina-1-

carboxilato (68 mg, 44 µmol, 9 % de rendimiento) se obtuvo como un sólido blanco.

[001030] LC-MS: MS (ESI^+): t_R = 0,597 min, m/z = 563,4 [M + H^+]

[001031] A una solución de ter-butil 4-[4-[[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]carbamoil]fenil]piperazina-1-carboxilato (68 mg, 121 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (768 mg, 6,73 mmol, 0,5 ml, 55,7 eq). La mezcla se agitó a 25 °C durante 1 hora. La mezcla de reacción se filtró y se concentró a presión reducida para obtener un residuo. El compuesto N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-piperazin-1-ilbenzamida (68 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001032] LC-MS: MS (ESI^+): t_R = 0,524 min, m/z = 463,2 [M + H^+]

[001033] A una solución de N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]-4-piperazin-1-il-benzamida (68 mg) y 4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexanocarbaldehído (63 mg, 118 µmol, 1,0 eq) en DCM (5 ml) se agregó Et_3N (119 mg, 1,18 mmol, 164 µl, 10,0 eq) y $NaBH(OAc)_3$ (125 mg, 590 µmol, 5,0 eq). La mezcla de reacción se agitó a 25 °C durante 12 h. A continuación la mezcla de reacción se diluyó con EtOAc (50 ml) y agua (10 ml). Los extractos orgánicos combinados se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener un residuo crudo. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 100/1 a 10/1). El residuo se purificó mediante HPLC preparativa (columna FA: Unisil 3-100 C18 Ultra 150 × 50 mm × 3 µm; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto deseado 4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]metil]piperazin-1-il]-N-[(1R)-3-(4-ciano-3-metoxifenoxi)-1-isopropil-2,2-dimetilpropil]benzamida (9 mg, 8,86 µmol, 8 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino.

[001034] ^{1}H (400 MHz, CLOROFORMO-d) δ = 7,70 (d, *J* = 8,8 Hz, 2H), 7,54 (d, *J* = 5,6 Hz, 1H), 7,46 (d, *J* = 8,8 Hz, 1H), 7,43 - 7,38 (m, 1H), 7,05 (s, 1H), 6,96 - 6,85 (m, 3H), 6,71 - 6,34 (m, 3H), 6,12 (d, *J* = 8,0 Hz, 1H), 4,26 (s, 1H), 4,17 - 4,12 (m, 2H), 4,05 (s, 1H), 4,00 - 3,83 (m, 9H), 3,80 - 3,61 (m, 3H), 3,45 - 3,17 (m, 4H), 2,94 - 2,84 (m, 2H), 2,81 (t, *J* = 5,6 Hz, 1H), 2,75 (t, *J* = 5,6 Hz, 1H), 2,66 - 2,47 (m, 4H), 2,31 - 2,20 (m, 2H), 2,30 - 2,16 (m, 1H), 2,12 - 2,04 (m, 5H), 2,01 (s, 5H), 1,25 (d, *J* = 10,0 Hz, 12H), 1,14 - 1,06 (m, 2H)

[001035] LC-MS: MS (ESI^+): t_R = 3,043 min, m/z = 983,8 [M + H^+]

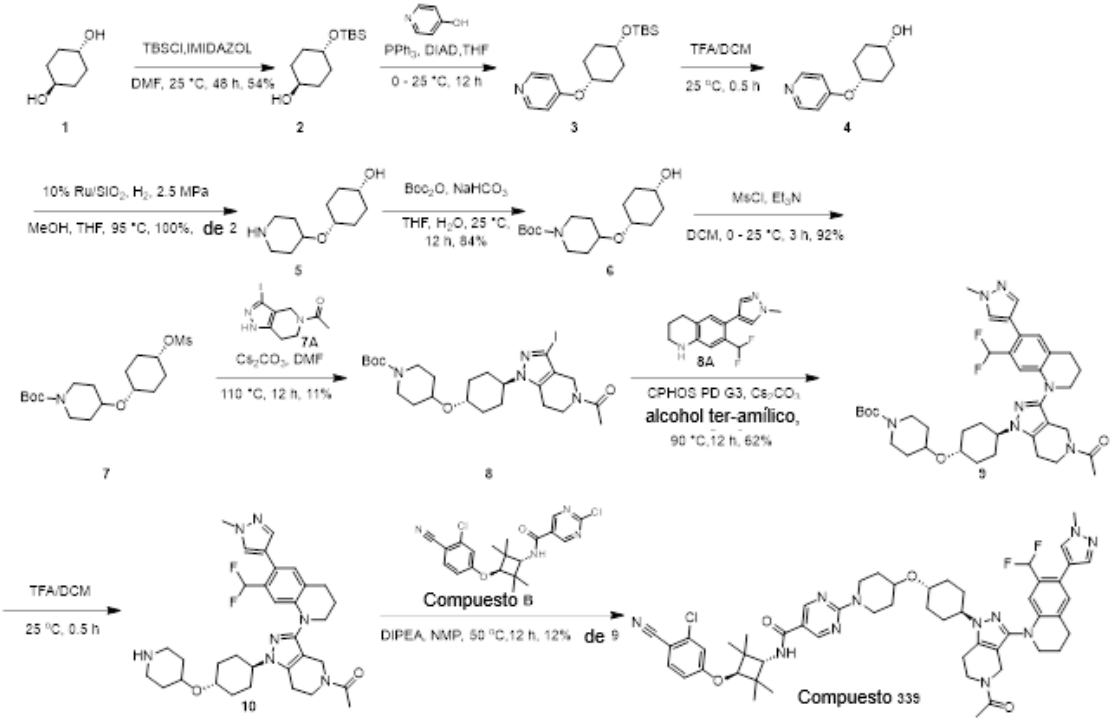
[001036] Los compuestos que se muestran a continuación se prepararon de manera

similar a como se describe en el Ejemplo 53.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
318	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]metil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,72 (s, 2 H) 7,59 (d, *J*=8,8 Hz, 1 H) 7,55 (d, *J*=5,2 Hz, 1 H) 7,42 (d, *J*=6,0 Hz, 1 H) 7,06 (s, 1 H) 7,02 - 6,96 (m, 1 H) 6,88 (d, *J*=3,6 Hz, 1 H) 6,82 (m, 1 H) 6,72 - 6,35 (m, 1 H) 5,94 (d, *J*=8,0 Hz, 1 H) 4,28 (s, 1 H) 4,17 - 4,12 (m, 2 H) 4,06 (s, 1 H) 4,00 - 3,89 (m, 9 H) 3,79 - 3,68 (m, 3 H) 2,92 - 2,74 (m, 4 H) 2,49 (m, 4 H) 2,24 (m, 2 H) 2,18 (s, 1 H) 2,14 – 1,99 (m, 10 H) 1,27 (s, 6 H) 1,23 (s, 6 H) 1,11 (m, 2 H)	989,7
319	4-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]metil]piperazin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,75 (d, *J* = 8,4 Hz, 1H), 7,53 (d, *J* = 8,4 Hz, 2H), 7,09 (d, J = 8,4 Hz, 2H), 6,98 (d, *J* = 8,4 Hz, 1H), 6,75 (s, 1H), 6,63 (m, 1H), 4,26-4,23 (m, 1H), 4,13-3,93 (m, 2H), 3,89-3,81 (m, 2H), 3,68 (s, 2H), 3,35-3,01 (m, 2H), 2,91 (s, 3H), 2,85 (s, 3H), 2,64-2,63 (m, 2H), 2,55-2,53 (m, 1H), 2,19-2,04 (m, 1H), 1,91-1,75 (m, 1H), 1,41-1,15 (m, 1H).	985,7
320	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]metil]piperazin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(CD_3OD) δ = 8,74 (s, 2H), 7,73 - 7,71 (d, *J* = 8,4 Hz, 1H), 7,64 (s, 1H), 7,51 (s, 1H), 7,13 - 7,09 (m, 2H), 6,99 - 6,97 (d, *J* = 8,8 Hz, 1H), 6,75 (s, 1H), 6,75 - 6,42 (m, 1H), 4,27 - 4,23 (m, 3H), 4,13 (m, 2H), 3,93 (m, 7H), 3,89 (m, 1H), 3,68 - 3,67 (m, 1H), 3,65 (m, 2H), 2,92 (m, 3H), 2,85 (m, 1H), 2,55 - 2,52 (m, 6H), 2,18 (s, 2H), 2,10 - 2,04 (m, 3H), 1,93 (m, 2H), 1,75 - 1,72 (m, 4H), 1,28 (s, 6H), 1,21 (s, 6H)	989,7

[001037] Ejemplo 54: Síntesis de 2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]-1-

piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 339**)



[001038] A una solución de -1,4-bromo-4-cloro1,0-fluoropiridina (8,80 g, 129,26 mmol, 1 eq) en DMF (100 ml) se agregó NaOMe (5,4 M, 11,65 ml, 1 eq). La mezcla se agitó a 25 °C durante 48 h y luego se vertió en agua (300 ml). La fase acuosa se extrajo con acetato de etilo (100 ml x 2). La capa orgánica combinada se lavó con salmuera (200 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto 4-[ter-butil(dimetil)silil]oxiciclohexanol (10,80 g, 46,87 mmol, 54 % de rendimiento) se obtuvo como un aceite incoloro.

[001039] ^{1}H NMR (400 MHz, $CDCl_3$): δ 3,75-3,53 (m, 2H), 2,01-1,90 (m, 2H), 1,89-1,78 (m, 1H), 1,43-1,28 (m, 1H), 0,88 (s, 9H), 0,05 (s, 6H).

[001040] A una solución de 4-[ter-butil(dimetil)silil]oxiciclohexanol (15,67 g, 68,01 mmol, 1,0 eq), piridin-4-ol (6,47 g, 68,01 mmol, 1,0 eq) y PPh_3 (17,84 g, 68,01 mmol, 1,0 eq) en THF (160 ml) se agregó DIAD (16,50 g, 81,61 mmol, 15,82 ml, 1,2 eq) a 0 °C. La mezcla se agitó a 25 °C durante 12 h. La mezcla se vertió en agua (50 ml). La fase acuosa se extrajo con acetato de etilo (50 ml x 2). La capa orgánica combinada se lavó con salmuera (100 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : Se obtuvieron 25,57 g del compuesto ter-butil-dimetil-[4-(4-

piridiloxi)ciclohexoxi]silano como un aceite incoloro.

[001041] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8,41 (s, 1H), 6,81 - 6,76 (m, 2H), 4,44 - 4,30 (m, 1H), 3,91 - 3,77 (m, 1H), 2,02 - 1,94 (m, 1H), 1,80 - 1,69 (m, 1H), 1,64 (s, 2H), 0,90 (s, 3H), 0,06 (s, 3H).

[001042] LC-MS: MS (ESI^+): t_R = 0,504 min, m/z = 308,1 [M + H^+]

[001043] A una solución de ter-butil-dimetil-[4-(4-piridiloxi)ciclohexoxi]silano (22,57 g, 73,40 mmol, 1,0 eq) en diclorometano (90 ml) se le agregó ácido trifluoroacético (138,15 g, 1,21 mol, 90 ml, 16,51 eq). La mezcla se agitó a 25 °C durante 0,5 h y luego se vertió en agua (30 ml). La mezcla acuosa se ajustó a pH = 7 usando $NaHCO_3$. La fase acuosa se extrajo con acetato de etilo (30 ml x 2). La capa orgánica combinada se lavó con salmuera (70 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (10 % - 100 % de acetato de etilo en éter de petróleo y 0 % - 20 % de metanol en diclorometano). Se obtuvo el compuesto 4 (6,07 g, 31,41 mmol, 42 % de rendimiento) como un sólido blanco.

[001044] ^{1}H NMR (400 MHz, CDCl**3**): δ 8,25-8,48 (m, 2H), 6,70-6,89 (m, 2H), 4,48 (d, $_J$= 3,6 Hz, 1H), 5,8 (d, J= 2,8 Hz, 1H), 3,82-2,96 (m, 1H), 2,74-2,64 (m, 1H), 2,01-2,10 (m, 2H), 1,63-1,86 (m, 6H).

[001045] Solución 1: {4-(4-piridiloxi)ciclohexanol, 1 eq, 6,07 g} en {MeOH, 91,05 ml} y {THF, 30,35 ml}

[001046] El lecho fijo (denominado FLR1, volumen 20 ml) se llenó completamente con catalizador granular 10 % Ru/SiO_2 (1,00 eq) 10,00 g. El regulador de contrapresión de H_2 se ajustó a 2,5 MPa, y el caudal de H_2 fue de 60 ml/min. Luego, la solución S1 fue bombeada por la Bomba 1 {S1, P1, 1,212 ml/min} al lecho fijo {FLR1, SS, lecho fijo, 9,525(1/2") mm, 20 ml, 95 °C}. A continuación, se recogió la mezcla de reacción a la salida del reactor. El lecho fijo se lavó con 91,05 ml adicionales de {MeOH}. Se obtuvo el compuesto 4 (6,28 g, 31,51 mmol, 100 % de rendimiento) como un aceite amarillo.

[001047] A una solución de 4-(4-piperidiloxi)ciclohexanol (6,28 g, 31,51 mmol, 1,0 eq) en THF (60 ml) y agua (30 ml) se añadieron $NaHCO_3$ (13,24 g, 157,56 mmol, 6,13 ml, 5,0 eq) y Boc_2O (10,32 g, 47,27 mmol, 10,86 ml, 1,5 eq). La mezcla se agitó a 25 °C durante 12 h y luego se vertió en agua (70 ml). La fase acuosa se extrajo con acetato de etilo (100 ml x 2). La capa orgánica combinada se lavó con salmuera (200 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto 4-(4-hidroxiciclohexoxi)piperidina-1-carboxilato de ter-butilo (7,94 g, 26,52 mmol, 84 % de rendimiento) se obtuvo como un aceite incoloro.

[001048] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3,74 (d, J = 3,2 Hz, 1H), 3,58-3,43 (m, 2H), 3,10 (d, **J** = 3,2 Hz, 1H), 9,2-5,12 (m, 1H), 1,81-1,73 (m, 4H), 1,71-3,95 (m, 1H), 1,56-1,48 (m, 3H), 1,45 (s, 3H).

[001049] LC-MS: MS (ESI$^+$): t_R = 0,492 min, m/z = 244,1 [M - 55]

[001050] A una solución de 4-(4-hidroxiciclohexoxi)piperidina-1-carboxilato de ter-butilo (7,94 g, 26,52 mmol, 1,0 eq) en diclorometano (80 ml) se le añadieron Et_3N (21,47 g, 212,15 mmol, 29,53 ml, 8,0 eq) y MsCl (4,00 g, 34,92 mmol, 2,70 ml, 1,3 eq) a 0 °C. La mezcla se agitó a 25 °C durante 3 h. La mezcla se vertió en agua helada (200 ml). La fase acuosa se extrajo con acetato de etilo (100 ml x 2). La fase orgánica combinada se lavó con salmuera (200 ml × 3), se secó con sulfato de sodio anhidro, se filtró y se concentró al vacío. La mezcla de reacción se concentró a presión reducida para obtener el producto. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto ter-butil 4-(4-metilsulfoniloxiciclohexoxi)piperidina-1-carboxilato (9,24 g, 24,48 mmol, 92 % de rendimiento) se obtuvo como un aceite incoloro.

[001051] ^{1}H NMR $_{(400\ MHz,\ CDCl3):}$ δ 4,80-4,70 (m, 1H), 3,82-3,64 (m, 1H), 3,58-3,43 (m, 3H), 3,14-3,06 (m, 3H), 2,03-1,96 (m, 1H), 1,79-1,73 (m, 6H), 1,47-1,41 (m, 13H).

[001052] A una solución de 1-(3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridin-5-il)etanona (3,00 g, 10,31 mmol, 1,0 eq) y 4-(4-metilsulfoniloxiciclohexoxi)piperidina-1-carboxilato de ter-butilo (4,67 g, 12,37 mmol, 1,2 eq) en DMF (35 ml) se agregó Cs_2CO_3 (10,07 g, 30,92 mmol, 3,0 eq). La mezcla de reacción se agitó a 110 °C durante 12 h. La mezcla de reacción se diluyó con acetato de etilo (150 ml). La fase acuosa se extrajo con acetato de etilo (100 ml x 2). La capa orgánica combinada se lavó con salmuera (200 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante HPLC preparativa (columna: Welch Ultimate XB-CN 250*70*10um; fase móvil: [Hexano-EtOH]; gradiente: 10 %-50 % B durante 15 min) para obtener el compuesto deseado. El compuesto ter-butil 4-[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexoxi]piperidina-1-carboxilato (660 mg, 1,15 mmol, 11 % de rendimiento) se obtuvo como un sólido blanco.

[001053] **^{1}H** (400 MHz, $CDCl_3$) δ = 4,41-4,24 (m, 2H), 3,91-3,85 (m, 2H), 3,79 (d, J = 10,9 Hz, 2H), 3,71 (t, J = 5,7 Hz, 1H), 3,60-3,53 (m, 1H), 3,50-3,41 (m, 1H), 3,06 (ddd, J = 13,2, 9,6, 3,2 Hz, 2H), 2,76-2,65 (m, 2H), 2,19-2,17 (m, 3H), 2,14-2,08 (m, 2H), 2,03-1,98 (m, 1H), 1,96-1,89 (m, 2H), 1,79 (d, J = 9,8 Hz, 2H), 1,66 (s, 1H), 1,53-1,40 (m, 13H)

[001054] LC-MS: MS (ESI$^+$): t_R = 0,558 min, m/z = 573,1 [M + H$^+$]

[001055] A una solución de ter-butil 4-[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexoxi]piperidina-1-carboxilato (300 mg, 524,04 µmol, 1,0 eq), 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (206 mg, 786,06 µmol, 1,5 eq) en alcohol terc-amílico (5 ml) se agregó Cs_2CO_3 (512 mg, 1,57 mmol, 3,0 eq) y Cphos Pd G_3 (42 mg, 52,40 µmol, 0,1 eq). La mezcla se agitó a 90 °C durante 12 horas en N_2. El residuo se vertió en agua (70 ml). La fase acuosa se extrajo con acetato de etilo (100 ml x 2). La capa orgánica combinada se lavó con salmuera (200 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 15/1 a 10/1). El compuesto ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]piperidina-1-carboxilato (230 mg, 324,93 µmol, 62 % de rendimiento) se obtuvo como un sólido amarillo.

[001056] LC-MS: MS (ESI^+): t_R = 0,574 min, m/z = 708,4 [M + H^+]

[001057] A una solución de ter-butil 4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]piperidina-1-carboxilato (115 mg, 162,46 µmol, 1,0 eq) en diclorometano (3 ml) se le agregó ácido trifluoroacético (4,61 g, 40,39 mmol, 3 ml, 248,6 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El compuesto 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[4-(4-piperidiloxi)ciclohexil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (98 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001058] LC-MS: MS (ESI^+): t_R = 0,442 min, m/z = 608,3 [M + H^+]

[001059] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[4-(4-piperidiloxi)ciclohexil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (98 mg) en NMP (3 ml) se le agregó DIPEA (416 mg, 3,23 mmol, 561,74 µl, 20,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (67 mg, 161,25 µmol, 1,0 eq). La mezcla se agitó a 50 °C durante 12 h y luego se vertió en agua (50 ml). La capa acuosa se extrajo con DCM (50 ml x 2). La capa orgánica combinada se lavó con salmuera (100 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. El residuo se purificó mediante TLC preparativa (SiO_2, diclorometano: metanol = 40: 1) dos veces. El residuo se purificó mediante HPLC preparativa (columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua (FA)-ACN]; gradiente: 60 %-90 % B durante 10 min) para obtener el compuesto deseado. Luego fue liofilizado. El compuesto 2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-

4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (20,19 mg, 19,95 µmol, 12,37 % de rendimiento) se obtuvo como un sólido blanco.

[001060] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8,70 (s, 2H), 7,67-7,49 (m, 2H), 7,41 (d, J = 6,4 Hz, 1H), 7,08-6,95 (m, 2H), 6,88 (d, J = 5,9 Hz, 1H), 6,81 (dd, J = 8,8, 2,4 Hz, 1H), 6,70-6,35 (m, 1H), 5,93 (d, J = 8,1 Hz, 1H), 4,33 (dt, J = 13,1, 5,0 Hz, 2H), 4,26 (s, 1H), 4,15-4,08 (m, 2H), 4,05 (s, 1H), 3,96 (d, J = 2,1 Hz, 3H), 3,94-3,85 (m, 2H), 3,82-3,63 (m, 4H), 3,62-3,46 (m, 3H), 2,99-2,84 (m, 2H), 2,80 (t, J = 5,5 Hz, 1H), 2,74 (t, J = 5,5 Hz, 1H), 2,19-2,13 (m, 3H), 2,13-2,07 (m, 2H), 2,07-1,95 (m, 6H), 1,91 (td, J = 6,4, 3,1 Hz, 2H), 1,63-1,60 (m, 2H), 1,51-1,42 (m, 2H), 1,24 (d, J = 13,1 Hz, 12H)

[001061] **LC-MS:** MS (ESI^+): t_R = 3,280 min, m/z = 990,7 [$M + H^+$]

[001062] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 54.

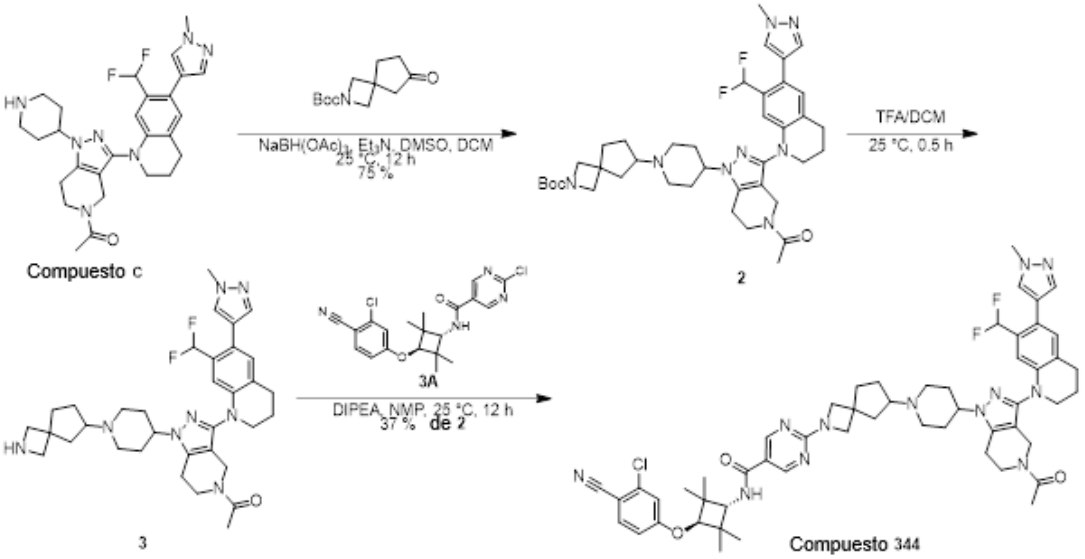
Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
338	2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,61 - 7,48 (m, 2H), 7,45 - 7,34 (m, 1H), 7,08 - 6,94 (m, 2H), 6,92 - 6,85 (m, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,71 - 6,31 (m, 1H), 5,96 (d, J = 9,2 Hz, 1H), 4,34 - 4,18 (m, 3H), 4,15 - 4,11 (m, 2H), 4,04 (s, 1H), 3,95 (d, J = 2,4 Hz, 4H), 3,90 (t, J = 5,6 Hz, 1H), 3,78 - 3,64 (m, 7H), 2,93 - 2,71 (m, 4H), 2,44 - 2,26 (m, 2H), 2,16 (s, 1H), 2,10 - 2,01 (m, 6H), 1,93 - 1,85 (m, 2H), 1,76 (d, J = 12,8 Hz, 3H), 1,69 - 1,61 (m, 3H), 1,61 - 1,52 (m, 2H), 1,23 (d, J = 12,0 Hz, 10H)	990,6
340	2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,71 (s, 2H), 7,62 - 7,50 (m, 2H), 7,41 (d, *J* = 6,4 Hz, 1H), 7,03 (br d, *J* = 21,6 Hz, 1H), 6,97 (d, *J* = 2,4 Hz, 1H), 6,87 (d, *J* = 6,0 Hz, 1H), 6,81 (dd, *J* = 2,4, 8,8 Hz, 1H), 6,53 (dt, *J* = 10,4, 55,6 Hz, 1H), 5,97 - 5,88 (m, 1H), 4,62 - 4,51 (m, 1H), 4,50 - 4,38 (m, 2H),	962,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		4,26 (s, 1H), 4,14 - 4,09 (m, 4H), 4,05 (s, 1H), 3,96 (d, *J* = 2,0 Hz, 3H), 3,94 - 3,88 (m, 2H), 3,80 - 3,65 (m, 3H), 3,52 - 3,39 (m, 1H), 2,87 (td, *J* = 6,0, 11,9 Hz, 2H), 2,83 - 2,77 (m, 1H), 2,74 (br t, *J* = 5,6 Hz, 1H), 2,19 - 2,13 (m, 3H), 2,12 - 1,98 (m, 8H), 1,56 - 1,42 (m, 3H), 1,24 (d, *J* = 13,2 Hz, 12H)	
308	4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 8,04 - 7,99 (m, 1H), 7,72 - 7,64 (m, 2H), 7,57 - 7,51 (m, 1H), 7,49 - 7,37 (m, 2H), 7,07 - 6,97 (m, 1H), 6,96 - 6,84 (m, 3H), 6,75 - 6,34 (m, 3H), 6,13 (d, *J* = 8,0 Hz, 1H), 4,25 (s, 1H), 4,17 - 4,12 (m, 2H), 4,05 (s, 1H), 3,98 - 3,86 (m, 8H), 3,83 - 3,68 (m, 4H), 3,62 (d, *J* = 3,6 Hz, 3H), 3,14 (t, *J* = 9,2 Hz, 2H), 2,96 (s, 1H), 2,91 - 2,79 (m, 4H), 2,78 - 2,74 (m, 1H), 2,39 - 2,26 (m, 2H), 2,16 (s, 1H), 2,12 - 1,99 (m, 6H), 1,98 - 1,91 (m, 2H), 1,83 (s, 2H), 1,61 - 1,52 (m, 2H), 1,25 (d, *J* = 10,0 Hz, 12H)	984,7
309	4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,74 - 7,63 (m, 2H), 7,58 - 7,51 (m, 1H), 7,49 - 7,43 (m, 1H), 7,43 - 7,38 (m, 1H), 7,08 - 6,98 (m, 1H), 6,93 (d, *J* = 8,8 Hz, 2H), 6,87 (d, *J* = 6,0 Hz, 1H), 6,73 - 6,42 (m, 2H), 6,41 - 6,33 (m, 1H), 6,18 - 6,04 (m, 1H), 4,26 (s, 1H), 4,18 - 4,10 (m, 2H), 4,05 (s, 1H), 3,96 (d, *J* = 2,0 Hz, 3H), 3,93 - 3,90 (m, 4H), 3,78 - 3,60 (m, 6H), 3,56 - 3,45 (m, 1H), 3,09 (t, *J* = 10,0 Hz, 2H), 2,91 - 2,72 (m, 4H), 2,17 (s, 3H), 2,09 - 1,93 (m, 9H), 1,75 - 1,66 (m, 3H), 1,54 - 1,39 (m,	984,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		3H), 1,25 (d, *J* = 10,0 Hz, 12H)	
341	-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,72 (s, 2H), 7,59 - 7,52 (m, 2H), 7,43 - 7,38 (m, 1H), 7,05 - 6,98 (m, 1H), 6,97 (d, *J* = 2,4 Hz, 1H), 6,91 - 6,86 (m, 1H), 6,81 (dd, *J* = 2,4, 8,7 Hz, 1H), 6,69 - 6,35 (m, 1H), 6,06 - 5,93 (m, 1H), 4,58 - 4,49 (m, 1H), 4,43 (dd, *J* = 6,4, 9,9 Hz, 2H), 4,26 (s, 1H), 4,17 (dd, *J* = 4,4, 10,7 Hz, 2H), 4,13 (t, *J* = 3,9 Hz, 2H), 4,05 (s, 1H), 3,99 - 3,92 (m, 4H), 3,90 (t, *J* = 5,8 Hz, 1H), 3,79 - 3,65 (m, 4H), 2,93 - 2,78 (m, 3H), 2,75 (t, *J* = 5,7 Hz, 1H), 2,39 - 2,29 (m, 2H), 2,17 (s, 1H), 2,11 - 2,02 (m, 6H), 1,81 - 1,77 (m, 2H), 1,62 (d, *J* = 14,0 Hz, 2H), 1,24 (d, *J* = 14,4 Hz, 12H)	962,6
342	4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,67 (d, *J*=8,50 Hz, 2 H), 7,67 (d, *J*=8,50 Hz, 2 H), 7,54 (d, *J*=5,00 Hz, 1 H), 7,45 (d, *J*=8,50 Hz, 1 H), 7,41 (d, *J*=6,13 Hz, 1 H), 7,03 (d, *J*=21,51 Hz, 1 H), 6,87 (d, *J*=6,25 Hz, 1 H), 6,68-6,38 (m, 5 H), 6,10 (d, *J*=8,00 Hz, 1H), 4,58 (q, *J*=5,50 Hz, 1 H), 4,31-4,17 (m, 3 H), 4,16-4,12 (m, 2 H), 4,05 (s, 1 H), 3,96 (d, *J*=1,75 Hz, 3 H), 3,94-3,88 (m, 5 H), 3,79 (dd, *J*=7,94, 4,69 Hz, 2 H), 3,77-3,64 (m, 3 H), 3,51-3,37 (m, 1 H), 2,88 (dt, *J*=11,82, 6,10 Hz, 2 H), 2,83-2,71 (m, 2 H), 2,18-2,13 (m, 3 H), 2,12-1,96 (m, 8 H), 1,51-1,41 (m, 2 H) 1,25 (d, *J*=9,88 Hz, 12 H)	956,6
343	4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-	δ = 7,66 (d, J = 8,5 Hz, 2H), 7,56 - 7,51 (m, 1H), 7,45 (d, J = 8,5 Hz, 1H), 7,43 - 7,38 (m, 1H), 7,04 (s, 1H), 6,90 -	956,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	4H-pirazolo[4,3-c]piridin-1-il]ciclohexoxi]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	6,84 (m, 1H), 6,70 - 6,49 (m, 1H), 6,48 - 6,45 (m, 2H), 6,44 (s, 1H), 6,42 - 6,38 (m, 1H), 6,10 (d, J = 7,9 Hz, 1H), 4,59 - 4,49 (m, 1H), 4,25 (s, 1H), 4,20 (t, J = 7,2 Hz, 2H), 4,15 (d, J = 8,3 Hz, 1H), 4,12 (s, 1H), 4,05 (s, 1H), 3,96 (d, J = 1,6 Hz, 4H), 3,92 (s, 3H), 3,91 - 3,88 (m, 1H), 3,85 (dd, J = 4,9, 7,6 Hz, 2H), 3,78 - 3,64 (m, 4H), 2,94 - 2,84 (m, 2H), 2,84 - 2,78 (m, 1H), 2,75 (br t, J = 5,5 Hz, 1H), 2,38 - 2,25 (m, 2H), 2,17 (s, 1H), 2,08 (br d, J = 5,5 Hz, 2H), 2,05 (s, 4H), 1,78 (d, J = 10,8 Hz, 2H), 1,56 (s, 2H), 1,25 (d, J = 9,8 Hz, 12H)	

[001063] Ejemplo 55: Síntesis de 2-[6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,4]octan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 344**)



[001064] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (300 mg, 549 µmol, 1,0 eq, sal de HCl), 6-oxo-2-azaespiro[3,4]octano-2-carboxilato de ter-butilo

(247 mg, 1,10 mmol, 2,0 eq) en una mezcla de DCM (4 ml) y DMSO (2 ml) se agregó Et_3N (166 mg, 1,65 mmol, 229 µl, 3,0 eq). La mezcla de reacción se agitó a 25 °C durante 0,5 h, y luego se agregó $NaBH(OAc)_3$ (582 mg, 2,75 mmol, 5,0 eq). La reacción se agitó a 25 °C durante 11,5 h. A la mezcla de reacción se le agregó agua (30 ml) y la mezcla se extrajo con DCM (30 ml × 3). Las fases orgánicas combinadas se lavaron con salmuera (20 ml), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron. El residuo se purificó mediante cromatografía en columna (SiO_2, diclorometano/metanol = 30/1 a 10/1). El compuesto ter-butil 6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,4]octano-2-carboxilato (300 mg, 417 µmol, 75 % de rendimiento) se obtuvo como un sólido amarillo.

[001065] LC-MS: MS (ESI^+): t_R = 0,534 min, m/z = 719,4 [M + H^+]

[001066] A una solución de 6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,4]octano-2-carboxilato de ter-butilo (300 mg, 417 µmol, 1,0 eq) en DCM (6 ml) se le agregó TFA (3,07 g, 26,9 mmol, 2 ml, 64,5 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se ajustó a pH = 8 con NaHCO3 $saturado_3$ y la mezcla se extrajo con DCM (30 ml × 3). La fase orgánica combinada se lavó con salmuera (20 ml x 3), se secó en Na_2SO_4 anhidro, se filtró y se concentró a presión reducida. El compuesto 1-[1-[1-(2-azaespiro[3,4]octan-6-il)-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (260 mg) se obtuvo como un sólido marrón y se utilizó directamente en el siguiente paso sin purificación adicional.

[001067] LC-MS: MS (ESI^+): t_R = 0,469 min, m/z = 619,3 [M + H^+]

[001068] A una solución de 1-[1-[1-(2-azaespiro[3,4]octan-6-il)-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (80 mg), 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (54 mg, 129 µmol, 1,0 eq) en NMP (1 ml) se le agregó DIPEA (84 mg, 646 µmol, 112 µl, 5,0 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se purificó mediante HPLC preparativa (columna: Phenomenex Luna C18 150*25mm*10um; fase móvil: [agua(FA)-ACN]; gradiente: 33 %-63 % B durante 10 min). El compuesto 2-[6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,4]octan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (48,23 mg, 48 µmol, 37 % de rendimiento

en dos pasos) se obtuvo como un sólido amarillo.

[001069] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,70 (s, 2H), 8,42 (s, 1H), 7,57 (d, *J* = 8,8 Hz, 1H), 7,54 (d, *J* = 4,8 Hz, 1H), 7,41 (d, *J* = 5,2 Hz, 1H), 7,04 (d, *J* = 18,0 Hz, 1H), 6,99 - 6,88 (m, 2H), 6,84 - 6,77 (m, 1H), 6,73 - 6,36 (m, 1H), 6,06 - 5,93 (m, 1H), 4,32 (s, 1H), 4,21 - 4,07 (m, 5H), 4,05 (s, 1H), 4,01 (s, 2H), 3,96 (s, 3H), 3,91 (t, *J* = 5,6 Hz, 1H), 3,76 (t, *J* = 5,6 Hz, 1H), 3,72 - 3,63 (m, 2H), 3,46 - 3,28 (m, 2H), 3,15 - 2,95 (m, 2H), 2,92 - 2,69 (m, 7H), 2,25 (d, *J* = 7,6 Hz, 4H), 2,18 (s, 2H), 2,12 - 2,04 (m, 5H), 2,00 - 1,88 (m, 2H), 1,26 (s, 6H), 1,22 (s, 6H).

[001070] LC-MS: MS (ESI^+): t_R = 1,96 min, m/z = 1001,6 [M + H^+]

[001071] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 55.

Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
345	4-[6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,4]octan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	($CDCl_3$) δ 7,66 (d, *J* = 8,8 Hz, 2H), 7,54 (d, *J* = 4,8 Hz, 1H), 7,45 (d, *J* = 8,8 Hz, 1H), 7,41 (d, *J* = 6,0 Hz, 1H), 7,04 (d, *J* = 18,0 Hz, 1H), 6,97 - 6,84 (m, 1H), 6,72 - 6,51 (m, 1H), 6,47 (d, *J* = 2,0 Hz, 1H), 6,45 - 6,36 (m, 3H), 6,09 (d, *J* = 8,0 Hz, 1H), 4,30 (s, 1H), 4,16 - 4,12 (m, 2H), 4,05 (s, 1H), 3,96 (d, *J* = 1,2 Hz, 3H), 3,94 - 3,89 (m, 5H), 3,87 - 3,83 (m, 1H), 3,77 (s, 2H), 3,73 - 3,66 (m, 2H), 3,40 - 3,21 (m, 2H), 2,91 - 2,85 (m, 2H), 2,82 (d, *J* = 5,6 Hz, 1H), 2,74 (t, *J* = 5,6 Hz, 1H), 2,49 - 2,38 (m, 1H), 2,31 - 2,21 (m, 4H), 2,19 - 1,97 (m, 12H), 1,95 - 1,87 (m, 2H), 1,85 - 1,74 (m, 1H), 1,25 (d, *J* = 10,0 Hz, 12H)	995,2
346	2-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-6-azaespiro[3,4]octan-6-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ 7,92-8,75 (m, 1H), 8,15-8,12 (m, 2H), 7,93-7,86 (m, 2H), 7,73-7,64 (m, 1H), 7,50 (s, 1H), 7,25-7,18 (m, 1H), 7,11 (s, 2H), 7,05-6,97 (m, 2H), 6,64 (brs, 2H), 6,33-6,31 (m, 2H), 4,36-4,25 (m, 2H), 4,00 (s, 3H), 3,86 (s, 3H), 3,76-3,66 (m, 2H), 3,62-3,55 (m, 2H), 3,55-	1001,4

Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
		3,44 (m, 2H), 3,02-2,91 (m, 2H), 2,91-2,71 (m, 2H).	
347	4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-6-azaespiro[3,4]octan-6-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	8,22H NMR (400 MHz, CDCl7,68) δ 7,50 (s, 1H), 7,45 - 7,31 (m, 2H), 7,15 - 7,07 (m, 3H), 6,97 - 6,62 (m, 1H), 6,60 - 6,47 (m, 2H), 4,32 - 4,24 (m, 1H), 4,10 (s, 1H), 4,09 - 3,99 (m, 3H), 3,89 - 3,84 (m, 1H), 3,76 - 3,68 (m, 1H), 3,56 (s, 1H), 3,36 - 3,32 (m, 1H), 3,28 - 3,22 (m, 1H), 2,93 - 1,89 (m, 1H), 1,89 - 2,05 (m, 1H), 2,05 - 1,93 (m, 7H), 1,92 - 1,80 (m, 2H), 1,28 - 1,19 (m, 3H).	995,4
348	2-[6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ 8,03 (d, J = 8,4 Hz, 1H), 7,90 (d, J = 8,4 Hz, 2H), 7,72 (d, J = 8,4 Hz, 2H), 7,22 (d, J = 8,4 Hz, 1H), 7,11 (s, 1H), 6,99 (m, 1H), 6,97-6,62 (m, 1H), 4,22-4,09 (m, 2H), 4,08-3,99 (m, 2H), 3,87 (s, 2H), 3,78-3,67 (m, 2H), 3,56 (s, 3H), 2,82 (s, 3H), 2,76-2,64 (m, 2H), 2,40-2,32 (m, 1H), 2,11-2,04 (m, 1H), 2,03-1,94 (m, 1H), 1,93-1,83 (m, 1H).	987,4
349	4-[6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,3]heptan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,79 - 7,68 (m, 3H), 7,67 - 7,62 (m, 1H), 7,50 (s, 1H), 7,45 (d, J = 8,8 Hz, 1H), 7,10 (s, 1H), 6,94 - 6,62 (m, 3H), 6,58 - 6,49 (m, 1H), 6,40 (d, J = 8,4 Hz, 2H), 4,26 (s, 1H), 4,20 - 4,09 (m, 2H), 4,04 (d, J = 9,2 Hz, 2H), 3,90 (s, 5H), 3,87 (s, 3H), 3,79 (s, 2H), 3,75 - 3,66 (m, 2H), 3,62 - 3,56 (m, 2H), 2,91 - 2,81 (m, 5H), 2,76 - 2,61 (m, 2H), 2,33 (m, J = 8,4 Hz, 2H), 2,07 (s, 2H), 2,05 - 1,92 (m, 7H), 1,87 (m, J = 11,2 Hz, 4H), 1,21 (s, 6H), 1,17 - 1,05 (m, 6H).	981,7
426	4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-	1H NMR (400 MHz, CDCl7,71) δ 7,45 (s, 1H),	1009,8

Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
	metilimidazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,41 - 7,30 (m, 2H), 6,86 - 6,75 (m, 3H), 6,69 - 6,62 (m, 1H), 6,60 - 6,51 (m, 2H), 6,48 - 6,36 (m, 1H), 4,27 (s, 1H), 4,05 - 3,85 (m, 3H), 3,80 - 3,66 (m, 1H), 3,65 - 3,56 (m, 1H), 3,52 (s, 1H), 3,02 - 2,91 (m, 1H), 2,78 - 2,62 (m, 1H), 2,41 - 1,89 (m, 1H), 1,89 - 1,80 (m, 1H), 1,75 - 1,65 (m, 2H), 1,56 - 1,46 (m, 2H), 1,41 - 1,22 (m, 3H).	
428	4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	9,19H NMR (400 MHz, CDCl7,68) δ 7,39 (s, 1H), 7,22 - 7,15 (m, 2H), 7,01 - 6,78 (m, 3H), 6,72 - 6,61 (m, 1H), 6,57 - 6,51 (m, 2H), 6,48 - 6,36 (m, 1H), 4,27 (s, 1H), 4,10 - 3,95 (m, 3H), 3,81 - 3,66 (m, 1H), 3,66 - 3,56 (m, 1H), 3,55 (s, 1H), 3,02 - 2,81 (m, 1H), 2,81 - 2,62 (m, 1H), 2,45 - 1,89 (m, 1H), 1,89 - 1,85 (m, 1H), 1,78 - 1,64 (m, 2H), 1,56 - 1,47 (m, 2H), 1,41 - 1,22 (m, 3H).	1012,8
431	4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	($CDCl_3$) δ = 8,47 - 8,39 (m, 1H), 8,26 - 8,16 (m, 1H), 7,78 - 7,70 (m, 2H), 7,68 - 7,63 (m, 1H), 7,48 - 7,39 (m, 2H), 7,34 - 7,27 (m, 1H), 7,24 - 6,91 (m, 1H), 6,91 - 6,86 (m, 1H), 6,67 - 6,61 (m, 1H), 6,57 - 6,51 (m, 1H), 6,46 - 6,38 (m, 2H), 4,27 (s, 1H), 4,22 - 4,14 (m, 2H), 4,09 - 3,96 (m, 2H), 3,91 (s, 3H), 3,79 - 3,58 (m, 7H), 3,57 - 3,50 (m, 3H), 2,94 (br d, J = 7,5 Hz, 2H), 2,88 (br d, J = 5,4 Hz, 3H), 2,38 - 2,32 (m, 2H), 2,13 - 2,06 (m, 2H), 2,04 - 1,91 (m, 7H), 1,90 - 1,83 (m, 2H), 1,71 (br d, J = 9,9 Hz, 2H), 1,57 - 1,46 (m, 2H), 1,41 - 1,29 (m, 2H),	996,7

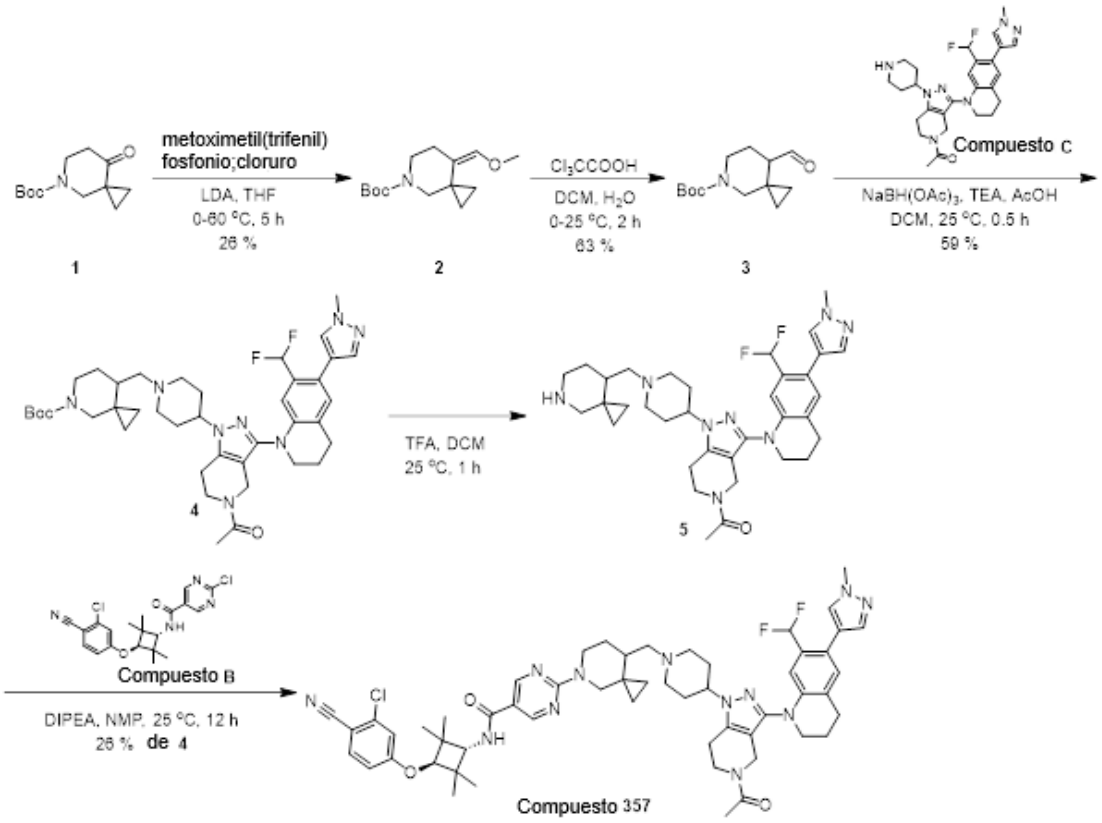
Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
		1,22 (s, 6H), 1,19 - 1,12 (m, 6H)	
432	4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-3-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	(400 MHz, $CDCl_3$, ppm) δ 7,61 (s, 1H), 7,51-7,23 (m, 1H), 6,83 (s, 1H), 6,66-6,61 (m, 1H), 6,57-6,51 (m, 1H), 6,49-6,45 (m, 2H), 6,44-6,35 (m, 2H), 4,26-4,10 (m, 1H), 4,09-3,92 (m, 1H), 3,86-3,68 (m, 1H), 3,80-3,65 (m, 1H), 3,65-3,56 (m, 2H), 3,02-2,91 (m, 2H), 2,86-2,62 (m, 1H), 2,36-2,23 (m, 3H), 2,07-1,90 (m, 1H), 1,90-1,80 (m, 1H), 1,62-1,45 (m, 3H), 1,38-1,22 (m, 3H).	1009,8
448	4-[7-[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,86 (s, 1H), 8,36 (s, 1H), 8,17 - 8,16 (m, 1H), 8,09 (d, J = 2,8 Hz, 2H), 7,89 - 7,85 (m, 1H), 7,79 (s ancho, 1H), 7,73 (d, J = 8,4 Hz, 2H), 7,64 (d, J = 8,6 Hz, 1H), 7,58 - 7,40 (m, 2H), 6,63 (d, J = 2,0 Hz, 1H), 6,53 (dd, J = 2,0, 8,7 Hz, 1H), 6,42 (d, J = 8,6 Hz, 2H), 4,57 (s ancho, 2H), 4,27 (s, 1H), 4,22 - 4,12 (m, 1H), 4,05 (d, J = 9,2 Hz, 1H), 3,91 (s, 6H), 3,81 (br d, J = 5,4 Hz, 2H), 3,63 (s, 2H), 3,55 (s, 2H), 3,02 (br d, J = 6,2 Hz, 2H), 2,94 (br s, 1H), 2,88 - 2,74 (m, 1H), 2,44 - 2,36 (m, 3H), 2,15 - 2,07 (m, 4H), 2,03 - 1,93 (m, 5H), 1,79 - 1,70 (m, 2H), 1,53 (br s, 2H), 1,37 (br d, J = 11,6 Hz, 2H), 1,22 (s, 6H), 1,14 (s, 6H)	955,8
449	4-[7-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,81 - 7,69 (m, 3H), 7,65 (d, *J* = 8,4 Hz, 1H), 7,52 (s, 1H), 7,43 (d, *J* = 9,6 Hz, 1H), 7,01 - 6,95 (m, 1H), 6,63 (d, *J* = 2,4 Hz, 1H), 6,57 - 6,50 (m, 1H), 6,41 (d, *J* = 8,8 Hz, 2H), 6,35 - 6,28 (m, 1H), 4,26 (s, 1H), 4,15 - 4,07 (m, 2H),	973,7

Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
		4,05 (d, *J* = 9,2 Hz, 1H), 4,01 - 3,93 (m, 1H), 3,90 (s, 3H), 3,84 (s, 3H), 3,77 - 3,68 (m, 2H), 3,62 (s, 2H), 3,58 - 3,51 (m, 4H), 2,98 - 2,88 (m, 2H), 2,87 - 2,68 (m, 4H), 2,38 - 2,25 (m, 3H), 2,19 - 2,14 (m, 3H), 2,07 (s, 2H), 2,02 - 1,80 (m, 9H), 1,74 - 1,65 (m, 2H), 1,51 (br t, *J* = 11,6 Hz, 2H), 1,42 - 1,28 (m, 2H), 1,21 (s, 6H), 1,14 (s, 6H)	
452	4-[7-[4-[5-acetil-3-[6-ciano-7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	($CDCl_3$) δ = 8,50 (s, 1H), 7,66 (d, J = 8,8 Hz, 2H), 7,45 (d, J = 8,8 Hz, 1H), 7,34 (d, J = 10,4 Hz, 1H), 6,94 - 6,59 (m, 2H), 6,47 (d, J = 2,4 Hz, 1H), 6,44 - 6,37 (m, 3H), 6,09 (d, J = 8,4 Hz, 1H), 4,28 (s, 1H), 4,18 - 4,09 (m, 2H), 4,05 (s, 1H), 4,00 - 3,86 (m, 5H), 3,80 - 3,68 (m, 3H), 3,64 (d, J = 16,8 Hz, 4H), 3,20 - 3,08 (m, 2H), 2,92 - 2,72 (m, 4H), 2,51 - 2,33 (m, 3H), 2,29 - 2,13 (m, 4H), 2,12 - 2,02 (m, 6H), 1,92 - 1,84 (m, 3H), 1,62 - 1,51 (m, 2H), 1,45 - 1,32 (m, 2H), 1,25 (d, J = 9,6 Hz, 12H)	954,8
455	4-[7-[4-[5-acetil-3-(6-ciano-7-metil-3,4-dihidro-2H-quinolin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,73 (d, *J* = 8,4 Hz, 2H), 7,64 (d, *J* = 8,4 Hz, 1H), 7,42 (d, *J* = 9,6 Hz, 1H), 7,32 (s, 1H), 6,63 (d, *J* = 2,0 Hz, 1H), 6,57 - 6,50 (m, 1H), 6,41 (d, *J* = 8,4 Hz, 2H), 6,36 - 6,29 (m, 1H), 4,26 (s, 1H), 4,14 - 4,08 (m, 2H), 4,07 - 3,95 (m, 2H), 3,90 (s, 3H), 3,77 - 3,68 (m, 2H), 3,64 - 3,57 (m, 4H), 3,54 (s, 2H), 2,94 (br d, *J* = 7,6 Hz, 2H), 2,88 - 2,69 (m, 4H), 2,40 - 2,29 (m, 3H), 2,23 (s, 3H), 2,08 (s, 2H), 2,00 - 1,82 (m, 9H), 1,70 (br d, *J* = 11,6 Hz, 2H), 1,57 - 1,45 (m, 2H), 1,41 - 1,27	918,7

Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
		(m, 2H), 1,21 (s, 6H), 1,14 (s, 6H)	
468	2-[7-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,74 (s, 2H), 8,30 - 8,25 (m, 1H), 7,95 - 7,88 (m, 1H), 7,81 - 7,69 (m, 2H), 7,53 (s, 1H), 7,22 (d, J = 2,4 Hz, 1H), 7,07 - 6,92 (m, 2H), 6,37 - 6,28 (m, 1H), 4,30 (s, 1H), 4,16 - 4,02 (m, 3H), 4,01 - 3,91 (m, 1H), 3,89 - 3,80 (m, 5H), 3,78 - 3,67 (m, 4H), 3,59 - 3,52 (m, 2H), 3,01 - 2,89 (m, 2H), 2,87 - 2,69 (m, 4H), 2,36 - 2,25 (m, 3H), 2,19 - 2,12 (m, 3H), 2,07 (s, 2H), 2,03 - 1,88 (m, 7H), 1,86 (br s, 2H), 1,76 - 1,64 (m, 2H), 1,57 - 1,46 (m, 2H), 1,41 - 1,29 (m, 2H), 1,21 (s, 6H), 1,11 (s, 6H)	979,6
469	2-[7-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,74 (s, 2H), 8,15 (s, 1H), 7,78 - 7,70 (m, 2H), 7,64 (d, J = 8,4 Hz, 1H), 7,52 (s, 1H), 7,01 - 6,96 (m, 1H), 6,64 (d, J = 2,0 Hz, 1H), 6,54 (m, 1H), 6,35 - 6,30 (m, 1H), 4,24 (s, 1H), 4,13 - 4,07 (m, 2H), 4,03 (d, J = 9,2 Hz, 2H), 3,90 (s, 3H), 3,84 (s, 3H), 3,82 (s, 2H), 3,75 (s, 2H), 3,70 (t, J = 5,6 Hz, 1H), 3,57 - 3,51 (m, 2H), 3,04 - 2,94 (m, 2H), 2,82 (s, 1H), 2,78 - 2,68 (m, 3H), 2,44 - 2,32 (m, 3H), 2,18 - 2,14 (m, 3H), 2,07 (s, 2H), 2,04 - 1,82 (m, 10H), 1,77 - 1,68 (m, 2H), 1,52 (t, J = 11,6 Hz, 2H), 1,42 - 1,33 (m, 2H), 1,22 (s, 6H), 1,13 (s, 6H)	975,9
471	2-[7-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metilfenoxi)-	($CDCl_3$) δ = 8,63 (s, 2H), 7,52 - 7,39 (m, 2H), 7,34 - 7,24 (m, 1H), 6,98 - 6,84 (m, 1H), 6,71 (d, J = 2,0 Hz, 1H), 6,65 - 6,55 (m, 1H), 6,31 (s, 1H), 5,88 (br d, J = 8,0 Hz, 1H), 4,24 - 4,01 (m,	959,8

Compuesto	Nombre	^{1}H NMR (300 MHz, DMSO-d_6):	LC-MS $(M+H)^+$:
	2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	3H), 3,97 (s, 1H), 3,92 - 3,76 (m, 9H), 3,76 - 3,53 (m, 3H), 3,21 - 3,01 (m, 2H), 2,81 - 2,62 (m, 4H), 2,55 - 2,28 (m, 7H), 2,23 - 2,06 (m, 8H), 1,99 - 1,95 (m, 5H), 1,84 (br d, J = 10,4 Hz, 2H), 1,53 (br t, J = 11,6 Hz, 2H), 1,40 - 1,25 (m, 2H), 1,16 (d, J = 10,4 Hz, 12H)	
472	2-[7-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-2,3-dimetilfenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ = 8,64 (s, 2H), 7,52 - 7,42 (m, 1H), 7,37 - 7,26 (m, 2H), 6,98 - 6,82 (m, 1H), 6,45 (d, J = 8,8 Hz, 1H), 6,35 - 6,23 (m, 1H), 5,89 (d, J = 8,0 Hz, 1H), 4,23 - 4,04 (m, 3H), 4,03 - 3,96 (m, 1H), 3,89 - 3,77 (m, 8H), 3,71 - 3,63 (m, 1H), 3,62 - 3,49 (m, 2H), 3,05 (br d, J = 11,6 Hz, 2H), 2,81 - 2,62 (m, 4H), 2,41 (s, 3H), 2,38 - 2,29 (m, 3H), 2,20 - 2,13 (m, 9H), 2,10 (s, 1H), 2,02 - 1,77 (m, 10H), 1,52 (br t, J = 12,0 Hz, 2H), 1,31 (br d, J = 11,6 Hz, 2H), 1,23 - 1,05 (m, 12H)	973,7
473	2-[7-[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	3 - 7,26 (m, 1H), 7,00 - 6,81 (m, 1H), 6,51 (d, $_J$ = 8,8 Hz, 1H), 5,88 (d, J = 8,0 Hz, 1H), 4,24 - 3,99 (m, 1H), 3,95 (s, 1H), 3,71 - 3,53 (m, 1H), 3,03 (br d, J = 10,4 Hz, 1H), 2,80 - 3,87 (m, 3H), 3,87 - 2,24 (m, 6H), 2,23 - 2,06 (m, 5H), 2,04 - 1,95 (m, 5H), 1,81 - 1,45 (m, 2H), 1,38 (s, 3H), 1,17 (d, J = 10,4 Hz, 3H).	993,8

[001072] Ejemplo 56: Síntesis de 2-[8-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-5-azaespiro[2,5]octan-5-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 357**)



[001073] A una solución de metoximetil(trifenil)fosfonio;cloruro (3,04 g, 8,88 mmol, 2,0 eq) en THF (14 ml) se agregó gota a gota LDA (2 M, 3,99 ml, 1,8 eq) bajo N_2 a 0 °C, la mezcla se agitó a 25 °C bajo N_2 durante 2 h, luego el 8-oxo-5-azaespiro[2,5]octano-5-carboxilato de ter-butilo (1,00 g, 4,44 mmol, 1,0 eq) en THF (5,6 ml) se agregó gota a gota a la mezcla de reacción, la mezcla se agitó a 60 °C bajo N_2 durante 3 h. La mezcla de reacción se neutralizó mediante la adición de una solución acuosa saturada de NH_4Cl (10 ml) a 0 °C, y luego se extrajo con EtoAc (10 ml x3). Las capas orgánicas combinadas se lavaron con salmuera (10 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 2 g, eluyente de gradiente de acetato de etilo/éter de petróleo de 0~10 % a 50 ml/min). El compuesto ter-butil (8Z)-8-(metoximetileno)-5-azaespiro[2,5]octano-5-carboxilato (300 mg, 1,18 mmol, 26 % de rendimiento) se obtuvo como un aceite incoloro.

[001074] LC-MS: MS (ESI^+): t_R = 0,865 min, m/z = 198,1 [M - 55]

[001075] A una solución de ter-butil (8Z)-8-(metoximetileno)-5-azaespiro[2,5]octano-5-carboxilato (300 mg, 1,18 mmol, 1,0 eq) en DCM (3 ml) y H_2O (1,5 ml) se agregó ácido 2,2,2-tricloroacético (773 mg, 4,74 mmol, 478 µl, 4,0 eq) a 0 °C. La mezcla se agitó a 25 °C durante 2 h. La mezcla resultante se basificó con una solución acuosa saturada de

$NaHCO_3$ para ajustar el pH a 8, y luego se extrajo con DCM (20 ml x 3). La fase orgánica se secó en Na_2SO_4, se filtró y se concentró a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 5/1). Se obtuvo el compuesto ter-butil 8-formil-5-azaespiro[2,5]octano-5-carboxilato (180 mg, 752 µmol, 63 % de rendimiento) como un sólido blanco.

[001076] LC-MS: MS (ESI^+): t_R = 0,757 min, m/z = 184,0 [M – 55]

[001077] A una solución de 8-formil-5-azaespiro[2,5]octano-5-carboxilato de ter-butilo (98 mg, 412 µmol, 1,5 eq) y 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (150 mg, 275 µmol, 1,0 eq) en DCM (1 ml) se agregó TEA (138 mg, 1,37 mmol, 191 µl, 5,0 eq) y $NaBH(OAc)_3$ (174 mg, 824 µmol, 3,0 eq) y AcOH (165 µg, 2,75 µmol, 1,57e-1 µl, 0,01 eq). La mezcla resultante se agitó a 25 °C durante 0,5 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). La capa orgánica combinada se secó en Na_2SO_4 anhidro, se filtró y se concentró a presión reducida. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH = 10:1). El compuesto ter-butil 8-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-5-azaespiro[2,5]octano-5-carboxilato (120 mg, 163 µmol, 59 % de rendimiento) se obtuvo como un sólido blanco.

[001078] LC-MS: MS (ESI^+): t_R = 0,757 min, m/z = 733,4 [M + H^+]

[001079] A una solución de ter-butil 8-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-5-azaespiro[2,5]octano-5-carboxilato (240 mg, 327,46 µmol, 1,0 eq) en DCM (3 ml) se le agregó TFA (1,54 g, 13,46 mmol, 1 ml, 41,1 eq). La mezcla se agitó a 25 °C durante 1 hora. La mezcla resultante se concentró a presión reducida para obtener un residuo. El producto crudo Compuesto 1-[1-[1-(5-azaespiro[2,5]octan-8-ilmetil)-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (207 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[001080] LC-MS: MS (ESI^+): t_R = 0,747 min, m/z = 633,4 [M + H^+]

[001081] A una solución de 1-[1-[1-(5-azaespiro[2,5]octan-8-ilmetil)-4-piperidil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (69 mg, 109 µmol, 1,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (45 mg, 109 µmol, 1,0 eq) en NMP (0,5 ml) se le agregó DIPEA (28 mg, 218 µmol, 38 µl, 2,0 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla resultante se concentró a presión reducida para

obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 29 %-59 % B durante 10 min). El compuesto 2-[8-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-5-azaespiro[2,5]octan-5-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (27,46 mg, 29,10 µmol, 26 % de rendimiento en dos pasos se obtuvo como un sólido blanco.

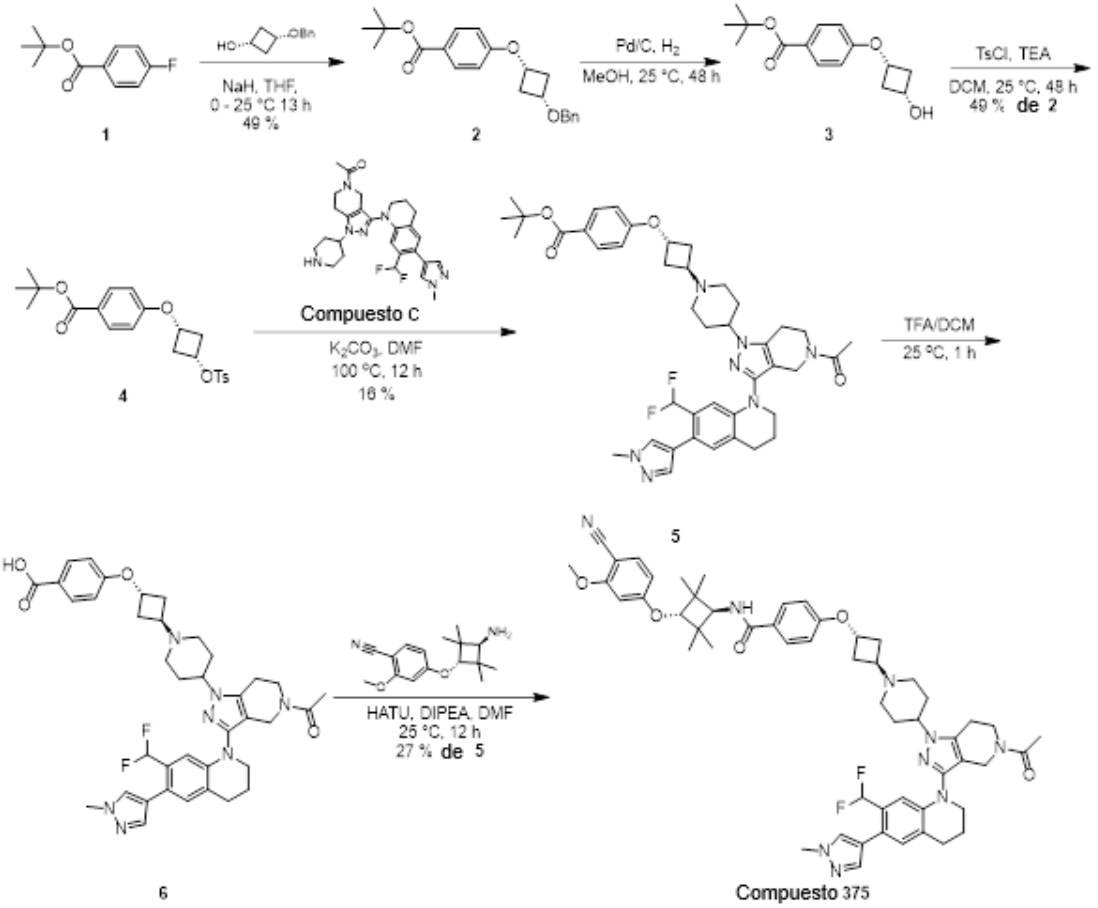
[001082] ^{1}H NMR (400 MHz, CLOROFORMO-**d**) δ = 8,67 (d, J = 2,9 Hz, 1H), 7,64 - 7,48 (m, 1H), 7,41 - 7,39 (m, 2H), 7,04 - 7,06 (m, 2H), 6,98 - 6,87 (m, 2H), 6,80 (br t, J = 8,8 Hz, 1H), 6,72 - 6,35 (m, 1H), 5,93 - 5,15 (m, 1H), 4,38 - 4,18 (m, 2H), 4,18 - 4,10 (m, 2H), 4,04 - 3,96 (m, 3H), 3,91 - 3,45 (m, 2H), 3,84 - 3,64 (m, 3H), 3,58 - 3,47 (m, 1H), 3,33 - 2,98 (m, 2H), 2,95 - 2,69 (m, 2H), 2,36 - 2,00 (m, 2H), 1,98 - 1,75 (m, 2H), 1,23 - 0,39 (m, 2H).

[001083] LC-MS: MS (ESI$^+$): t_R = 2,119 min, m/z = 1015,4 [M + H+]

[001084] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 56.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
362	2-[8-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-5-azaespiro[2,5]octan-5-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,67 (s, 2H), 7,53 (d, J = 5,6 Hz, 1H), 7,48 - 7,38 (m, 2H), 7,04 (br d, J = 18,4 Hz, 1H), 6,96 - 6,82 (m, 1H), 6,71 - 6,35 (m, 3H), 5,94 (br d, J = 7,6 Hz, 1H), 4,30 (br d, J = 1,2 Hz, 2H), 4,12 (br d, J = 8,4 Hz, 2H), 4,04 (s, 1H), 3,94 (br d, J = 15,2 Hz, 8H), 3,79 - 3,65 (m, 5H), 3,59 - 3,51 (m, 1H), 3,15 - 3,00 (m, 1H), 2,94 - 2,67 (m, 5H), 2,40 - 1,99 (m, 11H), 1,96 - 1,75 (m, 5H), 1,24 (d, J = 6,8 Hz, 12H), 0,55 - 0,40 (m, 4H)	1011,4

[001085] Ejemplo 57: Síntesis de 4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutoxi]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 375**)



[001086] A una solución de 3-benciloxiciclobutanol (5,00 g, 28,05 mmol, 1,0 eq) en THF (50 ml) se le agregó NaH (1,68 g, 42,08 mmol, 94 µl, 60 % de pureza, 1,5 eq) a 0 °C bajo N_2. La mezcla se agitó a 0 °C durante 1 h bajo N_2. Luego se le agregó 4-fluorobenzoato de ter-butilo (8,26 g, 42,08 mmol, 1,5 eq). La mezcla se agitó a 25 °C durante 12 h en N_2. La mezcla de reacción se inactivó con NH_4Cl (50 ml) y se extrajo con acetato de etilo (50 ml x 3). La capa orgánica combinada se lavó con salmuera (20 ml x 3), se secó en Na_2SO_4 anhidro, se filtró y se concentró a presión reducida. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 10 g, eluyente de un gradiente de acetato de etilo/éter de petróleo al 0-20 % a 50 ml/min). Se obtuvo el compuesto 3 (4,90 g, 13,82 mmol, 49 % de rendimiento) como un sólido blanco.

[001087] LC-MS: MS (ESI^+): t_R = 0,998 min, m/z = 299,1 [M – 55]

[001088] A una solución de 4-(3-benciloxiciclobutoxi)benzoato de ter-butilo (4,90 g, 13,82 mmol, 1,0 eq) en MeOH (25 ml) se le agregó Pd/C (500 mg, 470 µmol, 10 % de pureza, $3{,}40e^{-2}$ eq) bajo atmósfera de N_2. La suspensión se desgasificó y se purgó con H_2 3 veces. La mezcla se agitó bajo H_2 a 25 °C durante 48 h. La mezcla de reacción se

filtró y se concentró a presión reducida para obtener un residuo. El producto crudo 4-(3-hidroxiciclobutoxi)benzoato de ter-butilo (3,60 g) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[001089] LC-MS: MS (ESI^+): t_R = 0,552 min, m/z = 209,1 [M – 55]

[001090] A una solución de 4-(3-hidroxiciclobutoxi)benzoato de ter-butilo (500 mg) en DCM (5 ml) se le añadieron TEA (765 mg, 7,57 mmol, 1,05 ml, 4,0 eq) y TsCl (721 mg, 3,78 mmol, 2,0 eq). La mezcla resultante se agitó a 25 °C durante 12 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). Las fases orgánicas combinadas se lavaron con salmuera (30 ml), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 5/1). El compuesto 4-[3-(p-tolilsulfoniloxi)ciclobutoxi]benzoato de ter-butilo (400 mg, 955,79 µmol, 49 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[001091] LC-EM: EM (ESI+): tR = 0,720 min, m/z = 441,1 [M + Na+]

[001092] A una solución de 4-[3-(p-tolilsulfoniloxi)ciclobutoxi]benzoato de ter-butilo (201 mg, 481 µmol, 2,0 eq) en DMF (2 ml) se le añadieron K_2CO_3 (99 mg, 722 µmol, 3,0 eq) y 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (150 mg, 240 µmol, 1,0 eq). La mezcla se agitó a 100 °C durante 12 h. La mezcla resultante se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto ter-butil 4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutoxi]benzoato (30 mg, 39,69 µmol, 16 % de rendimiento) se obtuvo como un sólido blanco.

[001093] LC-MS: MS (ESI^+): t_R = 0,567 min, m/z = 756,4 [M + H^+]

[001094] A una solución de ter-butil 4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutoxi]benzoato (20 mg, 26 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (767 mg, 6,73 mmol, 0,5 ml, 254,4 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El producto crudo ácido 4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutoxi]benzoico (21 mg) se obtuvo como un sólido blanco y se utilizó directamente en el siguiente paso sin purificación adicional.

[001095] LC-MS: MS (ESI$^+$): t_R = 0,719 min, m/z = 700,3 [M + H$^+$]

[001096] A una solución de 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2-metoxi-benzonitrilo (10 mg, 26 µmol, 1,0 eq) y ácido 4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutoxi]benzoico (21 mg) en DMF (0,5 ml) se le agregó DIPEA (6 mg, 52 µmol, 9 µl, 2,0 eq) y HATU (12 mg, 34 µmol, 1,3 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua (FA)-ACN]; gradiente: 30 %-60 % B durante 10 min). El compuesto 4-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutoxi]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (6,88 mg, 7,09 µmol, 27 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[001097] ^{1}H NMR (400 MHz, CLOROFORMO-**d**) δ = 7,66 (d, J = 8,8 Hz, 1H), 7,86 - 7,74 (m, 2H), 7,48 - 7,31 (m, 1H), 7,04 - 6,92 (m, 4H), 6,71 (br d, J = 8,8 Hz, 1H), 6,51 - 6,05 (m, 1H), 4,90 (s, 1H), 4,51 - 4,28 (m, 4H), 4,15 - 4,27 (m, 1H), 4,07 - 4,14 (m, 2H), 3,99 (s, 1H), 3,91 (s, 1H), 3,80 (s, 2H), 3,73 - 3,53 (m, 5H), 3,38 (s, 1H), 2,85 - 2,78 (m, 2H), 2,95 - 2,46 (m, 2H), 2,19 - 1,91 (m, 4H), 1,20 - 1,43 (m, 4H), 1,17 - 1,22 (m, 2H).

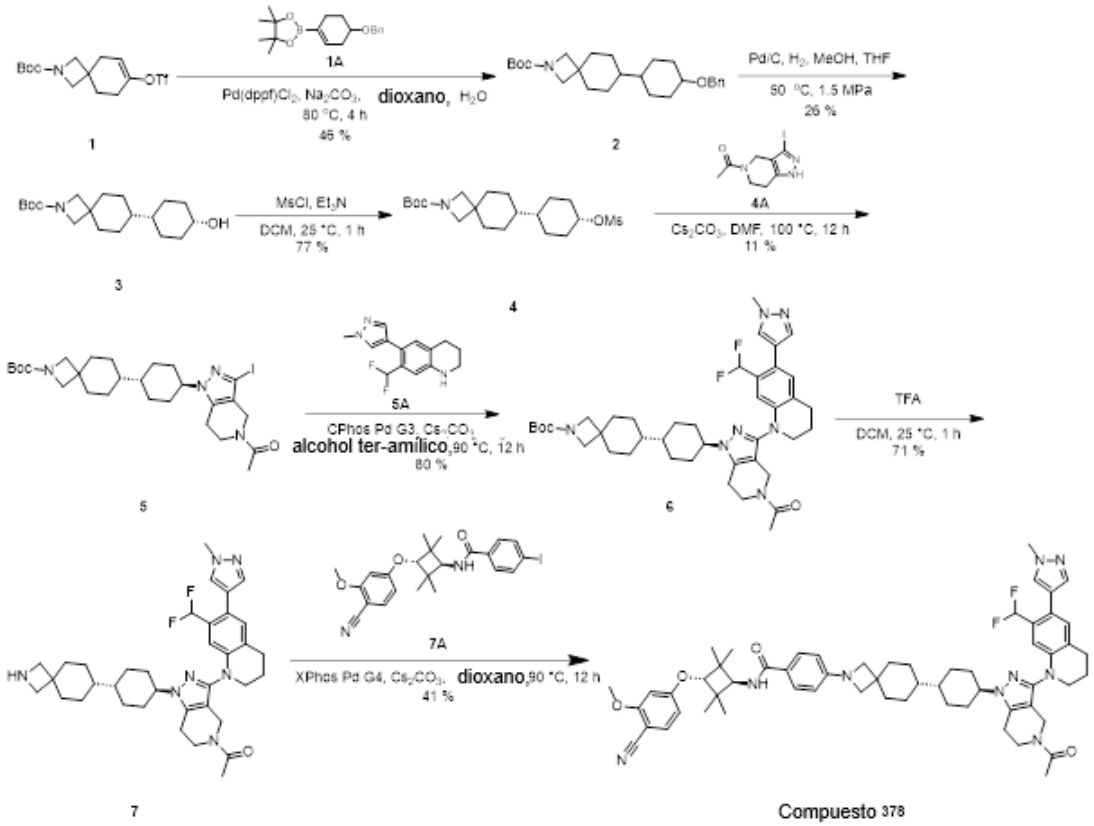
[001098] LC-MS: MS (ESI$^+$): t_R = 3,027 min, m/z = 956,7 [M + H$^+$]

[001099] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 57.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS (M+H)$^+$:**
376	2-[3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclobutoxi]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,83 (s, 2H), 8,37 (s, 1H), 7,57 - 7,43 (m, 2H), 7,35 (d, J = 5,1 Hz, 1H), 7,03 - 6,70 (m, 4H), 6,66 - 6,27 (m, 1H), 6,17 - 6,01 (m, 1H), 5,37 - 5,22 (m, 1H), 4,20 (s, 1H), 4,12 - 3,95 (m, 4H), 3,93 - 3,79 (m, 4H), 3,76 - 3,54 (m, 3H), 3,38 - 3,00 (m, 3H), 2,87 - 2,71 (m, 3H), 2,70 - 2,50 (m, 3H), 2,42 - 2,32 (m, 2H), 2,26 - 2,13 (m, 3H), 2,10 (s, 2H), 2,05 - 1,94 (m, 6H), 1,24 - 1,14 (m, 12H)	962,7
381	4-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-	$_6$H NMR (400 MHz, DMSO-d6) δ = 7,76 (s, 1H), 7,70 (d, J = 4,8 Hz, 2H), 7,54 (d,	984,8

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
	2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclohexoxi]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	J = 4,8 Hz, 1H), 6,82 - 6,53 (m, 3H), 4,42 - 4,34 (m, 2H), 4,30 - 4,26 (m, 1H), 4,20 - 4,11 (m, 1H), 4,06 - 7,24 (m, 1H), 4,03 - 3,97 (m, 1H), 3,91 – 3,87 (m, 1H), 3,76 - 3,68 (m, 1H), 3,61 - 3,57 (m, 3H), 3,02 - 2,80 (m, 5H), 2,80 - 2,68 (m, 1H), 2,46 - 2,29 (m, 1H), 2,16 - 2,05 (m, 2H), 2,03 – 1,91 (m, 1H), 1,91 - 1,78 (m, 2H), 1,52 - 1,35 (m, 2H), 1,23 - 1,15 (m, 1H).	
382	2-[4-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]ciclohexoxi]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	(DMSO-d_6): δ = 8,96 (s, 2H), 8,03 (d, J = 9,2 Hz, 1H), 7,90 (d, J = 8,8 Hz, 1H), 7,75 (s, 1H), 7,50 (s, 1H), 7,22 (d, J = 2,0 Hz, 1H), 7,10 (s, 1H), 7,04 - 6,98 (m, 1H), 6,96 - 6,63 (m, 2H), 5,02 - 4,89 (m, 1H), 4,30 (s, 1H), 4,19 - 4,10 (m, 2H), 4,06 (br d, J = 9,2 Hz, 2H), 3,86 (s, 3H), 3,76 - 3,67 (m, 2H), 3,62 - 3,56 (m, 2H), 3,08 - 3,00 (m, 2H), 2,92 - 2,68 (m, 5H), 2,61 - 2,55 (m, 1H), 2,17 (br s, 2H), 2,09 - 1,82 (m, 12H), 1,50 (br s, 4H), 1,23 (s, 6H), 1,12 (s, 6H)	990,8

[001100] Ejemplo 58: Síntesis de 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 378**)



[001101] La síntesis de **1** se informó en WO2021/216661 A1.

[001102] La síntesis de **1A** se informó en WO2019/236487 A1.

[001103] Una mezcla de 2-(4-benciloxiciclohexen-1-il)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (7,11 g, 22,6 mmol, 1,2 eq), 7-(trifluorometilsulfoniloxi)-2-azaespiro[3,5]non-6-eno-2-carboxilato de ter-butilo (7,00 g, 18,8 mmol, 1,0 eq), Na_2CO_3(5,99 g, 56,5 mmol, 3,0 eq) y $Pd(dppf)Cl_2$ (1,38 g, 1,88 mmol, 0,1 eq) en dioxano (200 ml) y H_2O (20 ml) se desgasificó y purgó con N_2 durante 3 veces, y luego la mezcla se agitó a 80 °C durante 4 h bajo atmósfera de N_2. La mezcla se diluyó con agua (200 ml) y se extrajo con EtOAc (50 ml × 3). La fase orgánica combinada se lavó con salmuera (30 ml x 2), se secó con Na_2SO_4 anhidro, se filtró y se concentró a vacío. El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 100 : El compuesto 7-(4-benciloxiciclohexen-1-il)-2-azaespiro[3,5]non-6-eno-2-carboxilato de ter-butilo (3,60 g, 8,79 mmol, 46 % de rendimiento) se obtuvo como un aceite amarillo.

[001104] LC-MS: MS (ESI^+): t_R = 0,681 min, m/z = 354,1 [M - tBu+]

[001105] Solución 1: {7-(4-benciloxiciclohexen-1-il)-2-azaespiro[3,5]non-6-eno-2-carboxilato de ter-butilo (3,60 g, 8,79 mmol, 1,0 eq) en MeOH (20 ml) y THF (20 ml). El lecho fijo (denominado FLR1, volumen 5 ml) se rellenó con catalizador granular de 5 %

Pd/C (WXC1030, 3,00 g). El regulador de contrapresión H_2 se ajustó a 1,5 MPa y el caudal de H_2 fue de 20 ml/min. Luego, la solución S1 fue bombeada por la bomba 1{S1,P1,0,303 ml / min } al lecho fijo{FLR1,SS,Fixed bed,6,350(1/4") mm,1 ml,50 °C }. A continuación, se recogió la mezcla de reacción a la salida del reactor. Una vez finalizada la inyección del fluido de reacción, el lecho fijo se lavó con metanol adicional (20 ml). El residuo se purificó mediante cromatografía en gel de sílice (éter de petróleo:acetato de etilo = 1 : El compuesto 7-(4-hidroxiciclohexil)-2-azaespiro[3,5]nonano-2-carboxilato de ter-butilo (750 mg, 2,32 mmol, 26 % de rendimiento) se obtuvo como un sólido blanco.

[001106] A una solución de 7-(4-hidroxiciclohexil)-2-azaespiro[3,5]nonano-2-carboxilato de ter-butilo (1,20 g, 3,71 mmol, 1,0 eq) en DCM (15 ml) se le añadieron Et_3N (1,13 g, 11,13 mmol, 1,55 ml, 3,0 eq) y metanosulfonato de metilsulfonilo (1,29 g, 7,42 mmol, 2,0 eq). La mezcla resultante se agitó a 25 °C durante 1 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 10/0). El compuesto 7-(4-metilsulfoniloxiciclohexil)-2-azaespiro[3,5]nonano-2-carboxilato de ter-butilo (1,16 g, 2,89 mmol, 77 % de rendimiento) se obtuvo como un aceite incoloro.

[001107] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4,97 (s, 1H), 3,56 (d, **J** = 14,4 Hz, 1H), 2,08 (d, J = 12,0 Hz, 1H), 1,90 (d, J = 13,2 Hz, 2H), 1,68 (d, J = 12,0 Hz, 2H), 1,59 (s, 4H), 1,44 (s, 4H).

[001108] A una solución de 7-(4-metilsulfoniloxiciclohexil)-2-azaespiro[3,5]nonano-2-carboxilato de ter-butilo (1,06 g, 2,64 mmol, 1,0 eq) en DMF (10 ml) se añadieron Cs_2CO_3 (2,58 g, 7,92 mmol, 3,0 eq) y 1-(3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridin-5-il)etanona (768 mg, 2,64 mmol, 1,0 eq). La mezcla se agitó a 100 °C durante 12 h. La reacción se detuvo añadiendo agua (100 ml) a 25 °C y, a continuación, se extrajo con EtOAc (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 250*50mm*10 um; fase móvil: [agua(TFA)-ACN]; gradiente: 55 %-85 % B durante 21 min) y HPLC preparativa (columna: Welch Ultimate XB-CN 250*50*10um; fase móvil: [hexano-etanol]; gradiente: 1 %-40 % B durante 15 min). El compuesto ter-butil 7-[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]-2-azaespiro[3,5]nonano-2-carboxilato (190 mg, 318 µmol, 11 % de

rendimiento) se obtuvo como un sólido blanco.

[001109] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4,45 - 4,20 (m, 2H), 3,92 - 3,67 (m, 2H), 3,56 (d, **J** = 16,8 Hz, 1H), 2,78 - 2,62 (m, 1H), 2,24 - 2,14(m, 1H), 1,90 - 1,65 (m, 1H), 1,45 (s, 2H), 1,43 - 1,33(m, 1H), 1,23 - 0,93 (m, 1H).

[001110] Una mezcla de 7-[4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)ciclohexil]-2-azaespiro[3,5]nonano-2-carboxilato de ter-butilo (180 mg, 301 µmol, 1,0 eq), 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (95 mg, 362 µmol, 1,2 eq), CPhos Pd G3 (24 mg, 30 µmol, 0,1 eq), Cs_2CO_3 (295 mg, 905 µmol, 3,0 eq) en 2-metilbutan-2-ol (5 ml) fue desgasificada y se purgó con N_2 tres veces, y luego la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (60 ml) y se extrajo con EtOAc (50 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante TLC preparativa (SiO_2, DCM/MeOH = 15/1). El compuesto ter-butil 7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2-azaespiro[3,5]nonano-2-carboxilato (178 mg, 243 µmol, 80 % de rendimiento) se obtuvo como un sólido amarillo.

[001111] LC-MS: MS (ESI$^+$): t_R = 0,651 min, m/z = 732,4 [M + H$^+$]

[001112] A una solución de 7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2-azaespiro[3,5]nonano-2-carboxilato de ter-butilo (178 mg, 243 µmol, 1,0 eq) en DCM (2 ml) se le agregó TFA (2 ml). La mezcla se agitó a 25 °C durante 1 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex Luna C18 150*25mm*10um; fase móvil: [H_2O (0,225 % FA)-ACN]; gradiente: 18 %-48 % B durante 15,0 min). El compuesto 1-[1-[4-(2-azaespiro[3,5]nonan-7-il)ciclohexil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (110 mg, 174 µmol, 71 % de rendimiento) se obtuvo como un sólido blanco.

[001113] LC-MS: MS (ESI$^+$): t_R = 0,442 min, m/z = 632,5 [M + H$^+$]

[001114] Una mezcla de 1-[1-[4-(2-azaespiro[3,5]nonan-7-il)ciclohexil]-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (100 mg, 158 µmol, 1,0 eq), N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-iodobenzamida (87 mg, 174 µmol, 1,1 eq), Xphos Pd G4 (13 mg, 15 µmol, 0,1 eq), Cs_2CO_3 (154 mg, 474 µmol, 3,0 eq) en dioxano (8 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 90 °C

durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (40 ml) y se extrajo con EtOAc (20 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex Luna C18 150*25mm*10um; fase móvil: [H_2O (0,225 % FA)-ACN]; gradiente: 80 %-100 % B durante 9,0 min). El compuesto 4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (66,16 mg, 65,62 µmol, 41 % de rendimiento) se obtuvo como un sólido blanco.

[001115] **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7,76 - 7,70 (m, 3H), 7,65 (d, J = 8,4 Hz, 1H), 7,50 (s, 1H), 7,44 (d, J = 9,2 Hz, 1H), 7,09 (s, 1H), 6,81 - 6,61 (m, 3H), 6,53 (m, 1H), 6,41 (d, J = 8,8 Hz, 2H), 4,26 (s, 1H), 4,18 - 4,10 (m, 2H), 4,04 (d, J = 9,6 Hz, 1H), 3,97 (d, J = 4,4 Hz, 1H), 3,90 (s, 3H), 3,86 (s, 3H), 3,75 - 3,66 (m, 2H), 3,61 - 3,52 (m, 6H), 3,36 (s, 5H), 2,86 - 2,81 (m, 3H), 2,75 - 2,69 (m, 1H), 2,07 (s, 2H), 1,96 (s, 3H), 1,92 (d, J = 12,4 Hz, 4H), 1,85 - 1,73 (m, 4H), 1,66 (m, 2H), 1,52 - 1,42 (m, 2H), 1,21 (s, 6H), 1,14 (s, 7H).

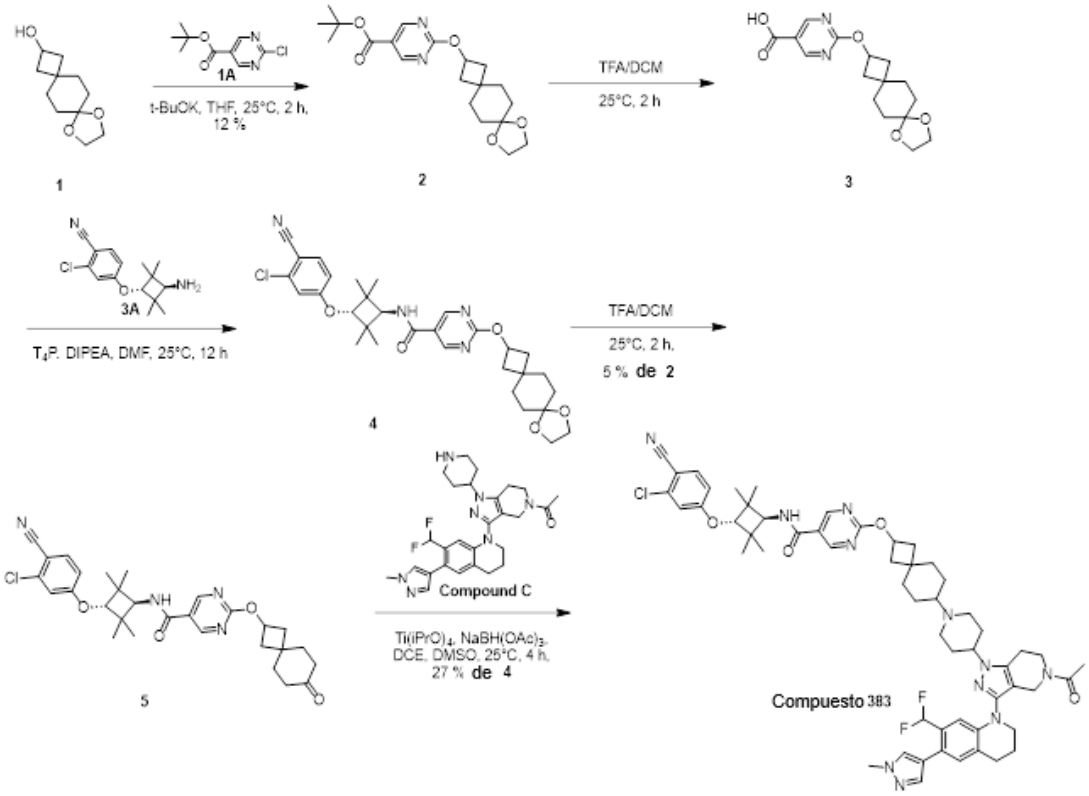
[001116] **LC-MS:** MS (ESI$^+$): t_R = 3,661 min, m/z = 1008,8 [M + H$^+$]

[001117] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 58.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
377	2-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,72 (s, 2 H), 7,60-7,58 (d, *J*=8,8 Hz, 1 H), 7,56-7,54 (d, *J*=5,6 Hz, 1 H), 7,42-7,41 (m, 1 H), 7,06 (s, 1 H), 6,98-6,97 (m, 1 H), 6,88 (s, 1 H), 6,83-6,81 (d, *J*=10,8 Hz, 1 H), 6,54-6,41 (m, 1 H), 5,94-5,92 (d, *J*=7,2 Hz, 1 H), 4,80 (s, 1H), 4,27 (s, 1H), 4,14-4,13 (m, 2H), 4,12 (s, 1H), 4,06 (s, 3H), 3,91-3,90 (m, 6 H), 3,85-3,73 (m, 3H), 2,91-2,90 (m, 2H), 2,75-2,74 (m, 1 H), 2,74-2,73 (m, 1 H), 2,18(s, 1H), 2,09-2,08 (m, 4H), 2,03-2,02(m, 5H), 2,01-1,95 (m, 3 H), 1,77-1,74 (m, 2 H), 1,60-1,55 (m,	1014,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2 H), 1,26-1,23 (m, 12 H), 1,14-1,09 (m, 5 H)	
379	2-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]ciclohexil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,57 (d, J = 8,8 Hz, 1H), 7,54 (d, J = 5,2 Hz, 1H), 7,41 (d, J = 6,4 Hz, 1H), 7,06 - 6,99 (m, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,92 (d, J = 9,6 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,69 - 6,36 (m, 1H), 5,92 (d, J = 8,0 Hz, 1H), 4,31 - 4,13 (m, 2H), 4,12 (d, J = 8,4 Hz, 1H), 4,04 (s, 1H), 4,00 (td, J = 4,4, 9,6 Hz, 1H), 3,96 (d, J = 2,0 Hz, 3H), 3,92 - 3,88 (m, 1H), 3,85 (d, J = 14,0 Hz, 4H), 3,80 - 3,64 (m, 3H), 2,92 - 2,84 (m, 2H), 2,82 - 2,70 (m, 2H), 2,19 - 2,03 (m, 7H), 2,02 - 1,94 (m, 4H), 1,87 (d, J = 12,0 Hz, 2H), 1,75 (dd, J = 1,6, 9,6 Hz, 2H), 1,59 - 1,45 (m, 5H), 1,33 - 1,29 (m, 1H), 1,23 (d, J = 12,4 Hz, 12H), 1,01 - 0,88 (m, 2H)	1014,7
380	4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4Hpirazolo[4,3-c]piridin-1-il]ciclohexil]-2-azaespiro[3,5]nonan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	(400 MHz, DMSO-$_d$7,78, ppm) δ 7,60 (s, 1H), 7,40 (s, 1H), 6,95-6,85 (m, 3H), 6,63 (s, 1H), 6,54-6,51 (m, 1H), 6,45-4,30 (m, 3H), 4,30-4,16 (m, 3H), 4,09-4,03 (m, 1H), 3,87-3,63 (m, 2H), 3,59-3,45 (m, 1H), 2,85-2,61 (m, 1H), 2,07-1,89 (m, 1H), 1,88-1,62 (m, 4H), 1,55-1,42 (m, 1H), 1,39-1,36 (m, 1H), 1,35-1,12 (m, 3H), 0,95-0,85 (m, 3H).	1008,7

[001118] Ejemplo 59: Síntesis de 2-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil] espiro[3,5]nonan-2-il]oxi-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 383**)



[001119] La síntesis de **1** se informó en WO2022/122876 A1.

[001120] La síntesis de **1A** fue reportada en US10836749 B1.

[001121] La síntesis de **3A** fue reportada en US2017/8904 A1.

[001122] A una solución de 2-cloropirimidina-5-carboxilato de ter-butilo (220 mg, 1,02 mmol, 1,0 eq) se le agregó t-BuOK (1 M, 2 ml, 2,0 eq) a 25 °C. La mezcla se agitó a 60 °C durante 2 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 3/1 a 0/1). Se obtuvo el compuesto ter-butil 2-(8,11-dioxadiespiro [3,2,47,24] tridecan-2-iloxi) pirimidina-5-carboxilato (45 mg, 120 µmol, 12 % de rendimiento) como un sólido blanco.

[001123] LC-MS: MS (ESI^+): t_R = 0,645 min, m/z = 377,2 [M + H^+]

[001124] A una solución de 2-(8,11-dioxadiespiro[3,2,47,24]tridecan-2-iloxi)pirimidina-5-carboxilato de ter-butilo (45 mg, 120 µmol, 1,0 eq) en DCM (0,5 ml) se le agregó TFA (0,5 ml) a 25 °C. La mezcla se agitó a 25 °C durante 2 h. Luego, al residuo se le añadieron 50 ml de diclorometano/metanol (10/1), y se ajustó el pH a 7-8 con hidróxido de amonio, se secó sobre sulfato de sodio anhidro, se filtró y se concentró al vacío para obtener un residuo. Compuesto Ácido 2-(8,11-dioxadiespiro[3,2,47,24]tridecan-2-iloxi)pirimidina-5-carboxílico (38 mg) se obtuvo como un sólido amarillo y se utilizó

directamente en el siguiente paso sin purificación adicional.

[001125] LC-MS: MS (ESI^+): t_R = 0,483 min, m/z = 321,1 [M + H^+]

[001126] A una solución de ácido 2-(8,11-dioxadiespiro[3,2,47,24]tridecan-2-iloxi)pirimidina-5-carboxílico (35 mg), 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-clorobenzonitrilo (38 mg), DIPEA (111 mg, 861 µmol, 150 µl, 7,9 eq) en DMF (0,5 ml) se agregó T_4P (160 mg, 222 µmol, 50 % de pureza, 2,0 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla se vertió en 50 ml de agua, se agregó acetato de etilo (50 ml × 3) a la mezcla y se separó la fase orgánica, la mezcla resultante se lavó con salmuera (50 ml × 2). Las fases orgánicas combinadas se secaron en sulfato de sodio y se filtraron y se concentraron a vacío. El compuesto N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-(8,11-dioxadiespiro[3,2,47,24]tridecan-2-iloxi)pirimidina-5-carboxamida (45 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001127] LC-MS: MS (ESI^+): t_R = 0,700 min, m/z = 581,3 [M + H^+]

[001128] A una solución de N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-(8,11-dioxadiespiro[3,2,47,24]tridecan-2-iloxi)pirimidina-5-carboxamida (45 mg) en DCM (1 ml) se le agregó TFA (110 mg, 966 µmol, 71,4 µl, 12 eq). La mezcla se agitó a 25 °C durante 1 h. La mezcla se vertió en 50 ml de agua, se agregó acetato de etilo (50 ml × 3) a la mezcla y se separó la fase orgánica, la mezcla resultante se lavó con salmuera (50 ml × 2). Las fases orgánicas combinadas se secaron en sulfato de sodio y se filtraron y se concentraron a vacío. El producto crudo se purificó mediante HPLC de fase inversa (columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 50 %-80 % B durante 10 min). El compuesto N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-(7-oxospiro[3,5]nonan-2-il)oxipirimidina-5-carboxamida (32 mg, 59,6 µmol, 55 % de rendimiento en tres pasos) se obtuvo como un sólido blanco.

[001129] LC-MS: MS (ESI^+): t_R = 0,655 min, m/z = 537,3 [M + H^+]

[001130] A una solución de N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]-2-(7-oxospiro[3,5]nonan-2-il)oxipirimidina-5-carboxamida (32 mg, 59,6 µmol, 1,0 eq), 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (31 mg, 60,8 µmol, 1,0 eq) en DCE (0,3 ml) y DMSO (0,3 ml) se agregó $Ti(Oi\text{-}Pr)_4$ (254 mg, 894 µmol, 263 µl, 15 eq) a 25 °C. La mezcla se agitó a 25 °C durante 2 h. Se agregó $NaBH(OAc)_3$ (189 mg, 894 µmol, 15 eq) y se agitó a 25 °C durante 2 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El producto crudo se purificó mediante HPLC de fase inversa

(columna: Phenomenex luna C18 150 × 25 mm × 10 µm; fase móvil: [agua (FA)-ACN]; gradiente: 32 %-62 % B durante 10 min). El compuesto 2-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil] espiro[3,5]nonan-2-il]oxi-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (16,63 mg, 15,97 µmol, 27 % de rendimiento) se obtuvo como un sólido blanco.

[001131] ^{1}H NMR (400 MHz, DMSO-d**6**) δ = 8,95 (s, 1H), 8,07 (d, J = 4,8 Hz, 2H), 7,90 (d, J = 4,8 Hz, 1H), 7,75 - 7,50 (m, 3H), 7,22 - 7,71 (m, 2H), 7,12 - 7,54 (m, 1H), 7,04 - 6,99 (m, 1H), 6,97 - 6,62 (m, 1H), 5,27 - 5,12 (m, 1H), 4,49 – 4,24 (m, 1H), 4,21 - 4,09 (m, 1H), 4,05 - 3,86 (m, 3H), 3,78 - 3,67 (m, 2H), 3,62 - 3,56 (m, 1H), 3,29 - 3,22 (m, 1H), 2,88 - 2,73 (m, 2H), 2,34 – 2,27 (m, 1H), 2,19 - 1,70 (m, 2H), 1,58 - 1,36 (m, 2H), 1,23 - 1,12 (m, 1H).

[001132] LC-MS: MS (ESI$^+$): t_R = 3,143 min, m/z = 1030,7 [M + H$^+$]

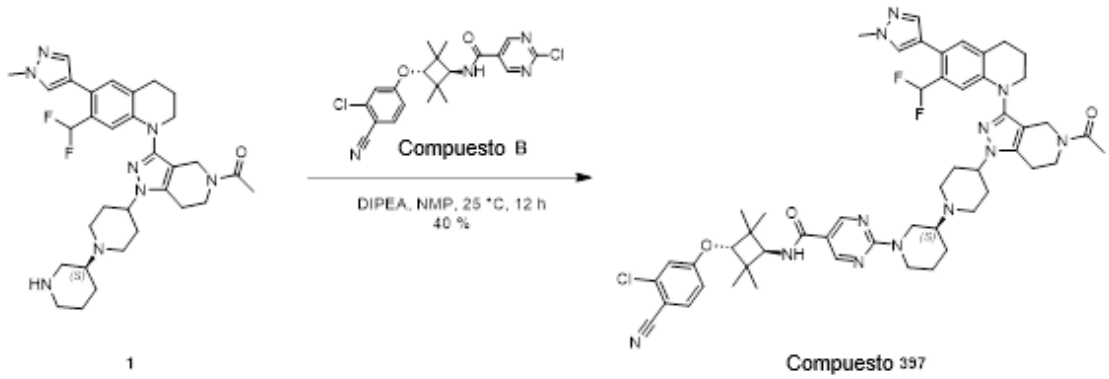
[001133] Los compuestos que se muestran a continuación se prepararon de forma similar a como se describe en el Ejemplo 59.

Compuesto	**Nombre**	**RMN ^{1}H (400 MHz, DMSO-d6):**	**LC-MS (M+H)$^+$:**
384	4-[7-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil] espiro[3,5]nonan-2-il]oxi-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 8,38 (s, 1H), 7,80 (d, J = 8,8 Hz, 2H), 7,75 (s, 1H), 7,69 - 7,62 (m, 2H), 7,49 (s, 1H), 7,10 (s, 1H), 6,90 (d, J = 8,8 Hz, 2H), 6,79 - 6,51 (m, 4H), 4,77 (br t, J = 6,8 Hz, 1H), 4,26 (s, 1H), 4,16 - 4,08 (m, 2H), 4,04 (d, J = 9,0 Hz, 1H), 3,96 (br d, J = 4,6 Hz, 1H), 3,88 (d, J = 16,6 Hz, 6H), 3,74 - 3,66 (m, 2H), 3,63 - 3,55 (m, 3H), 2,96 - 2,80 (m, 6H), 2,77 - 2,69 (m, 1H), 2,28 (br d, J = 9,6 Hz, 3H), 2,07 (s, 2H), 1,99 - 1,91 (m, 5H), 1,88 - 1,76 (m, 4H), 1,74 - 1,58 (m, 4H), 1,45 - 1,29 (m, 4H), 1,22 (s, 6H), 1,14 (s, 6H)	1024,8
385	2-[6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]espiro[3,3]heptan-2-il]oxi-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-	1H NMR (400 MHz, METANOL-d4) δ = 8,02 (s, 1H), 7,91 (d, J = 8,8 Hz, 1H), 7,76 – 7,51 (m, 1H), 7,28 - 7,19 (m, 1H), 7,14 - 7,10 (m, 2H), 7,05 - 7,00 (m, 1H), 6,96 - 6,65 (m, 1H), 5,19 - 5,07 (m, 1H),	1002,7

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
	tetrametilciclobutil]pirimidina-5-carboxamida	4,35 (d, J = 5,3 Hz, 1H), 4,20 - 3,99 (m, 1H), 3,76 - 3,66 (m, 1H), 3,56 (br t, J = 4,5 Hz, 1H), 2,93 - 2,80 (m, 1H), 2,76 - 2,69 (m, 1H), 2,65 - 2,59 (m, 1H), 2,45 (br d, J = 13,7 Hz, 1H), 2,26 - 2,97 (m, 2H), 2,97 - 2,05 (m, 1H), 2,04 - 1,94 (m, 1H), 1,94 - 1,80 (m, 1H), 1,16 - 1,09 (m, 2H).	
386	4-[6-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]espiro[3,3]heptan-2-il]oxi-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,81 - 7,79 (d, *J* = 8,8 Hz, 2H), 7,75 (s, 1H), 7,68 - 7,66 (d, *J* = 8,8 Hz, 2H), 7,50 (s, 1H), 7,11 (s, 1H), 6,91 - 6,80 (m, 4H), 6,65 - 6,64 (d, *J* = 2,0 Hz, 1H), 6,56 - 6,53 (m, 1H), 4,73 - 4,68 (m, 1H), 4,27 (s, 1H), 4,17 - 4,12 (m, 2H), 4,06 - 4,04 (m, 2H), 3,91 - 3,87 (m, 6H), 3,69 (m, 2H), 3,60 - 3,57 (m, 2H), 2,85 (m, 6H), 2,67 - 2,65 (m, 3H), 2,10 - 2,08 (m, 4H), 2,00 - 1,96 (m, 6H), 1,88 - 1,83 (m, 6H), 1,23 (s, 6H), 1,15 (s, 6H)	996,8
395	2-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]espiro[3,5]nonan-7-il]oxi-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ = 8,84 (s, 2H), 7,52 - 7,42 (m, 2H), 7,33 (d, J = 5,6 Hz, 1H), 7,03 - 6,83 (m, 3H), 6,74 (dd, J = 2,4, 8,8 Hz, 1H), 6,64 - 6,31 (m, 1H), 6,20 (br d, J = 8,0 Hz, 1H), 5,00 (br d, J = 3,2 Hz, 1H), 4,39 - 4,19 (m, 2H), 4,15 - 4,05 (m, 2H), 4,02 (s, 1H), 3,94 - 3,78 (m, 4H), 3,75 - 3,47 (m, 4H), 3,43 - 3,00 (m, 4H), 2,87 - 2,58 (m, 6H), 2,50 - 2,22 (m, 3H), 2,10 (s, 2H), 2,05 - 1,97 (m, 5H), 1,85 - 1,41 (m, 9H), 1,21 (s, 6H), 1,18 - 1,13 (m, 6H)	1030,7
396	4-[2-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-	($CDCl_3$) δ = 8,50 (s, 1H), 7,65 (d, J = 8,8 Hz, 2H), 7,50 - 7,43 (m, 1H), 7,38 (d, J = 8,8 Hz, 1H), 7,33 (d, J = 7,2 Hz, 1H), 7,00 - 6,76 (m,	1024,8

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
	1-piperidil]espiro[3,5]nonan-7-il]oxi-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	4H), 6,64 - 6,41 (m, 1H), 6,39 (d, J = 2,0 Hz, 1H), 6,35 - 6,29 (m, 1H), 6,06 (d, J = 8,0 Hz, 1H), 4,25 (br d, J = 3,2 Hz, 1H), 4,17 (s, 1H), 4,10 - 4,02 (m, 2H), 3,98 (s, 1H), 3,93 - 3,79 (m, 8H), 3,73 - 3,54 (m, 3H), 2,97 (br d, J = 7,2 Hz, 2H), 2,84 - 2,60 (m, 5H), 2,17 (br d, J = 9,6 Hz, 2H), 2,08 (s, 1H), 2,04 - 1,95 (m, 6H), 1,81 - 1,47 (m, 10H), 1,46 - 1,37 (m, 2H), 1,18 (d, J = 10,4 Hz, 12H)	

[001134] Ejemplo 60: Síntesis de 2-[(3S)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 397**)



[001135] A una mezcla de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3S)-3-piperidil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (60 mg, 93 µmol, 1,0 *eq*) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (39 mg, 93 µmol, 1,0 *eq*) en NMP (1 ml) se agregó DIPEA (60 mg, 469 µmol, 81 µl, 5,0 *eq*), la mezcla se agitó a 25 °C durante 12 h. La mezcla se filtró y se concentró para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua(FA)-ACN]; gradiente: 30 %-50 % B durante 10 min). El compuesto 2-[(3S)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-

2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (38,2 mg, 38,48 µmol, 40 % de rendimiento) se obtuvo como un sólido amarillo.

[001136] ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8,78 (s, 1H), 7,94 - 7,86 (m, 1H), 7,84 - 7,68 (m, 2H), 7,50 - 7,55 (m, 2H), 7,25 - 7,28 (m, 1H), 7,28 - 7,08 (m, 2H), 7,05 - 6,98 (m, 1H), 6,97 - 6,61 (m, 1H), 5,02 - 4,69 (m, 2H), 4,66 - 4,47 (m, 1H), 4,29 - 4,77 (m, 1H), 4,21 - 4,09 (m, 1H), 4,08 - 4,00 (m, 1H), 3,87 - 3,67 (m, 1H), 3,65 - 3,56 (m, 2H), 3,30 - 2,96 (m, 5H), 2,93 - 2,70 (m, 2H), 2,61 - 2,54 (m, 1H), 2,21 - 1,62 (m, 1H), 1,53 - 1,34 (m, 1H), 1,27 - 1,18 (m, 1H), 1,16 - 1,07 (m, 1H).

[001137] LC-MS: MS (ESI$^+$): t_R = 3,047 min, m/z = 975,6 [M + H$^+$]

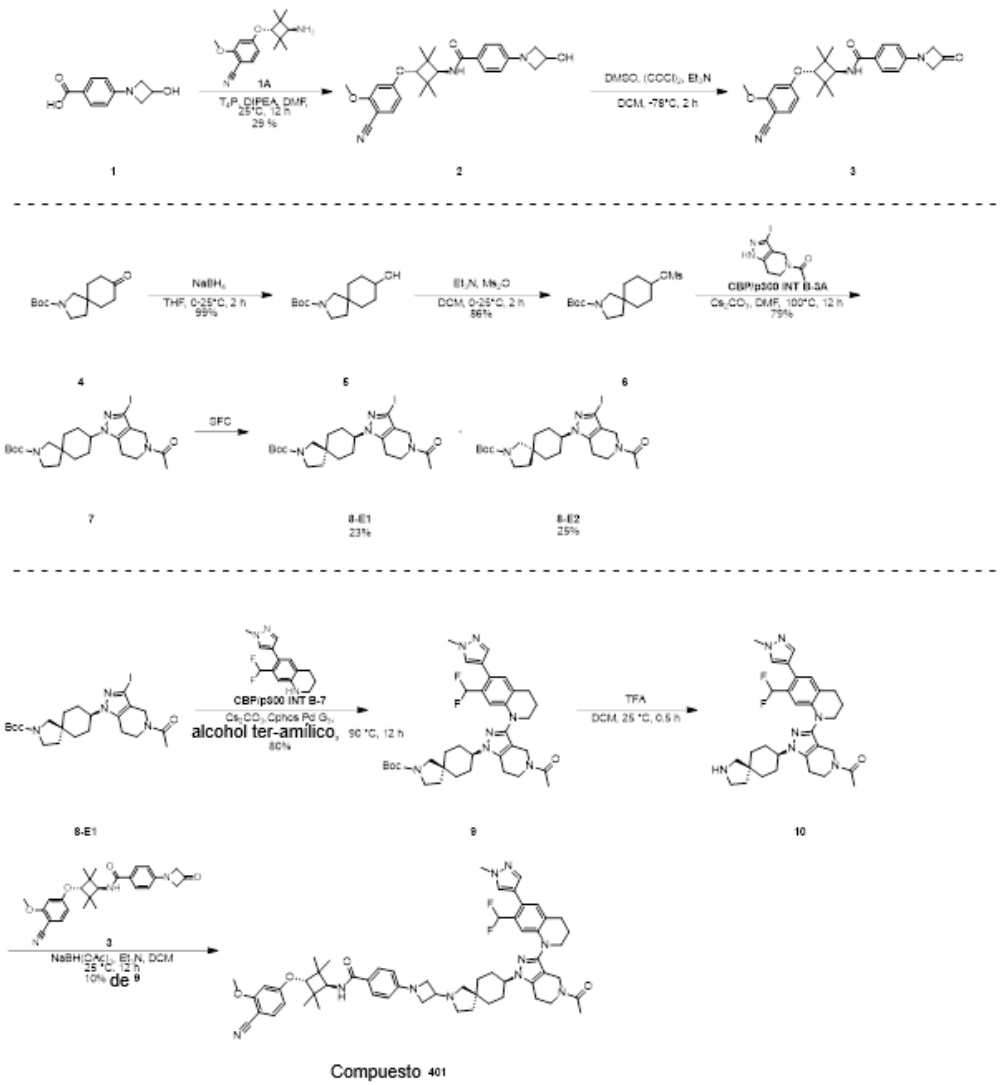
[001138] SFC: t_1 = 1,375 min, 100 %

[001139] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 60.

Compuesto	**Nombre**	**^{1}H NMR (300 MHz, $CDCl_3$):**	**LC-MS (M+H)$^+$:**
398	2-[(3R)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,70 (s, 2H), 7,61 - 7,50 (m, 2H), 7,44 - 7,37 (m, 1H), 7,09 - 6,94 (m, 2H), 6,90 - 6,77 (m, 2H), 6,71 - 6,36 (m, 1H), 5,94 (d, J = 8,0 Hz, 1H), 4,99 - 4,84 (m, 1H), 4,75 - 4,62 (m, 1H), 4,29 - 4,08 (m, 3H), 4,04 (s, 1H), 4,00 - 3,86 (m, 5H), 3,79 - 3,66 (m, 3H), 3,32 - 3,10 (m, 2H), 3,06 - 2,93 (m, 2H), 2,92 - 2,79 (m, 3H), 2,78 - 2,71 (m, 1H), 2,54 - 2,33 (m, 3H), 2,31 - 2,19 (m, 2H), 2,17 (s, 1H), 2,12 - 2,01 (m, 5H), 2,00 - 1,85 (m, 3H), 1,60 - 1,45 (m, 2H), 1,30 - 1,19 (m, 12H)	975,6
399	4-[(3S)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	$_6$H NMR (400 MHz, DMSO-d6) δ = 7,60 (s, 1H), 7,54 - 7,45 (m, 1H), 7,16 - 7,08 (m, 2H), 6,99 - 6,61 (m, 2H), 6,58 - 7,28 (m, 1H), 7,28 - 4,09 (m, 2H), 4,07 - 3,97 (m, 1H), 3,95 - 3,89 (m, 1H), 3,86 - 5,41 (m, 2H), 3,84 - 3,78 (m, 1H), 3,77 - 3,67 (m, 1H), 3,63 - 3,56 (m, 1H), 3,47 - 3,41 (m, 1H), 3,10 - 2,96 (m, 1H), 2,90 - 2,69 (m, 6H),	969,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
		2,47 - 2,37 (m, 2H), 2,11 - 2,04 (m, 2H), 2,04 - 1,84 (m, 1H), 1,81 - 1,72 (m, 1H), 1,58 - 1,41 (m, 1H), 1,26 - 1,19 (m, 1H), 1,18 - 1,11 (m, 1H).	
400	4-[(3R)-3-[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,69 (d, J = 8,8 Hz, 2H), 7,53 (d, J = 6,4 Hz, 1H), 7,46 (d, J = 8,8 Hz, 1H), 7,43 - 7,37 (m, 1H), 7,07 - 6,99 (m, 1H), 6,91 (d, J = 9,2 Hz, 2H), 6,88 - 6,83 (m, 1H), 6,76 - 6,50 (m, 1H), 6,47 (d, J = 2,0 Hz, 1H), 6,43 - 6,37 (m, 1H), 6,12 (d, J = 8,0 Hz, 1H), 4,26 (s, 1H), 4,20 - 4,09 (m, 2H), 4,05 (s, 1H), 3,96 (d, J = 2,4 Hz, 5H), 3,94 - 3,89 (m, 4H), 3,82 - 3,68 (m, 4H), 3,28 - 3,10 (m, 2H), 2,94 - 2,78 (m, 4H), 2,78 - 2,67 (m, 3H), 2,63 - 2,46 (m, 2H), 2,30 - 2,20 (m, 2H), 2,17 (s, 1H), 2,11 - 2,00 (m, 6H), 1,91 - 1,84 (m, 2H), 1,51 (br d, J = 11,6 Hz, 2H), 1,25 (d, J = 10,4 Hz, 12H)	969,9

[001140] Ejemplo 61: Síntesis de 4-[3-[8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decan-2-il]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (**Compuesto 401**)



[001141] La síntesis de **1** se informó en WO2012/177606 A1.

[001142] La síntesis de **1A** se informó en WO2021/127443 A1.

[001143] La síntesis de **4** se informó en WO2015/94803 A1.

[001144] A una solución de ácido 4-(3-hidroxiazetidin-1-il)benzoico (700 mg, 2,28 mmol, 1,0 eq, TFA) y 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-metoxibenzonitrilo (885 mg, 2,28 mmol, 1,0 eq, TFA) en DCM (10 ml) se le agregó DIPEA (1,47 g, 11,39 mmol, 1,98 ml, 5,0 eq) y T_4P (3,28 g, 4,56 mmol, 50 % de pureza, 2,0 eq). La mezcla de reacción se agitó a 20 °C durante 1 h. La mezcla de reacción se diluyó con agua (5 ml) y se extrajo con EtOAc (10 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se trituró con éter de petróleo/acetato de etilo = 10/1 a 25 °C durante 1 h. Se obtuvo el compuesto N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-(3-hidroxiazetidin-1-il)benzamida (300 mg,

667 µmol, rendimiento del 29,29 %) como un sólido blanco.

[001145] LC-MS: MS (ESI^+): t_R = 0,549 min, m/z = 450,3 [M + H^+]

[001146] Una solución de $(COCl)_2$ (106 mg, 834 µmol, 73 µl, 1,5 eq) en DCM (3 ml) se enfrió a -78 °C, se agregó DMSO (130 mg, 1,67 mmol, 1305 µl, 3,0 eq) a la mezcla a -78 °C y se agitó a -78 °C durante 0,5 h. N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]-4-(3-hidroxiazetidin-1-il)benzamida (250 mg, 556 µmol, 1,0 eq) en DCM (3 ml) se agregó a la mezcla a -78 °C y se agitó a -78 °C durante 1 h. Et_3N (338 mg, 3,34 mmol, 464 µl, 6,0 eq) se agregó a la mezcla a -78 °C y se agitó a -78 °C durante 0,5 h. La mezcla se neutralizó con agua (10 ml), se extrajo con EtOAc (20 ml x 3), se lavó con salmuera (20 ml), se secó sobre Na_2SO_4, se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida para obtener un residuo. El producto crudo fue N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]-4-(3-oxoazetidin-1-il)benzamida (250 mg) se obtuvo como un sólido amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001147] LC-MS: MS (ESI^+): t_R = 0,584 min, m/z = 448,1 [M + H^+]

[001148] A una solución agitada de etil 8-dioxaespiro [4,5]decano-2-carboxilato (10,00 g, 39,47 mmol, 1,0 equiv.) en THF (100 ml), se le agregó LDA (350 ml, 63,17 mmol, 1,6 equiv) a 0 °C en atmósfera de N_2. La mezcla se agitó a 25 °C durante 1 h. La reacción se detuvo añadiendo 100 ml de solución saturada de cloruro de amonio y, a continuación, se extrajo con EtOAc (200 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 3), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto ter-butil 8-hidroxi-2-azaespiro[4,5]decano-2-carboxilato (10,00 g, 39,16 mmol, 99 % de rendimiento) se obtuvo como un aceite incoloro.

[001149] A una solución de 8-hidroxi-2-azaespiro[4,5]decano-2-carboxilato de ter-butilo (10,00 g, 39,16 mmol, 1,0 eq) en DCM (100 ml) se le añadieron Et_3N (11,89 g, 117,48 mmol, 16,4 ml, 3,0 eq) y metanosulfonato de metilsulfonilo (13,64 g, 78,32 mmol, 2,0 eq) a 0 °C. La mezcla se agitó a 25 °C durante 2 h. La reacción se detuvo añadiendo 30 ml de agua y, a continuación, se extrajo con DCM (20 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 20/1 a 10/1). El compuesto ter-butil 8-metilsulfoniloxi-2-azaespiro[4,5]decano-2-carboxilato (11,20 g, 33,59 mmol, 86 % de rendimiento) se obtuvo como un aceite incoloro.

[001150] A una solución de 8-metilsulfoniloxi-2-azaespiro[4,5]decano-2-carboxilato de ter-butilo (11,20 g, 33,59 mmol, 1,0 eq) en DMF (200 ml) se le añadieron Cs_2CO_3 (32,83 g, 100,77 mmol, 3,0 eq) y 1-(3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridin-5-il)etanona (9,78 g, 33,59 mmol, 1,0 eq). La mezcla de reacción se agitó a 45 oC durante 12 h. La mezcla de reacción se inactivó con agua (100 ml) y se extrajo con acetato de etilo (100 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 1/1). El compuesto ter-butil 8-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[4,5]decano-2-carboxilato (14,00 g, 26,49 mmol, 79 % de rendimiento) se obtuvo como un sólido blanco.

[001151] LC-MS: MS (ESI^+): t_R = 0,581 min, m/z = 529,1 [M + H^+]

[001152] El 8-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[4,5]decano-2-carboxilato de ter-butilo (14,00 g, 26,49 mmol, 1,0 eq) se separó por SFC tres veces: el primer método (columna: DAICEL CHIRALPAK AD (250 mm * 50 mm, 10 µm); fase móvil: [CO_2-EtOH (0,1 % NH_3H_2O)]; B%: 32 %, modo de elución isocrática), el segundo método (columna: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 µm); fase móvil: [CO_2-EtOH(0,1 %NH_3H_2O)];B%:20 %, modo de elución isocrática), el tercer método (columna: DAICEL CHIRALCEL OD(250mm*30mm,10um);fase móvil: [CO_2-EtOH(0,1 %NH_3H_2O)];B%:30 %, modo de elución isocrática). El compuesto ter-butil 8-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[4,5]decano-2-carboxilato (3,25 g, 6,01 mmol, 23 % de rendimiento) se obtuvo como un sólido blanco. El compuesto ter-butil 8-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[4,5]decano-2-carboxilato (3,55 g, 6,65 mmol, 25 % de rendimiento) se obtuvo como un sólido blanco.

[001153] ^{1}H NMR (400 MHz, DMSO-$\mathbf{d}_6$) δ = 4,28 - 7,84 (m, 1H), 4,21 - 7,72 (m, 2H), 4,16 - 4,05 (m, 1H), 3,80 - 3,69 (m, 2H), 3,36 - 3,28 (m, 2H), 3,25 - 3,19 (m, 1H), 5,84 - 5,61 (m, 2H), 2,86 - 2,67 (m, 1H), 4,65 - 4,30 (m, 2H), 2,16 - 2,09 (m, 3H), 1,87 - 1,75 (m, 4H), 1,73 - 1,64 (m, 4H), 1,55 - 1,42 (m, 11H).

[001154] LC-MS: MS (ESI^+): t_R = 0,573 min, m/z = 473,0 [M - tBu^+]

[001155] SFC: t_R= 1,281 min, 98,004 %

[001156] ^{1}H NMR (400 MHz, DMSO-$\mathbf{d}_6$) δ = 4,28 (s, 1H), 7,80 - 4,22 (m, 2H), 4,14 - 4,07 (m, 1H), 3,80 - 3,69 (m, 2H), 3,38 - 3,31 (m, 2H), 3,06 - 6,61 (m, 1H), 2,87 - 2,68 (m, 2H), 2,16-5,37 (m, 1H), 4,66 - 2,10 (m, 3H), 1,96 - 1,74 (m, 6H), 1,71 - 1,62 (m, 2H), 1,59 - 1,48 (m, 2H), 1,44 - 1,52 (m, 1H), 1,14 - 1,09 (m, 3H).

[001157] LC-MS: MS (ESI^+): t_R = 0,578 min, m/z = 529,0 [M + H^+]

[001158] SFC: t_R= 1,839 min, 99,338 %

[001159] Una mezcla de 8-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[4,5]decano-2-carboxilato de ter-butilo (1,00 g, 1,89 mmol, 1,0 eq), 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (598 mg, 2,27 mmol, 1,2 eq), Cphos Pd G3 (153 mg, 189 µmol, 0,1 eq), Cs_2CO_3 (2,47 g, 7,57 mmol, 4,0 eq) en 2-metilbutan-2-ol (15 ml) se desgasificó y purgó con N_2 durante 3 veces, y luego la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (30 ml) y se extrajo con EtOAc (20 ml × 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto ter-butil 8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decano-2-carboxilato (1,00 g, 1,51 mmol, 80 % de rendimiento) se obtuvo como un sólido amarillo.

[001160] A una solución de ter-butil 8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decano-2-carboxilato (100 mg, 151 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (1 ml). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto 1-[1-(2-azaespiro[4,5]decan-8-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (80 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001161] A una solución de 1-[1-(2-azaespiro[4,5]decan-8-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (80 mg) en DCM (2 ml) se le agregó Et_3N (43 mg, 425 µmol, 59 µl, 3,0 eq), N-[3-(4-ciano-3-metoxi-fenoxi)-2,2,4,4-tetrametil-ciclobutil]-4-(3-oxoazetidin-1-il)benzamida (95 mg, 213 µmol, 1,5 eq) y $NaBH(OAc)_3$ (150 mg, 709 µmol, 5,0 eq). La mezcla de reacción se agitó a 45 oC durante 12 h. La mezcla de reacción se inactivó con agua (20 ml) y se extrajo con acetato de etilo (20 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 33 %-63 % B durante 11 min). El compuesto 4-[3-[8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-

dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decan-2-il]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida (14,23 mg, 14,30 µmol, 10,07 % de rendimiento en dos pasos) se obtuvo como un sólido blanco,

[001162] ^{1}H NMR (400 MHz, DMSO-**d_6**) δ = 7,78 - 7,69 (m, 2H), 7,65 (d, J = 8,6 Hz, 1H), 7,51 - 7,45 (m, 1H), 7,14 - 7,07 (m, 1H), 6,96 - 7,71 (m, 1H), 7,71 - 6,51 (m, 1H), 6,48 - 6,37 (m, 1H), 4,30 - 4,24 (m, 1H), 4,22 - 4,11 (m, 1H), 4,08 - 4,01 (m, 1H), 3,97 (br d, J = 7,4 Hz, 1H), 3,89 (d, J = 12,8 Hz, 1H), 3,77 - 3,67 (m, 1H), 3,61 - 3,54 (m, 1H), 3,48 – 3,43 (m, 1H), 2,88 - 2,71 (m, 2H), 2,58 - 2,55 (m, 1H), 2,48 - 2,43 (m, 1H), 2,11 (s, 1H), 1,97 (s, 2H), 1,85 - 1,70 (m, 1H), 1,62 - 1,55 (m, 1H), 1,54 - 1,44 (m, 1H), 1,22 - 1,14 (m, 1H).

[001163] LC-MS: MS (ESI$^+$): t_R = 3,072 min, m/z = 995,7 [M + H$^+$]

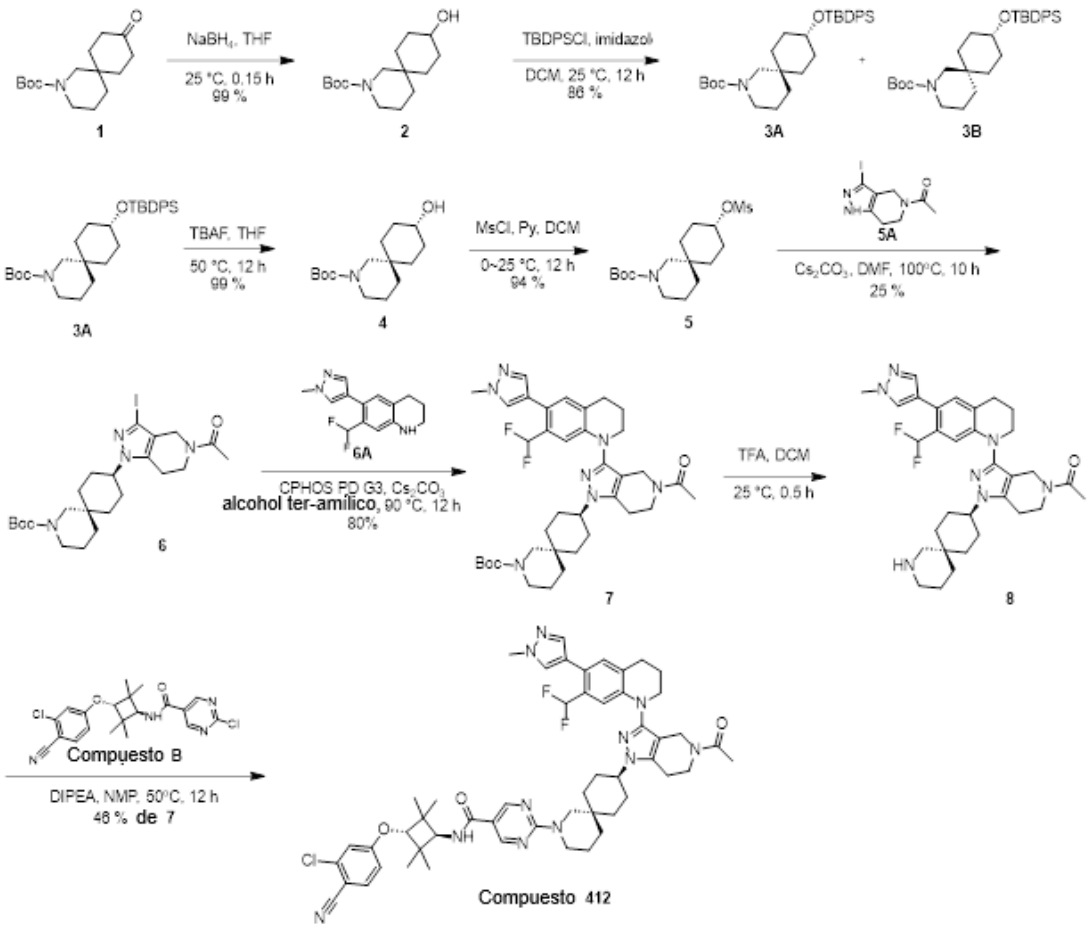
[001164] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 61.

Compuesto	**Nombre**	**RMN ^{1}H (400 MHz, DMSO-d6):**	**LC-MS (M+H)$^+$:**
402	4-[3-[8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4Hpirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decan-2-il]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 8,51 - 8,45 (m, 1H), 7,79 - 7,71 (m, 3H), 7,65 (d, J = 8,4 Hz, 1H), 7,55 - 7,41 (m, 2H), 7,14 - 7,05 (m, 1H), 6,95 - 6,62 (m, 3H), 6,58 - 6,50 (m, 1H), 6,47 - 6,40 (m, 2H), 4,27 (s, 1H), 4,22 - 4,11 (m, 2H), 4,09 - 4,04 (m, 1H), 4,03 - 3,94 (m, 3H), 3,89 (d, J = 17,2 Hz, 6H), 3,77 - 3,66 (m, 4H), 3,63 - 3,55 (m, 2H), 3,45 - 3,37 (m, 2H), 2,90 - 2,70 (m, 4H), 2,60 - 2,56 (m, 2H), 2,38 - 2,29 (m, 2H), 2,08 (s, 2H), 1,97 (s, 3H), 1,90 - 1,78 (m, 3H), 1,73 - 1,61 (m, 4H), 1,57 - 1,45 (m, 2H), 1,23 (s, 6H), 1,15 (s, 6H).	995,6
405	4-[8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,78 - 7,71 (m, 3H), 7,65 (d, J = 8,4 Hz, 1H), 7,53 - 7,49 (m, 1H), 7,38 (d, J = 9,2 Hz, 1H), 7,11 (s, 1H), 6,95 - 6,65 (m, 2H), 6,64 (d, J = 2,0 Hz, 1H), 6,62 - 6,52 (m, 3H), 4,30 - 4,25 (m, 1H), 4,22 - 4,15 (m, 2H), 4,14 - 4,02 (m, 2H), 3,91 (s, 3H), 3,87 (s, 3H), 3,79 - 3,68 (m, 2H),	940,9

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
		3,65 - 3,57 (m, 2H), 3,40 - 3,34 (m, 3H), 3,30 - 3,24 (m, 2H), 2,91 - 2,73 (m, 4H), 2,09 (s, 2H), 2,03 - 1,96 (m, 3H), 1,92 - 1,83 (m, 5H), 1,77 (br d, J = 13,0 Hz, 2H), 1,64 - 1,53 (m, 2H), 1,27 - 1,19 (m, 6H), 1,18 - 1,11 (m, 6H)	
406	4-[8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decan-2-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,78 - 7,70 (m, 3H), 7,65 (d, J = 8,4 Hz, 1H), 7,50 (s, 1H), 7,40 (d, J = 9,2 Hz, 1H), 7,10 (s, 1H), 6,95 - 6,61 (m, 3H), 6,57 - 6,48 (m, 3H), 4,27 (s, 1H), 4,20 - 4,12 (m, 2H), 4,05 (d, J = 9,2 Hz, 2H), 3,91 (s, 3H), 3,87 (s, 3H), 3,78 - 3,66 (m, 2H), 3,63 - 3,56 (m, 2H), 3,40 - 3,36 (m, 2H), 3,13 (s, 2H), 2,90 - 2,71 (m, 4H), 2,08 (s, 2H), 1,97 (s, 7H), 1,88 - 1,80 (m, 2H), 1,78 - 1,69 (m, 2H), 1,66 - 1,55 (m, 2H), 1,22 (s, 6H), 1,14 (s, 6H)	940,6
407	2-[8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[4,5]decan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,75 (br d, J = 8,0 Hz, 2H), 8,42 - 8,38 (m, 1H), 7,90 (d, J = 8,8 Hz, 1H), 7,76 (s, 1H), 7,69 (d, J = 9,2 Hz, 1H), 7,51 (s, 1H), 7,21 (d, J = 2,4 Hz, 1H), 7,12 (s, 1H), 7,01 (dd, J = 2,4, 8,8 Hz, 1H), 6,96 - 6,62 (m, 2H), 4,29 (s, 1H), 4,21 - 4,07 (m, 3H), 4,03 (d, J = 9,2 Hz, 1H), 3,87 (s, 3H), 3,78 - 3,68 (m, 2H), 3,65 - 3,53 (m, 6H), 2,91 - 2,72 (m, 4H), 2,09 (s, 2H), 2,02 - 1,95 (m, 3H), 1,86 (br d, J = 6,4 Hz, 6H), 1,75 (br d, J = 12,0 Hz, 2H), 1,64 - 1,52 (m, 2H), 1,21 (s, 6H), 1,15 - 1,07 (m, 6H)	946,8
408	2-[8-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-	δ 8,75 (d, J = 8,4 Hz, 1H), 7,90 (d, J = 8,4 Hz, 2H), 7,71 (d, J = 8,4 Hz, 2H), 7,21 (d, J = 8,4 Hz, 1H), 7,10 (s, 1H), 7,00 (m, 1H),	946,7

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
	2-azaespiro[4,5]decan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	6,95-6,63 (m, 1H), 4,21-4,11 (m, 2H), 4,04-3,35 (m, 2H), 3,87 (s, 2H), 3,78-3,66 (m, 2H), 3,55 (s, 3H), 3,39 (s, 3H), 2,90-2,70 (m, 2H), 2,03-1,90 (m, 1H), 1,88-1,78 (m, 1H), 1,77-1,68 (m, 1H), 1,66-1,54 (m, 1H).	

[001165] Ejemplo 62: Síntesis de 2-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[5,5]undecan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 412**)



[001166] Se agregó 9-oxo-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (1 g, 3,74 mmol, 1 eq) en THF (10 ml) a $NaBH_4$ (71 mg, 1,87 mmol, 0,5 eq) en THF (4 ml) y EtOH (6 ml). La reacción se agitó a 25 °C durante 0,15 h. La mezcla de reacción se detuvo añadiendo agua (30 ml) a 0 °C, y luego se diluyó con agua (30 ml) y se extrajo

con acetato de etilo (30 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 20 g, eluyente de gradiente de acetato de etilo/éter de petróleo al 0-30 % a 80 ml/min). El compuesto deseado 9-hidroxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (1 g, 3,71 mmol, 99 % de rendimiento) se obtuvo como un aceite incoloro (HNMR EW48069-636-P1A).

[001167] ^{1}H NMR (400 MHz, $CDCl_3$): δ 3,74 (d, **J** = 2,8 Hz, 1H), 3,80-3,54 (m, 5 H), 3,36 (d, J = 2,8 Hz, 1H), 3,13 (s, 1H), 1,84 - 1,73 (m, 1H), 1,66 - 1,51 (m, 1H), 1,46 - 4,36 (m, 1H), 1,37 - 1,31 (m, 1H), 1,28 (s, 2H).

[001168] A una solución de 9-hidroxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (950 mg, 3,53 mmol, 1 eq) en DCM (10 ml) se le agregó imidazol (600 mg, 8,82 mmol, 2,5 eq) y TBDPSCl (1,45 g, 5,29 mmol, 1,35 ml, 1,5 eq). La mezcla de reacción se agitó a 25 °C durante 12 h. La mezcla se concentró hasta secarse. El residuo se purificó mediante HPLC preparativa (condiciones de FA: columna: Phenomenex luna C18 150*40mm* 15um; fase móvil: [agua(FA)-ACN]; gradiente: 95 %-100 % B durante 15 min). El compuesto deseado 9-[ter-butil(difenil)silil]oxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (780 mg, 1,53 mmol, 86 % de rendimiento) se obtuvo como un aceite amarillo. El compuesto deseado 9-[ter-butil(difenil)silil]oxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (920 mg, 1,81 mmol, 51 % de rendimiento) se obtuvo como un aceite rojo.

[001169] ^{1}H NMR (400 MHz, $CDCl_3$): **δ =** 7,68 (d, J = 8,0 Hz, 1H), 7,49-7,31 (m, 2H), 3,73-3,55 (m, 1H), 3,34-3,26 (m, 1H), 1,62-1,54 (m, 2H), 1,50 (s, 11H), 1,06 (s, 3H), 1,00 (s, 3H).

[001170] LC-MS: MS (ESI$^+$): t_R = 0,796 min, m/z = 508,4 [M + H$^+$]

[001171] A una solución de ter-butil 9-[4-(3,5-dimetilpirazol-2-il)fenil]azetidin-2-carboxilato (780 mg, 1,54 mmol) en THF (10 ml) se agregó TBAF (3,07 ml). La mezcla de reacción se agitó a 50 °C durante 12 h. La mezcla se concentró hasta secarse. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 12 g, eluyente de gradiente de acetato de etilo/éter de petróleo al 0-30 % a 80 ml/min). El compuesto 9-hidroxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (410 mg, 1,52 mmol, 99 % de rendimiento) se obtuvo como un aceite incoloro.

[001172] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3,62 (d, **J** = 0,8 Hz, 1H), 3,36 (d, J = 2,8 Hz,

1H), 1,86-1,74 (m, 2H), 1,57-1,42 (m, 14H), 1,39 (s, 3H), 1,19-1,09 (m, 2H).

[001173] A una solución de 9-hidroxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (410 mg, 1,52 mmol, 1 eq) y Py (392 mg, 4,96 mmol, 0,4 ml, 3,26 eq) en DCM (10 ml) se le agregó metanosulfonato de metilsulfonilo (400 mg, 2,30 mmol, 1,51 eq) a 0 °C. La mezcla de reacción se agitó a 25 °C durante 12 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 20 g, eluyente de gradiente de acetato de etilo/éter de petróleo al 0-30 % a 100 ml/min). El compuesto 9-metilsulfoniloxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (500 mg, 1,44 mmol, 94 % de rendimiento) se obtuvo como un aceite incoloro.

[001174] ^{1}H NMR (400 MHz, $CDCl_3$): **δ** 3,37 (s, 3H), 3,27 (s, 3H), 2,00 - 1,77 (m, 4H), 1,74 - 1,63 (m, 3H), 1,53 - 1,47 (m, 2H), 1,40 - 1,34 (m, 2H), 1,29 - 1,17 (m, 2H).

[001175] A una solución de 9-metilsulfoniloxi-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (500 mg, 1,44 mmol, 1 eq) y 1-(3-iodo-1,4,6,7-tetrahidropirazolo[4,3-c]piridin-5-il)etanona (419 mg, 1,44 mmol, 1 eq) en DMF (5 ml) se agregó Cs_2CO_3 (1,41 g, 4,32 mmol, 3 eq). La mezcla de reacción se agitó a 45 oC durante 12 h. La mezcla de reacción se inactivó con agua (30 ml) y se extrajo con acetato de etilo (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía rápida en gel de sílice (ISCO®; columna rápida de sílice SepaFlash® de 20 g, eluyente de gradiente de acetato de etilo/éter de petróleo de 0~100 % a 80 ml/min). El residuo se purificó mediante HPLC preparativa (condición neutra: columna: Welch Ultimate XB-CN 250*50*10um; fase móvil: [Hexano-EtOH]; gradiente: 1 %-35 % B durante 15 min). El compuesto ter-butil 9-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[5,5]undecano-2-carboxilato (200 mg, 368,70 µmol, 25 % de rendimiento) se obtuvo como un sólido blanco.

[001176] 85 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4,25 (s, 1H), 3,89 (t, **J** = 5,6 Hz, 8H), 3,71 (t, J = 5,6 Hz, 1H), 3,38 – 3,11 (m, 2H), 2,79 – 2,60 (m, 8H), 2,24 – 2,17 (m, 8H), 2,15 – 2,00 (m, 2H), 1,74 (qd, J = 1,69, 3,4 Hz, 8H), 1,53 – 1,46 (m, 9H), 1,33 – 1,18 (m, 2H).

[001177] LC-MS: MS (ESI$^+$): t_R = 0,573 min, m/z = 543,2 [M + H$^+$]

[001178] A una solución de 7-(difluorometil)-6-(1-metilpirazol-4-il)-1,2,3,4-tetrahidroquinolina (131 mg, 497,74 µmol, 1,5 eq) y 9-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (180 mg, 331,83 µmol, 1 eq) en 2-metilbutan-2-ol (10 ml) se añadieron CPHOS PD G_3 (27 mg,

33,18 µmol, 0,1 eq) y Cs_2CO_3 (324 mg, 995,48 µmol, 3 eq). La mezcla de reacción se agitó a 90 °C durante 12 h en N_2. La mezcla de reacción se diluyó con agua (30 ml) y se extrajo con acetato de etilo (30 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía en capa fina preparativa (sílice, éter de petróleo/acetato de etilo = 1:3). El compuesto ter-butil 9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[5,5]undecano-2-carboxilato (180 mg, 265,56 µmol, 80 % de rendimiento) se obtuvo como un aceite amarillo claro.

[001179] LC-MS: MS (ESI^+): t_R = 0,633 min, m/z = 678,3 [M + H^+]

[001180] A una solución de 9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[5,5]undecano-2-carboxilato de ter-butilo (180 mg, 265,56 µmol, 1 eq) en DCM (5 ml) se le agregó TFA (91 mg, 796,67 µmol, 59,18 µl, 3 eq). La mezcla de reacción se agitó a 25 °C durante 0,5 h. La mezcla se concentró hasta secarse. El compuesto 1-[1-(2-azaespiro[5,5]undecan-9-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (184 mg, crudo, TFA) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001181] LC-MS: MS (ESI^+): t_R = 0,435 min, m/z = 578,3 [M + H^+]

[001182] A una solución de 1-[1-(2-azaespiro[5,5]undecan-9-il)-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (92 mg) y DIPEA (172 mg, 1,33 mmol, 231,66 µl, 10 eq) en NMP (2 ml) se agregó 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (61 mg, 146,30 µmol, 1,1 eq). La mezcla de reacción se agitó a 50 °C durante 12 h. La mezcla de reacción se neutralizó añadiendo agua (10 ml) a 25 °C, y luego se diluyó con agua (20 ml) y se extrajo con acetato de etilo (30 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (30 ml x 3), se secaron en sulfato de sodio anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante cromatografía preparativa en capa fina (sílice, DCM: MeOH = 10: 1). El residuo se purificó mediante HPLC preparativa (condiciones de FA: columna: Unisil 3-100 C18 Ultra 150*50mm*3 um; fase móvil: [agua(FA)-ACN]; gradiente: 65 %-85 % B durante 10 min). El compuesto 2-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-

1-il]-2-azaespiro[5,5]undecan-2-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (60,17 mg, 62,49 µmol, rendimiento del 46 % en dos pasos) se obtuvo como un sólido blanco.

[001183] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8,68 (s, 2H), 7,63 - 7,50 (m, 2H), 7,40 (d, J = 6,8 Hz, 1H), 7,07 - 6,95 (m, 2H), 6,89 (d, J = 8,8 Hz, 1H), 6,81 (dd, J = 2,4, 8,8 Hz, 1H), 6,51 (dt, J = 11,2, 55,6 Hz, 1H), 5,93 (d, J = 8,0 Hz, 1H), 4,29 - 4,09 (m, 3H), 4,04 (s, 1H), 3,95 (d, J = 2,4 Hz, 3H), 3,92 - 3,82 (m, 4H), 3,80 - 3,63 (m, 5H), 2,86 (td, J = 6,0, 11,6 Hz, 2H), 2,80 - 2,67 (m, 2H), 2,20 - 2,01 (m, 7H), 1,83 - 1,70 (m, 8H), 1,38 (t, J = 13,2 Hz, 2H), 1,24 (d, J = 14,8 Hz, 12H)

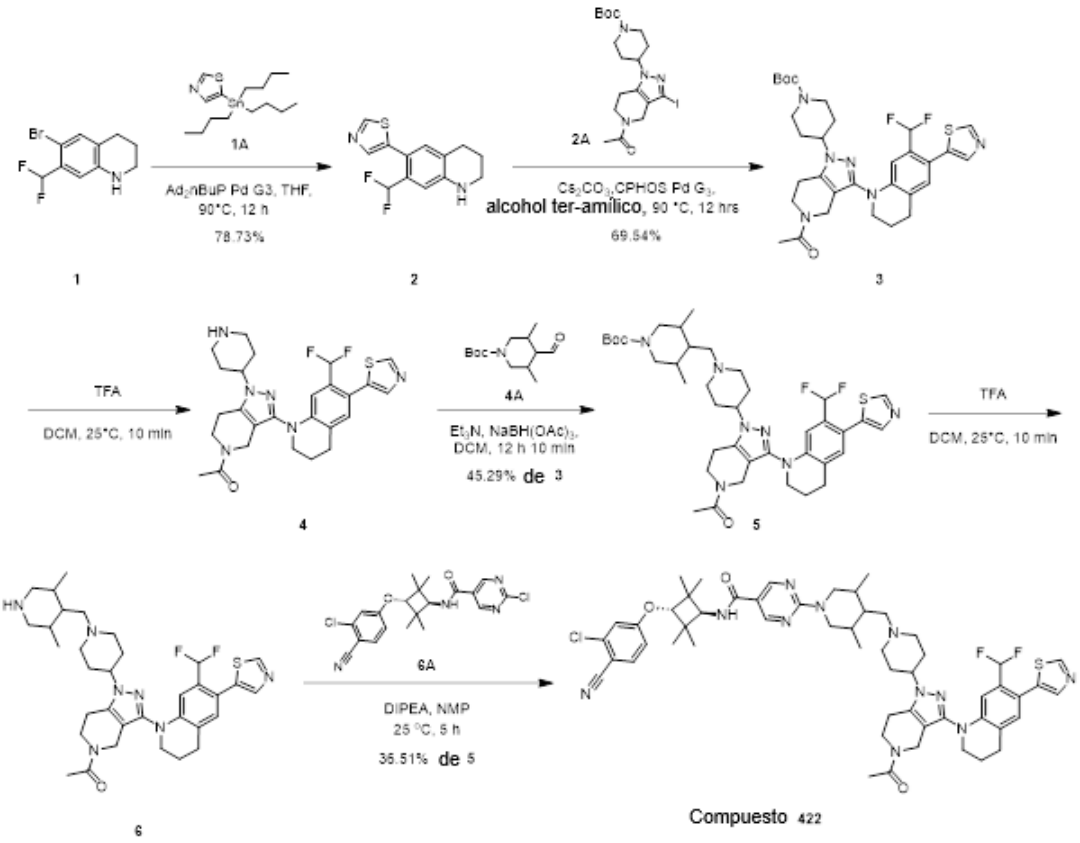
[001184] **LC-MS:** MS (ESI^+): t_R = 3,289 min, m/z = 960,6 [M + H^+]

[001185] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 62.

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
414	2-[3-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-2-azaespiro[5,5]undecan-2-il]azetidin-1-il]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,76 (s, 2H), 7,91 (d, J = 8,8 Hz, 1H), 7,77-7,75 (m, 2H), 7,50 (s, 1H), 7,22 (d, J = 2,0 Hz, 1H), 7,10 (s, 1H), 6,92 (dd, J = 2,4, 8,8 Hz, 1H), 6,85-6,64 (m, 2H), 4,30 (s, 1H), 4,18-4,14 (m, 4H), 4,06-4,01 (m, 2H), 3,89-3,85 (m, 5H), 3,77-3,67 (m, 2H), 3,60-3,57 (m, 2H), 3,20-3,10 (m, 1H), 2,90-2,80 (m, 3H), 2,75-2,65 (m, 1H), 2,60-2,50 (m, 1H), 2,35-2,20 (m, 1H), 2,08 (s, 2H), 2,05-1,90 (m, 7H), 1,85-1,65 (m, 4H), 1,60-1,40 (m, 4H), 1,35-1,25 (m, 2H), 1,22 (s, 6H), 1,12 (s, 6H)	1015,6
415	4-[3-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4Hpirazolo[[4,3-c]piridin-1-il]-2-azaespiro[5,5]undecan-2-il]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ 7,76-7,64 (m, 1H), 7,52-7,40 (m, 2H), 7,13-6,64 (m, 2H), 6,58-6,38 (m, 1H), 4,26 (s, 1H), 4,25-4,10 (m, 1H), 3,95 (s, 2H), 3,66-3,99 (m, 2H), 3,91 (brs, 2H), 3,75-3,65 (m, 2H), 3,60-3,26 (m, 2H), 2,87 (s, 3H), 2,85 (s, 3H), 2,32-2,20 (m, 2H), 2,07-2,08 (m, 2H), 1,97-1,89 (m, 2H), 1,85-1,40 (m, 2H), 1,24-1,14 (m, 2H).	1009,7

Compuesto	Nombre	^{1}H NMR (300 MHz, $CDCl_3$):	LC-MS $(M+H)^+$:
416	4-[3-[9-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4Hpirazolo[4,3-c]piridin-1-il]-2-azaespiro[5,5]undecan-2-il]azetidin-1-il]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ =7,76-7,74 (m, 3H), 7,65 (d, *J*=8,8 Hz, 1H), 7,49 - 7,48 (m, 2H), 7,10 (s, 1H), 6,83-6,75 (m, 2H), 6,64 (s, 1H), 6,55-6,53 (dd, J_1= 8,8 Hz; J_2=2,4 Hz, 2H), 6,44 (d, *J*=8,4 Hz, 1H), 4,14 – 4,12 (m, 2H), 4,07 – 4,05 (m, 4H), 3,98 (s, 3H), 3,92 (s, 3H), 3,75 – 3,70 (m, 2H), 3,70 – 3,65 (m, 4H), 3,15-3,10 (m, 1H), 2,80 – 2,75 (m, 3H), 2,74 – 2,70 (m, 1H), 2,25 – 2,23 (m, 2H), 2,10 – 2,05 (m, 2H), 1,95 – 1,90 (m, 7H), 1,80 – 1,70 (m, 4H), 1,60 – 1,45 (m, 4H), 1,23 (s, 8H), 1,15 (s, 6H)	1009,7

[001186] Ejemplo 63: Síntesis de 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 422**)



[001187] Una mezcla de 6-bromo-7-(difluorometil)-1,2,3,4-tetrahidroquinolina (2,00 g, 7,63 mmol, 1,0 *eq*), tributil(tiazol-5-il)estannano (3,14 g, 8,39 mmol, 1,1 *eq*), Ad_2nBuP Pd G3 (cataCXium® A Pd G3) (556 mg, 763,09 µmol, 0,1 *eq*) en THF (30 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (60 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 3/1). Se obtuvo 5-[7-(difluorometil)-1,2,3,4-tetrahidroquinolin-6-il]tiazol (1,60 g, 6,01 mmol, 78,73 % de rendimiento) como un aceite amarillo.

[001188] LC-MS: MS (ESI^+): t_R = 0,503 min, m/z =266,9 [M + H^+]

[001189] Una mezcla de 5-[7-(difluorometil)-1,2,3,4-tetrahidroquinolin-6-il]tiazol (750 mg, 2,82 mmol, 1,2 *eq*), ter-butil 4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)piperidina-1-carboxilato (1,11 g, 2,35 mmol, 1,0 *eq*), Cs_2CO_3 (2,29 g, 7,04 mmol, 3,0 *eq*), CPHOS Pd G3 (189 mg, 234,69 µmol, 0,1 *eq*) en 2-metilbutan-2-ol (8 ml) se desgasificaron y se purgaron con N_2 tres veces, y luego la mezcla se agitó a 90 °C

durante 12 horas bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (80 ml) y se extrajo con EtOAc (50 ml × 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El 4-[5-acetil-3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de ter-butilo (1,00 g, 1,63 mmol, rendimiento del 69,54 %) se obtuvo como un aceite amarillo.

[001190] LC-MS: MS (ESI^+): t_R = 0,560 min, m/z = 613,2 [M + H^+]

[001191] A una solución de 4-[5-acetil-3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato de ter-butilo (150 mg, 244,81 µmol, 1,0 *eq*) en DCM (2 ml) se agregó TFA (3,07 g, 26,93 mmol, 2 ml, 109,99 *eq*). La mezcla se agitó a 25 °C durante 10 minutos. La mezcla de reacción se concentró a presión reducida para obtener un residuo. Se obtuvieron 150 mg de 1-[3-[7-(difluorometil)-6-tiazol-5-il-3, 4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6, 7-dihidro-4H-pirazolo[4, 3-c]piridin-5-il] etanona como un aceite amarillo y se utilizó en el siguiente paso sin purificación adicional.

[001192] LC-MS: MS (ESI^+): t_R = 0,419 min, m/z = 513,1 [M + H^+]

[001193] A una solución de 1-[3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (150 mg) en DCM (5 ml) se le agregó Et_3N (73 mg, 718,12 µmol, 99,95 µl, 3,0 *eq*) y 4-formil-3,5-dimetil-piperidina-1-carboxilato de ter-butilo (87 mg, 359,06 µmol, 1,5 *eq*), y luego la mezcla se agitó a 25 °C durante 10 min. Luego se agregó $NaBH(OAc)_3$ (254 mg, 1,20 mmol, 5,0 *eq*) a la mezcla de reacción a 25 °C y se agitó a 25 °C durante 12 h. La mezcla de reacción se neutralizó con agua (20 ml) y se extrajo con DCM (10 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante TLC preparativa (SiO_2, diclorometano : metanol=15:1). El ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (80 mg, 108,41 µmol, rendimiento del 45,29 % en dos pasos) se obtuvo como un sólido amarillo.

[001194] LC-MS: MS (ESI^+): t_R = 0,485 min, m/z = 738,3 [M + H^+]

[001195] A una solución de ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (80 mg, 108,41 µmol, 1,0 *eq*) en DCM (2 ml) se agregó

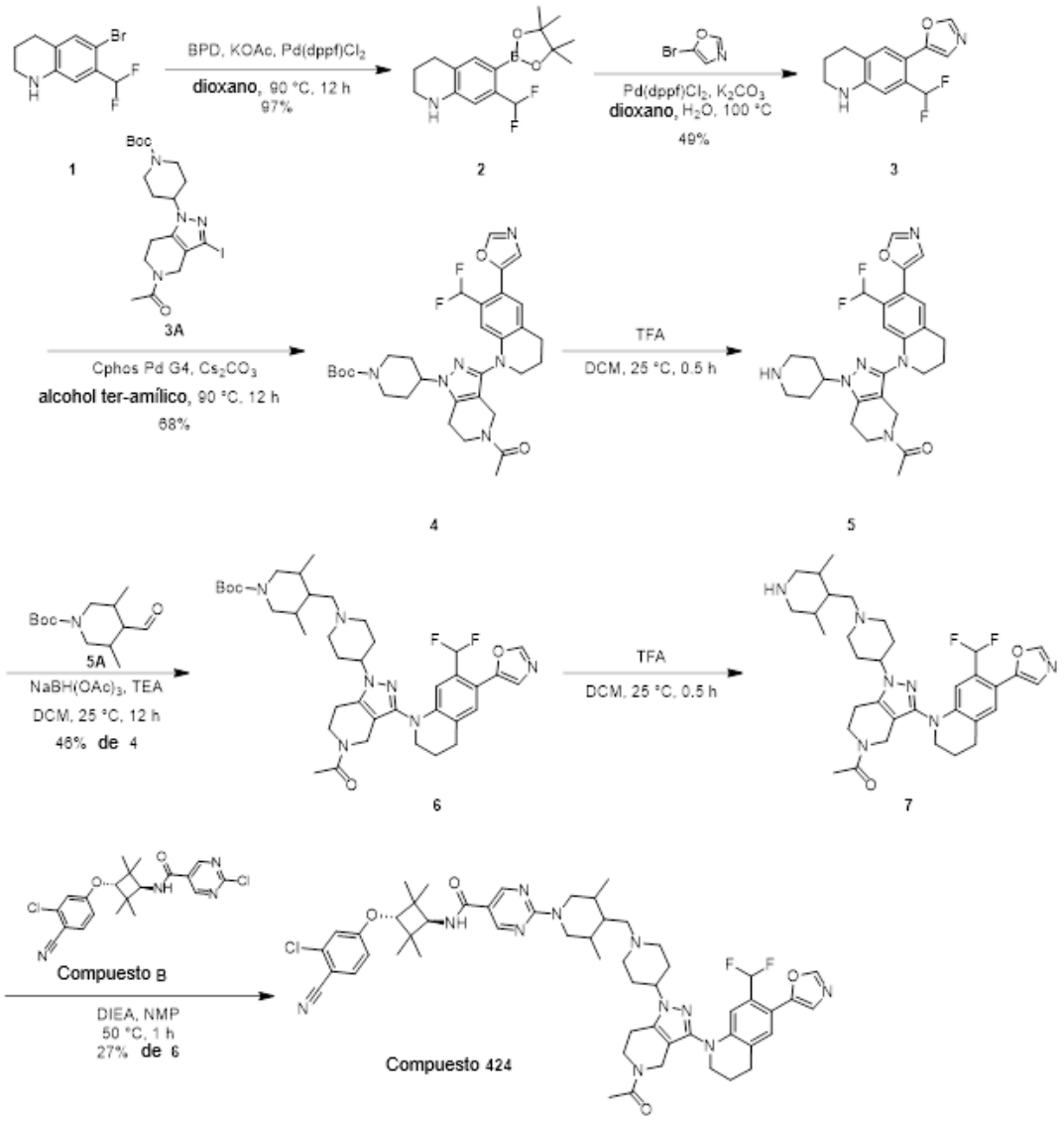
TFA (3,07 g, 26,93 mmol, 2 ml, 248,36 *eq*). La mezcla se agitó a 25 °C durante 10 minutos. La mezcla de reacción se concentró a presión reducida para obtener un residuo. Se obtuvieron 80 mg de 1-[3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona como un aceite amarillo y se utilizó en el siguiente paso sin purificación adicional.

[001196] A una solución de 1-[3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (80 mg) en NMP (3 ml) se agregó DIPEA (41 mg, 319,21 µmol, 55,60 µl, 3,0 *eq*). A la mezcla se le agregó 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (45 mg, 106,40 µmol, 1,0 *eq*) y se agitó a 25 °C durante 5 h. La mezcla se concentró a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 33 %-63 % B durante 10 min). 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-tiazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (39,65 mg, 38,85 µmol, 36,51 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[001197] ^{1}H NMR (400 MHz, DMSO-**d_6**) δ = 9,16 (s, 1H), 8,78 - 7,80 (m, 2H), 7,72 - 7,70 (m, 1H), 7,22 - 7,18 (m, 2H), 7,02 - 7,00 (m, 1H), 7,00 - 6,82 (m, 2H), 4,29 - 4,17 (m, 1H), 4,04 - 4,02 (m, 1H), 3,94 - 3,91 (m, 2H), 3,75 - 3,65 (m, 1H), 3,62 - 3,60 (m, 1H), 3,45 - 3,43 (m, 1H), 3,02 - 2,97 (m, 1H), 2,75 - 2,60 (m, 2H), 2,30 - 2,25 (m, 2H), 2,10 - 1,90 (m, 1H), 2,00 - 1,75 (m, 1H), 1,25 - 1,10 (m, 1H), 1,00 - 0,90 (m, 2H).

[001198] LC-MS: MS (ESI$^+$): t_R = 2,555 min, m/z = 1020,6 [M + H$^+$]

[001199] Ejemplo 64: Síntesis de 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 424**)



[001200] Una mezcla de 6-bromo-7-(difluorometil)-1,2,3,4-tetrahidroquinolina (2,00 g, 7,63 mmol, 1,0 eq), BPD (2,91 g, 11,45 mmol, 1,5 eq), $Pd(dppf)Cl_2$ (558 mg, 763 µmol, 0,1 eq), KOAc (2,25 g, 22,89 mmol, 3,0 eq) en dioxano (30 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (30 ml) y se extrajo con EtOAc (20 ml × 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 1/1 a 10/0). El compuesto 7-(difluorometil)-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,2,3,4-tetrahidroquinolina (2,30 g, 7,44 mmol, 97 % de rendimiento) se obtuvo como un sólido amarillo.

[001201] Una mezcla de 7-(difluorometil)-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,2,3,4-tetrahidroquinolina (1,88 g, 6,08 mmol, 1,5 eq), 5-bromooxazol (0,60 g, 4,06 mmol, 1,0 eq), Pd(dppf)Cl_2 (297 mg, 405 µmol, 0,1 eq), K_2CO_3 (1,5 M, 8,11 ml, 3,0 eq) en dioxano (20 ml) se desgasificó y se purgó con N_2 tres veces, y luego la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (30 ml) y se extrajo con EtOAc (20 ml × 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 3/1). El compuesto 5-[7-(difluorometil)-1,2,3,4-tetrahidroquinolin-6-il]oxazol (500 mg, 2,00 mmol, 49 % de rendimiento) se obtuvo como un sólido amarillo.

[001202] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8,43 (br, 1H), 8,37-4,08 (m, 1H), 7,27-7,22 (m, 2H), 7,22 – 6,91 (m, 1H), 6,83-2,45 (m, 1H), 6,47 (br, 1H), 3,31-3,25 (m, 1H), 2,79-2,73 (m, 2H), 1,88(s, 9H), 1,81-1,20 (m, 1H).

[001203] LC-MS: MS (ESI$^+$): t_R = 0,460 min, m/z = 250,9 [M + H$^+$]

[001204] Una mezcla de 4-(5-acetil-3-iodo-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il)piperidina-1-carboxilato de ter-butilo (700 mg, 1,48 mmol, 1,0 eq), 5-[7-(difluorometil)-1,2,3,4-tetrahidroquinolin-6-il]oxazol (388 mg, 1,55 mmol, 1,05 eq), Cphos Pd G3 (119 mg, 148 µmol, 0,1 eq), Cs_2CO_3 (1,44 g, 4,43 mmol, 3,0 eq) en 2-metilbutan-2-ol (10 ml) se desgasificó y se purgó con N_2 durante 3 veces, y luego la mezcla se agitó a 90 °C durante 12 h bajo atmósfera de N_2. La mezcla de reacción se inactivó con agua (30 ml) y se extrajo con EtOAc (20 ml × 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 1/1). El compuesto ter-butil 4-[5-acetil-3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (600 mg, 1,01 mmol, 68 % de rendimiento) se obtuvo como un sólido amarillo.

[001205] LC-MS: MS (ESI$^+$): t_R = 0,532 min, m/z = 597,3 [M + H$^+$]

[001206] A una solución de ter-butil 4-[5-acetil-3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (150 mg, 251 µmol, 1,0 eq) en DCM (2 ml) se le agregó TFA (2 ml). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto 1-[3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (120 mg) se obtuvo como un aceite amarillo y se utilizó

directamente en el siguiente paso sin purificación adicional.

[001207] LC-MS: MS (ESI^+): t_R = 0,394 min, m/z = 497,2 [M + H^+]

[001208] A una solución de 1-[3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (120 mg) y 4-formil-3,5-dimetil-piperidina-1-carboxilato de ter-butilo (79 mg, 326 µmol, 1,35 eq) en DCM (2 ml) se agregó $NaBH(OAc)_3$ (256 mg, 1,21 mmol, 5,0 eq) y Et_3N (73 mg, 725 µmol, 101 µl, 3,0 eq). La mezcla se agitó a 25 °C durante 2 h. La mezcla de reacción se neutralizó añadiendo 30 ml de agua y luego se extrajo con DCM (20 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera (20 ml x 2), se secaron en Na_2SO_4, se filtraron y se concentraron a presión reducida para obtener residuo crudo. El residuo se purificó mediante TLC preparativa (SiO_2, DCM: MeOH = 10:1). El compuesto ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (80 mg, 111 µmol, 46 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[001209] LC-MS: MS (ESI^+): t_R = 0,481 min, m/z = 722,4 [M + H^+]

[001210] A una solución de ter-butil 4-[[4-[5-acetil-3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (80 mg, 111 µmol, 1,0 eq) en DCM (1 ml) se le agregó TFA (1 ml). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla se concentró al vacío. El compuesto 1-[3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (65 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001211] LC-MS: MS (ESI^+): t_R = 0,399 min, m/z = 622,3 [M + H^+]

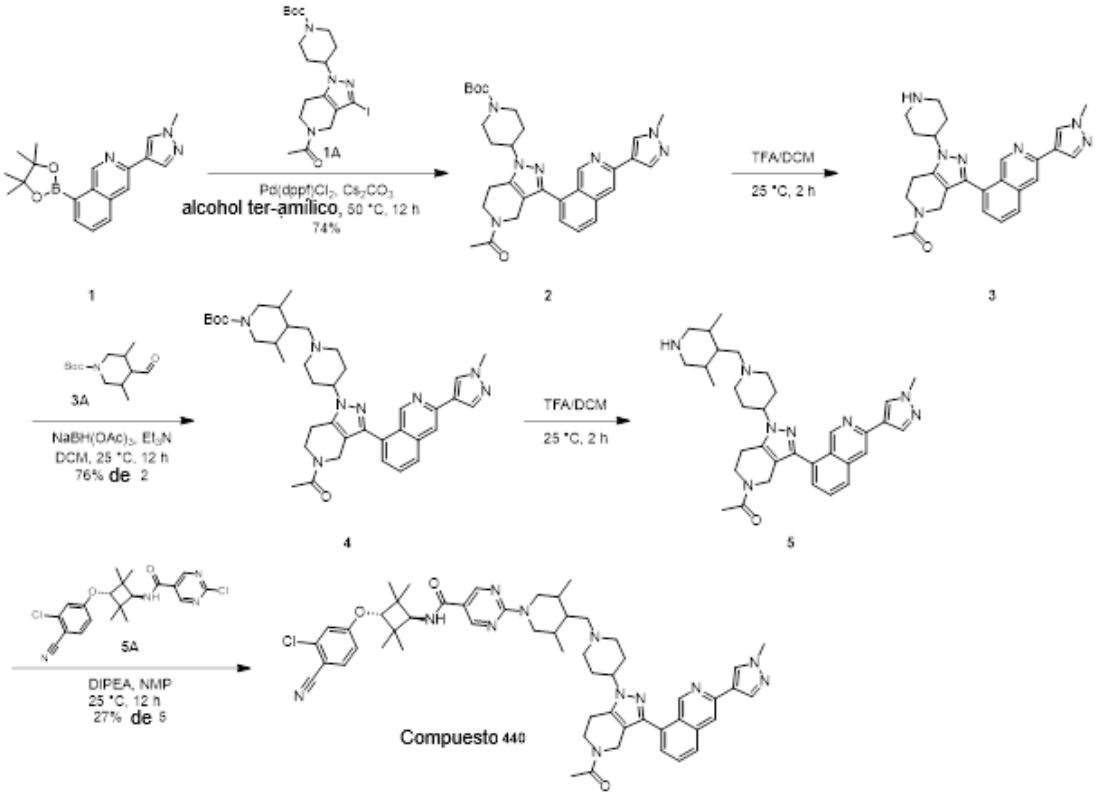
[001212] A una solución de 1-[3-[7-(difluorometil)-6-oxazol-5-il-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (65 mg) en NMP (1 ml) se le agregó DIPEA (68 mg, 523 µmol, 91,05 µl, 5,0 eq) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (44 mg, 105 µmol, 1,0 eq). La mezcla se agitó a 25 °C durante 12 h. La mezcla de reacción se neutralizó añadiendo 30 ml de agua y luego se extrajo con EtOAc (20 ml * 2). Las capas orgánicas combinadas se lavaron con salmuera (50 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El residuo se purificó mediante HPLC preparativa (columna: Phenomenex luna C18 150*25mm* 10um; fase móvil: [agua(FA)-ACN]; gradiente: 32 %-62 % B durante 10 min). El compuesto 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-oxazol-5-

il-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (28,49 mg, 28,36 µmol, 27,13 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino.

[001213] **^{1}RMN de 1H** (400 MHz, $CDCl_3$) δ =8,77 - 8,70 (m, 2H), 8,47 - 8,40 (m, 1H), 8,30 - 8,28 (m, 1H), 7,90 (d, J = 8,8 Hz, 1H), 7,70 (d ancho, J = 9,3 Hz, 1H), 7,44 - 7,40 (m, 1H), 7,30 (s, 1H), 7,22 (d, J = 2,1 Hz, 1H), 7,01 (dd, J = 2,3, 8,8 Hz, 2H), 6,91 - 6,86 (m, 1H), 4,29 (s, 1H), 4,24 - 4,15 (m, 2H), 4,03 (br d, J = 9,3 Hz, 2H), 3,97 - 3,90 (m, 2H), 3,79 - 3,68 (m, 2H), 3,67 - 3,59 (m, 2H), 3,47 (br dd, J = 8,7, 11,1 Hz, 3H), 3,03 (br d, J = 6,3 Hz, 2H), 2,92 - 2,72 (m, 4H), 2,36 - 2,29 (m, 2H), 2,09 (s, 3H), 2,04 (br d, J = 9,6 Hz, 3H), 1,98 (br s, 3H), 1,86 (br d, J = 9,4 Hz, 5H), 1,22 (s, 6H), 1,11 (s, 6H), 0,98 - 0,91 (m, 6H)

[001214] **LC-MS:** MS (ESI^+): t_R = 2,511 min, m/z = 1004,7 [M + H^+]

[001215] **Ejemplo 65**: Síntesis de 2-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (**Compuesto 440**)



[001216] A una solución de 3-(1-metilpirazol-4-il)-8-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)isoquinolina (650 mg, 2 mmol, 1,0 eq) y 4-(5-acetil-3-iodo-6,7-dihidro-

4H-pirazolo[4,3-c]piridin-1-il)piperidina-1-carboxilato de ter-butilo (920 mg, 2 mmol, 1,0 eq) en THF (20 ml) y H_2O (5 ml) se agregó Cs_2CO_3 (1,90 g, 6 mmol, 3,0 eq), la mezcla se purgó con N_2 3 veces y luego Pd(dppf)Cl_2 Se añadieron (142 mg, 194 µmol, 0,1 eq) a la mezcla. La mezcla de reacción se agitó a 20 °C durante 2 h. La mezcla de reacción se diluyó con agua (10 ml), se extrajo con EtOAc (10 ml x 20), se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 3/1 a 0/1). Compuesto ter-butil 4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (800 mg, 1 mmol, 74 % de rendimiento) como un sólido amarillo.

[001217] LC-MS: MS (ESI$^+$): t_R = 0,477 min, m/z = 556,4 [M + H$^+$]

[001218] A una solución de ter-butil 4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]piperidina-1-carboxilato (470 mg, 846 µmol, 1,0 eq) en DCM (5 ml) se le agregó TFA (4,50 g, 40 mmol, 3 ml, 56,1 eq). La mezcla se agitó a 25 °C durante 2 horas y la mezcla de reacción se concentró a presión reducida para obtener un residuo. El compuesto 1-[3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (500 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001219] LC-MS: MS (ESI$^+$): t_R = 0,452 min, m/z = 456,1 [M + H$^+$]

[001220] A una mezcla de 1-[3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-1-(4-piperidil)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (450 mg) y 4-formil-3,5-dimetil-piperidina-1-carboxilato de ter-butilo (358 mg, 2 mmol, 1,5 eq) en DCM (6 ml) se le agregó Et_3N (500 mg, 5 mmol, 687 µl, 5,0 eq) y $NaBH(OAc)_3$ (628 mg, 3 mmol, 3,0 eq), la mezcla se agitó a 25 °C durante 12 h y luego la mezcla de reacción se concentró a presión reducida para obtener un residuo. Luego, el residuo se purificó mediante cromatografía preparativa en capa fina (diclorometano: metanol = 20:1). El compuesto ter-butil 4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (517 mg, 753 µmol, 76 % de rendimiento en dos pasos) se obtuvo como un aceite amarillo.

[001221] LC-MS: MS (ESI$^+$): t_R = 0,503 min, m/z = 681,4 [M + H$^+$]

[001222] A una solución de ter-butil 4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-piperidina-1-carboxilato (517 mg, 759 µmol, 1,0 eq) en DCM (5,2 ml) se le agregó TFA (4,00 g, 35 mmol, 2,6 ml, 55,3 eq), luego la mezcla se agitó a 25 °C durante 2 h y luego la mezcla de reacción se concentró para obtener el residuo. El compuesto 1-[1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-

pirazolo[4,3-c]piridin-5-il]etanona (460 mg) se obtuvo como un aceite amarillo y se utilizó directamente en el siguiente paso sin purificación adicional.

[001223] LC-MS: MS (ESI$^+$): t_R = 0,455 min, m/z = 581,4 [M + H$^+$]

[001224] A una solución de 1-[1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (50 mg) y 2-cloro-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (36 mg, 86 µmol, 1,0 eq) en NMP (1 ml) se le agregó DIPEA (56 mg, 430 µmol, 75 µl, 5,0 eq). La mezcla se agitó a 25 °C durante 12 h y luego se vertió en agua (20 ml). La capa acuosa se extrajo con EtOAc (20 ml x 2). La capa orgánica combinada se lavó con salmuera (20 ml×3), se secó en sulfato de sodio anhidro, se filtró y se concentró. Luego el residuo se purificó mediante HPLC preparativa (columna: Phenomenex Luna C18 150*25mm*10um; fase móvil: [H_2O (0,225 % FA)-ACN]; gradiente: 21 %-51 % B durante 10,0 min). El compuesto 2-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (22,54 mg, 23,33 µmol, 27 % de rendimiento) se obtuvo como un sólido blanquecino.

[001225] ^{1}H NMR (DMSO-d**6**) δ = 9,81-8,73 (m, 1H), 8,14-8,09 (m, 2H), 7,92-7,86 (m, 1H), 7,70 (d, *J*=9,2 Hz, 1H), 7,60-7,49 (m, 2H), 7,21 (dd, $_J$=2,4, 8,8 Hz, 1H), 4,56-4,28 (m, 1H), 4,22-4,13 (m, 1H), 4,02-6,66 (m, 1H), 3,93-3,78 (m, 1H), 3,58-3,50 (m, 1H), 3,11-2,95 (m, 1H), 2,90-2,72 (m, 3H), 2,36-4,00 (m, 1H), 2,11 (s, 3H), 2,03-1,96 (m, 3H), 1,95-1,84 (m, 1H), 1,60-1,53 (m, 1H), 1,21-2,58 (m, 1H), 1,10-1,90 (m, 1H), 0,95 (br s, 1H).

[001226] LC-MS: MS (ESI$^+$): t_R = 1,475 min, m/z = 963,8 [M + H$^+$]

[001227] SFC: t_R = 2,831 min

[001228] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 65.

Compuesto	**Nombre**	**RMN ^{1}H (400 MHz, DMSO-d6):**	**LC-MS (M+H)$^+$:**
441	4-[4-[[4-[5-acetil-3-[3-(1-metilpirazol-4-il)-8-isoquinolil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 9,80 (s, 1H), 8,36 (s, 1H), 8,09 (s, 2H), 7,91 - 7,85 (m, 1H), 7,82 - 7,76 (m, 1H), 7,72 (d, J = 8,8 Hz, 2H), 7,64 (d, J = 8,8 Hz, 1H), 7,60 - 7,44 (m, 2H), 6,94 (d, J = 8,8 Hz, 2H), 6,63 (d, J = 2,0 Hz, 1H), 6,53 (d, J = 2,0, 8,6 Hz, 1H), 4,55 (s, 2H), 4,27 (s,	957,9

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
		1H), 4,22 - 4,10 (m, 1H), 4,04 (d, J = 9,2 Hz, 1H), 3,91 (d, J = 3,2 Hz, 6H), 3,87 - 3,77 (m, 2H), 3,38 (s, 2H), 3,09 (s, 2H), 2,98 - 2,73 (m, 4H), 2,33 - 2,25 (m, 2H), 2,15 - 1,90 (m, 11H), 1,86 - 1,77 (m, 1H), 1,22 (s, 6H), 1,14 (s, 6H), 1,02 (d, J = 6,8 Hz, 6H)	
425	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilimidazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	*1*H NMR (400 MHz, DMSO-d6) δ = 7,85 (s, 1H), 7,75 - 7,55 (m, 3H), 7,35 - 7,25 (m, 1H), 7,05 - 6,95 (m, 1H), 6,80 - 4,35 (m, 1H), 4,25 - 4,15 (m, 1H), 4,10 - 4,00 (m, 2H), 4,00 - 3,90 (m, 1H), 3,80 - 3,55 (m, 1H), 3,10 - 3,00 (m, 2H), 2,95 - 2,80 (m, 2H), 2,80 - 2,65 (m, 1H), 2,35 - 2,30 (m, 1H), 2,10 (s, 1H), 1,95 (s, 2H), 1,95 - 1,80 (m, 1H), 1,30 (s, 2H), 1,12 (s, 1H), 1,00 - 0,90 (m, 1H).	1017,8
444	2-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ = 8,74 - 8,65 (m, 2H), 7,62 - 7,51 (m, 2H), 7,41 - 7,33 (m, 1H), 7,03 - 6,90 (m, 2H), 6,84 - 6,77 (m, 1H), 6,42 - 6,33 (m, 1H), 5,93 (d, J = 8,0 Hz, 1H), 4,28 (s, 1H), 4,16 - 4,10 (m, 2H), 4,09 - 3,97 (m, 3H), 3,97 - 3,87 (m, 5H), 3,78 - 3,61 (m, 3H), 3,49 - 3,29 (m, 2H), 3,18 - 2,98 (m, 2H), 2,89 - 2,70 (m, 4H), 2,41 - 2,31 (m, 2H), 2,29 - 2,19 (m, 5H), 2,17 (s, 1H), 2,12 - 2,00 (m, 6H), 1,98 - 1,83 (m, 5H), 1,23 (d, J = 13,6 Hz, 12H), 1,08 - 0,99 (m, 6H)	981,7
446	2-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-	($CDCl_3$) δ = 8,69 (s, 2H), 7,64 - 7,50 (m, 2H), 7,46 - 7,33 (m, 1H), 7,09 - 6,93 (m, 2H), 6,82 (dd, J = 2,4, 8,8 Hz, 1H), 6,39 (s, 1H), 5,97 (br d, J = 8,4 Hz, 1H), 4,89 (br d, J = 12,0 Hz, 1H),	981,7

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
	2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	4,53 (br d, J = 12,8 Hz, 1H), 4,30 (s, 1H), 4,17 - 4,12 (m, 2H), 4,06 (s, 1H), 3,99 - 3,94 (m, 3H), 3,92 (br t, J = 5,6 Hz, 1H), 3,76 (br t, J = 5,6 Hz, 1H), 3,71 - 3,60 (m, 2H), 3,46 - 3,08 (m, 2H), 2,99 - 2,68 (m, 7H), 2,67 - 2,58 (m, 1H), 2,41 - 2,22 (m, 7H), 2,18 (s, 2H), 2,12 - 1,95 (m, 7H), 1,63 - 1,34 (m, 2H), 1,25 (d, J = 15,6 Hz, 12H), 1,07 (s, 3H), 0,80 (s, 3H)	
447	4-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	($CDCl_3$) δ = 7,67 (d, J = 8,8 Hz, 2H), 7,54 (d, J = 7,6 Hz, 1H), 7,45 (d, J = 8,8 Hz, 1H), 7,40 - 7,34 (m, 1H), 7,05 - 6,95 (m, 1H), 6,86 (d, J = 8,8 Hz, 2H), 6,47 (d, J = 2,0 Hz, 1H), 6,43 - 6,35 (m, 2H), 6,13 (d, J = 8,0 Hz, 1H), 4,29 (s, 1H), 4,18 - 4,11 (m, 2H), 4,05 (s, 1H), 3,97 - 3,88 (m, 7H), 3,84 - 3,73 (m, 2H), 3,70 - 3,52 (m, 3H), 3,39 (br d, J = 12,8 Hz, 2H), 2,97 - 2,70 (m, 7H), 2,61 (br d, J = 12,8 Hz, 2H), 2,25 (s, 4H), 2,20 (br d, J = 17,6 Hz, 3H), 2,09 - 2,00 (m, 4H), 1,81 - 1,45 (m, 6H), 1,25 (d, J = 10,8 Hz, 12H), 1,03 (s, 3H), 0,92 (s, 3H)	975,8
450	2-[4-[[4-[5-acetil-3-[6-ciano-7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ = 8,68 (s, 2H), 7,57 (d, J = 8,8 Hz, 1H), 7,34 (d, J = 10,8 Hz, 1H), 6,97 (d, J = 2,4 Hz, 1H), 6,91 - 6,54 (m, 3H), 5,93 (d, J = 8,0 Hz, 1H), 4,86 (br d, J = 12,4 Hz, 1H), 4,50 (br d, J = 13,2 Hz, 1H), 4,29 (s, 1H), 4,18 - 4,07 (m, 2H), 4,04 (s, 1H), 4,01 - 3,85 (m, 2H), 3,83 - 3,66 (m, 3H), 3,26 - 3,06 (m, 1H), 3,02 - 2,93 (m, 1H), 2,92 - 2,80 (m, 4H), 2,79 - 2,68 (m, 2H), 2,52 - 2,38 (m, 1H),	962,7

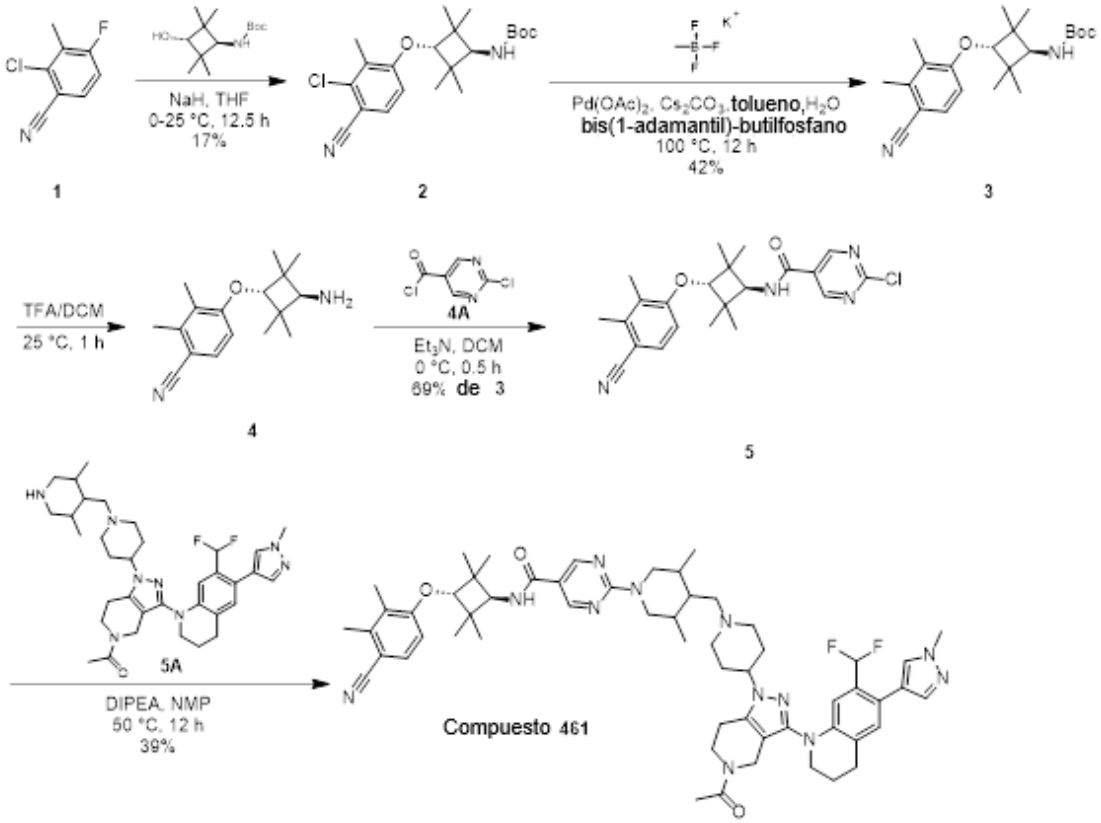
Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
		2,34 - 2,14 (m, 5H), 2,14 - 2,03 (m, 5H), 2,03 - 1,90 (m, 3H), 1,62 - 1,52 (m, 1H), 1,45 - 1,32 (m, 1H), 1,23 (d, J = 14,8 Hz, 12H), 1,05 (s, 3H), 0,78 (s, 3H)	
451	4-[4-[[4-[5-acetil-3-[6-ciano-7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	($CDCl_3$) δ = 7,66 (br d, J = 8,8 Hz, 2H), 7,45 (br d, J = 8,4 Hz, 1H), 7,33 (br d, J = 11,6 Hz, 1H), 6,88 (br d, J = 8,8 Hz, 2H), 6,81 - 6,74 (m, 1H), 6,63 - 6,38 (m, 2H), 6,11 (br d, J = 8,4 Hz, 1H), 4,32 - 4,04 (m, 4H), 3,92 (s, 5H), 3,87 - 3,61 (m, 4H), 3,38 (br d, J = 12,4 Hz, 1H), 3,19 - 3,06 (m, 1H), 3,03 - 2,69 (m, 6H), 2,68 - 2,55 (m, 1H), 2,48 - 2,37 (m, 1H), 2,31 - 2,04 (m, 9H), 1,94 (br s, 4H), 1,46 (br s, 2H), 1,24 (br d, J = 9,2 Hz, 12H), 1,02 (s, 3H), 0,99 - 0,83 (m, 3H)	956,8
457	4-[4-[[4-[5-acetil-3-(6-ciano-7-metil-3,4-dihidro-2H-quinolin-1-il)-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	7,73 (d, J = 8,8 Hz, 1H), 7,64 (d, J = 8,4 Hz, 1H), 7,48 (d, J = 9,2 Hz, 1H), 6,94 (d, J = 8,8 Hz, 1H), 6,63 (d, J = 2,0 Hz, 1H), 6,53 (br d, J = 8,8 Hz, 1H), 6,38 (br s, 1H), 4,27 (s, 1H), 4,18 - 4,09 (m, 2H), 4,09 - 3,98 (m, 3H), 3,80 - 3,68 (m, 2H), 3,59 - 3,39 (m, 2H), 3,11 - 2,95 (m, 1H), 2,68 (s, 3H), 2,34 - 2,20 (m, 1H), 2,11 - 1,78 (m, 1H), 1,00 (d, J = 7,2 Hz, 3H).	920,9
458	2-[4-[[4-[5-acetil-3-[6-ciano-7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-cianofenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ 8,73 (d, *J* = 8,4 Hz, 1H), 7,70 (d, *J* = 8,4 Hz, 2H), 7,21 (d, *J* = 8,4 Hz, 2H), 7,17 (d, J = 8,4 Hz, 1H), 4,28 (s, 1H), 4,24 (m, 1H), 4,10-3,99 (m, 1H), 3,98-3,85 (m, 2H), 3,81-3,68 (m, 2H), 3,67 (s, 2H), 3,51-3,40 (m, 2H), 2,94 (s, 3H), 2,91 (s, 3H), 2,35-2,24 (m, 2H), 2,10-1,92 (m, 1H), 1,91-	962,6

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
		1,79 (m, 1H), 1,21-1,10 (m, 1H), 1,03-0,89 (m, 1H).	
459	4-[4-[[4-[5-acetil-3-[6-ciano-7-(difluorometil)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-3-metoxifenoxi)-2,2,4,4-tetrametilciclobutil]benzamida	δ = 7,78 - 7,69 (m, 2H), 7,64 (d, *J* = 8,4 Hz, 1H), 7,58 (s, 1H), 7,54 - 7,43 (m, 1H), 7,16 - 6,85 (m, 3H), 6,80 - 6,72 (m, 1H), 6,67 - 6,61 (m, 1H), 6,57 - 6,49 (m, 1H), 4,27 (s, 1H), 4,22 - 4,12 (m, 2H), 4,10 - 3,98 (m, 2H), 3,90 (s, 3H), 3,78 - 3,69 (m, 2H), 3,67 - 3,58 (m, 2H), 3,42 - 3,35 (m, 2H), 3,07 - 2,96 (m, 2H), 2,91 - 2,70 (m, 6H), 2,33 - 2,20 (m, 2H), 2,10 - 1,77 (m, 14H), 1,22 (s, 6H), 1,14 (s, 6H), 1,06 - 0,95 (m, 6H)	956,7
460	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	δ = 8,73 (s, 2H), 7,85 - 7,67 (m, 3H), 7,50 (s, 1H), 7,10 (s, 1H), 6,96 - 6,61 (m, 3H), 4,26 (s, 1H), 4,20 - 4,10 (m, 2H), 4,08 - 3,97 (m, 2H), 3,96 - 3,89 (m, 2H), 3,86 (s, 3H), 3,78 - 3,65 (m, 2H), 3,63 - 3,55 (m, 2H), 3,52 - 3,42 (m, 2H), 3,07 - 2,99 (m, 2H), 2,89 - 2,81 (m, 3H), 2,77 - 2,70 (m, 1H), 2,36 - 2,29 (m, 5H), 2,11 - 1,93 (m, 9H), 1,93 - 1,81 (m, 5H), 1,22 (s, 6H), 1,12 (s, 6H), 0,94 (br d, J = 6,8 Hz, 6H)	1031,6
462	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-3-metil-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	δ = 8,73 (s, 2H), 7,75 (s, 1H), 7,69 (d, J = 8,8 Hz, 2H), 7,50 (s, 1H), 7,10 (s, 1H), 6,98 - 6,62 (m, 4H), 4,22 - 4,09 (m, 3H), 4,08 - 3,83 (m, 7H), 3,77 - 3,66 (m, 2H), 3,62 - 3,55 (m, 2H), 3,51 - 3,42 (m, 2H), 3,02 (br d, J = 5,6 Hz, 2H), 2,85 (br d, J = 6,0 Hz, 3H), 2,77 - 2,68 (m, 1H), 2,44 (s, 3H), 2,31 (br s, 2H), 2,07 (s, 2H), 2,05 - 1,80 (m, 11H), 1,47 - 1,16 (m, 7H), 1,10 (s, 6H), 1,04 - 0,89 (m, 6H)	997,7

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
463	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-[4-ciano-3-(trifluorometil)fenoxi]-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ =8,75 - 8,64 (m, 2H), 7,75 (d, J = 8,8 Hz, 1H), 7,53 (d, J = 5,6 Hz, 1H), 7,40 (d, J = 6,4 Hz, 1H), 7,24 (d, J = 2,4 Hz, 1H), 7,08 - 6,97 (m, 2H), 6,92 - 6,83 (m, 1H), 6,68 - 6,37 (m, 1H), 5,94 (d, J = 8,4 Hz, 1H), 4,68-4,64 (m, 1H), 4,32 - 4,21 (m, 1H), 4,17 - 4,09 (m, 3H), 4,03 - 3,95 (m, 4H), 3,91 (d, J = 5,6 Hz, 2H), 3,80 - 3,66 (m, 3H), 3,44 - 3,31 (m, 1H), 3,18 - 3,01 (m, 2H), 2,94 - 2,60 (m, 5H), 2,38 (s, 2H), 2,31 - 2,10 (m, 6H), 2,10 - 2,03 (m, 4H), 1,94 (s, 4H), 1,29 - 1,21 (m, 12H), 1,09 - 1,00 (m, 6H)	1051,7
465	2-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(4-ciano-2,3-dimetilfenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida	($CDCl_3$) δ = 8,62 (s, 2H), 7,51 - 7,44 (m, 1H), 7,38 - 7,25 (m, 2H), 6,98 - 6,82 (m, 1H), 6,45 (d, J = 8,8 Hz, 1H), 6,31 (s, 1H), 5,87 (d, J = 8,4 Hz, 1H), 4,86 - 4,71 (m, 1H), 4,42 (br d, J = 12,8 Hz, 1H), 4,25 - 4,03 (m, 3H), 3,99 (s, 1H), 3,89 - 3,86 (m, 3H), 3,67 (br t, J = 5,6 Hz, 3H), 3,64 - 3,53 (m, 2H), 3,11 - 2,97 (m, 1H), 2,91 - 2,79 (m, 2H), 2,79 - 2,70 (m, 3H), 2,70 - 2,60 (m, 2H), 2,42 (s, 3H), 2,37 - 2,28 (m, 1H), 2,26 - 2,08 (m, 10H), 2,07 - 1,95 (m, 5H), 1,94 - 1,81 (m, 4H), 1,51 - 1,44 (m, 1H), 1,36 - 1,27 (m, 1H), 1,17 (d, J = 10,4 Hz, 12H), 0,98 (s, 3H), 0,72 (s, 3H)	975,7
466	2-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(4-ciano-3-metil-fenoxi)-2,2,4,4-tetrametil-	δ = 8,61 (s, 2H), 7,54 - 7,40 (m, 2H), 7,36 - 7,26 (m, 1H), 6,96 - 6,85 (m, 1H), 6,71 (d, J = 2,0 Hz, 1H), 6,65 - 6,58 (m, 1H), 6,31 (s, 1H), 5,86 (d, J = 8,0 Hz, 1H), 4,79 (br d, J = 13,6 Hz, 1H), 4,43 (br d, J = 13,2 Hz,	961,8

Compuesto	Nombre	RMN ^{1}H (400 MHz, DMSO-d6):	LC-MS $(M+H)^+$:
	ciclobutil]pirimidina-5-carboxamida	1H), 4,25 - 4,00 (m, 3H), 3,97 (s, 1H), 3,91 - 3,54 (m, 8H), 3,06 (br d, J = 10,8 Hz, 1H), 2,97 - 2,60 (m, 7H), 2,44 (s, 3H), 2,41 - 2,32 (m, 1H), 2,29 - 2,01 (m, 9H), 2,00 - 1,89 (m, 7H), 1,51 (br d, J = 10,8 Hz, 1H), 1,37 - 1,27 (m, 1H), 1,16 (d, J = 12,0 Hz, 12H), 0,98 (s, 3H), 0,72 (s, 3H)	

[001229] Ejemplo 66: Síntesis de 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-2,3-dimetil-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 461**)



[001230] La síntesis de 4A se informó en WO2017/181177, 2017, A1

[001231] A una solución de 2-cloro-4-fluoro-3-metilbenzonitrilo (500 mg, 2,95 mmol, 1,0 eq), N-(3-hidroxi-2,2,4,4-tetrametilciclobutil)carbamato de ter-butilo (718 mg, 2,95 mmol, 1,0 eq) en THF (10 ml) se le agregó NaH (259 mg, 60 % p/p, 6,49 mmol, 2,2 eq). La

mezcla se agitó a 0 °C durante 0,5 h en N_2. Y luego se agregó 2-cloro-4-fluoro-3-metilbenzonitrilo (500 mg, 2,95 mmol, 1,0 eq) a 0 °C. La mezcla se agitó a 25 °C durante 12 h bajo N_2. La mezcla de reacción se detuvo con una solución acuosa saturada de NH_4Cl (20 ml) a 0 °C bajo N_2. La mezcla se extrajo con acetato de etilo (50 ml x 3). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 anhidro, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 50/1 a 5/1). El compuesto deseado, N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]carbamato de ter-butilo (200 mg, 509 µmol, 17 % de rendimiento), se obtuvo como un sólido amarillo.

[001232] LC-MS: MS (ESI^+): t_R = 1,133 min, m/z = 337,1 [M - 55]

[001233] A una solución de N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]carbamato de ter-butilo (200 mg, 509 µmol, 1,0 eq), trifluoro(metil)boranuro de potasio (200 mg, 1,64 mmol, 3,2 eq) en tolueno (6 ml), H_2O (2 ml) se agregó $Pd(OAc)_2$ (20 mg, 89 µmol, 0,2 eq), bis(1-adamantil)-butilfosfano (40 mg, 112 µmol, 0,2 eq), Cs_2CO_3 (350 mg, 1,07 mmol, 2,1 eq). La mezcla se agitó a 100 °C durante 30 min. La reacción se diluyó con agua (60 ml) y se extrajo con acetato de etilo (30 ml x 2). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron a sequedad. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 3/1 a 0/1). Se obtuvo el compuesto N-[3-(4-ciano-2,3-dimetilfenoxi)-2,2,4,4-tetrametilciclobutil]carbamato de ter-butilo (80 mg, 215 µmol, 42 % de rendimiento) como un aceite amarillo.

[001234] LC-MS: MS (ESI^+): t_R = 0,617 min, m/z = 373,2 [M + H^+]

[001235] A una solución de N-[3-(4-ciano-2,3-dimetilfenoxi)-2,2,4,4-tetrametilciclobutil]carbamato de ter-butilo (80 mg, 215 µmol, 1,0 eq) en DCM (2 ml) se le agregó TFA (1,54 g, 13,5 mmol, 62,7 eq). La mezcla se agitó a 25 °C durante 0,5 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El compuesto 4-(3-amino-2,2,4,4-tetrametil-ciclobutoxi)-2,3-dimetil-benzonitrilo (58 mg) se obtuvo como un aceite incoloro y se utilizó directamente en el siguiente paso sin purificación adicional.

[001236] LC-MS: MS (ESI^+): t_R = 0,617 min, m/z = 273,2 [M + H^+]

[001237] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2,3-dimetilbenzonitrilo (58 mg) en DCM (1 ml) se le agregó Et_3N (43 mg, 426 µmol, 2,0 eq). A continuación, se agregó cloruro de 2-cloropirimidina-5-carbonilo (45 mg, 256 µmol, 1,2 eq) en DCM (1 ml) a 0 °C. La mezcla se agitó a 0 °C durante 0,5 h. La mezcla de reacción se concentró a presión reducida para obtener un residuo. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 10/1 a 0/1). El

compuesto deseado 2-cloro-N-[3-(4-ciano-2,3-dimetilfenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (61 mg, 148 µmol, 69 % de rendimiento en dos pasos) se obtuvo como un sólido blanquecino.

[001238] LC-MS: MS (ESI^+): t_R = 0,664 min, m/z = 413,1 [M + H^+]

[001239] A una solución de 1-[3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-1-[1-[(3,5-dimetil-4-piperidil)metil]-4-piperidil]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (85 mg, 134 µmol, 1,0 eq), DIPEA (87 mg, 672 µmol, 5,0 eq) en NMP (2 ml) se agregó 2-cloro-N-[3-(4-ciano-2,3-dimetil-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (61 mg, 148 µmol, 1,1 eq). La mezcla se agitó a 50 °C durante 12 h. La mezcla de reacción se concentró y el residuo se diluyó con EA. El residuo se purificó mediante HPLC preparativa (condición FA; columna: Phenomenex Luna C18 150 × 25 mm × 10 µm; fase móvil: [H_2O(0,225 % FA)-ACN]; gradiente: 32 %-62 % B durante 10,0 min). El compuesto deseado 2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-2,3-dimetil-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (52,63 mg, 52,04 µmol, 39 % de rendimiento) se obtuvo como un sólido blanquecino.

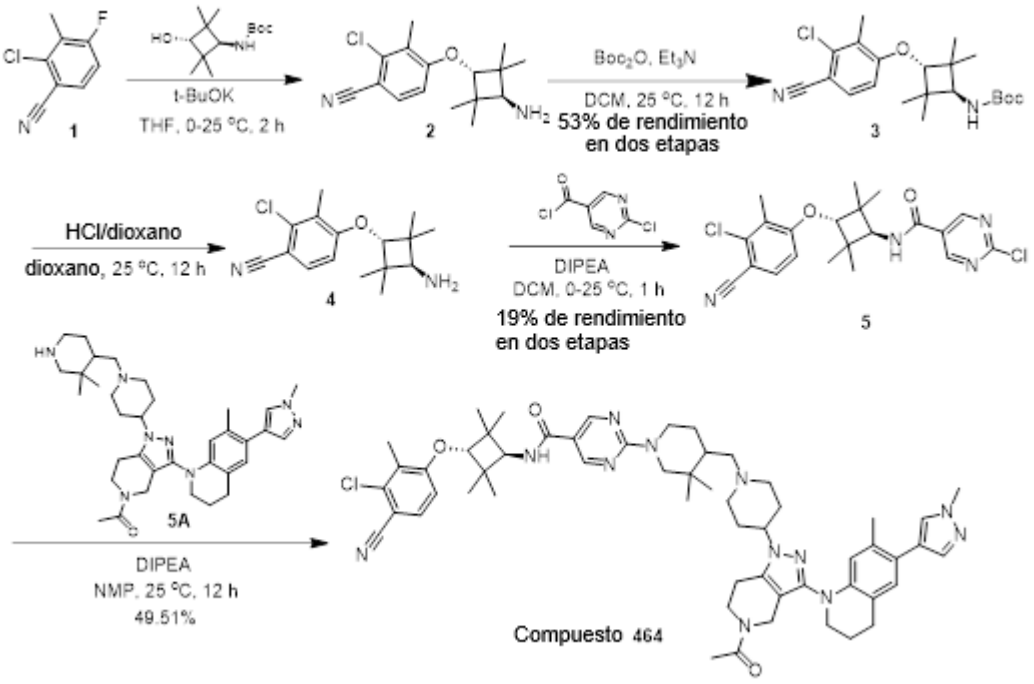
[001240] ^{1}H NMR (400 MHz, CLOROFORMO-**d**) δ = 8,78 (d, *J* = 5,6 Hz, 1H), 7,45 - 7,36 (m, 2H), 7,07 - 6,97 (m, 1H), 6,92 - 6,83 (m, 4H), 6,70 (br d, *J* = 8,0 Hz, 1H), 4,68 - 4,26 (m, 1H), 4,18 (s, 1H), 4,45 - 4,06 (m, 4H), 4,04 - 3,95 (m, 1H), 3,95 - 3,67 (m, 2H), 3,57 (s, 1H), 2,92 (s, 1H), 2,49 (s, 2H), 2,38 - 2,92 (m, 5H), 2,21 (s, 1H), 2,19 - 2,02 (m, 7H), 1,99 - 1,80 (m, 2H), 1,58 - 1,44 (m, 4H), 1,24 - 1,43 (m, 4H), 1,09 - 0,99 (m, 2H).

[001241] LC-MS: MS (ESI^+): t_R = 3,186 min, m/z = 1011,7 [M + H^+]

[001242] Los compuestos que se muestran a continuación se prepararon de manera similar a como se describe en el Ejemplo 66.

Compuesto	**Nombre**	**RMN ^{1}H (400 MHz, DMSO-d6):**	**LC-MS $(M+H)^+$:**
462	2-[4-[[4-[5-acetil-3-[7-(difluorometil)-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,5-dimetil-1-piperidil]-N-[3-(4-ciano-3-metil-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida	δ = 8,73 (s, 2H), 7,75 (s, 1H), 7,69 (d, J = 8,8 Hz, 2H), 7,50 (s, 1H), 7,10 (s, 1H), 6,98 - 6,62 (m, 4H), 4,22 - 4,09 (m, 3H), 4,08 - 3,83 (m, 7H), 3,77 - 3,66 (m, 2H), 3,62 - 3,55 (m, 2H), 3,51 - 3,42 (m, 2H), 3,02 (br d, J = 5,6 Hz, 2H), 2,85 (br d, J = 6,0 Hz, 3H), 2,77 - 2,68 (m, 1H), 2,44 (s, 3H), 2,31 (br s, 2H), 2,07 (s, 2H), 2,05 - 1,80 (m, 11H), 1,47 - 1,16 (m, 7H), 1,10 (s, 6H), 1,04 - 0,89 (m, 6H)	997,7

[001243] Ejemplo 67: Síntesis de 2-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(3-cloro-4-ciano-2-metil-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (**Compuesto 464**)



[001244] A una solución de 2-cloro-4-fluoro-3-metilbenzonitrilo (3,48 g, 21 mmol, 1,0 *eq*) y N-(3-hidroxi-2,2,4,4-tetrametilciclobutil)carbamato de ter-butilo (5,00 g, 21 mmol, 1,0 *eq*) en THF (15,0 ml) se agregó t-BuOK (1 M, 61,60 ml, 3,0 *eq*) a 0 °C. La mezcla se agitó a 25 °C durante 2 h. La mezcla se vertió en agua (100 ml) a 0 °C. La fase acuosa se extrajo con EtoAc (100 ml ×3). Las capas orgánicas combinadas se lavaron con salmuera (100 ml × 2), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron a presión reducida para obtener un residuo. El compuesto 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-cloro-3-metilbenzonitrilo (6,00 g) se obtuvo como un sólido amarillo se utilizó en el siguiente paso sin purificación adicional.

[001245] LC-MS: MS (ESI^+): t_R = 0,738 min, m/z = 293,0 [M + H^+]

[001246] A una solución de 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-cloro-3-metilbenzonitrilo (6,00 g) en DCM (60 ml) se le añadieron ET_3N (4,20 g, 41 mmol, 5,70 ml, 2,0 *eq*) y Boc_2O (4,50 g, 20 mmol, 4,70 ml, 1,0 *eq*). La mezcla de reacción se agitó a 25 °C durante 12 h. La mezcla se concentró hasta secarse. El residuo se purificó por cromatografía en columna (SiO_2, éter de petróleo/acetato de etilo = 20/1 a 10/1). El

producto crudo se trituró con PE: EA (3: 1 30 ml) a 25 ºC durante 30 min. El compuesto N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]carbamato de ter-butilo (4,30 g, 11 mmol, 53 % de rendimiento en dos pasos) se obtuvo como un sólido amarillo.

[001247] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7,47 (d, **J** = 8,4 Hz, 1H), 6,58 (d, J = 8,8 Hz, 1H), 4,70-4,01 (m, 1H), 3,73-2,37 (m, 3H), 1,48 (s, 9H), 1,31-1,06 (m, 12H).

[001248] LC-MS: MS (ESI$^+$): t_R = 0,735 min, m/z = 337,1 [M - 55]

[001249] A una solución de N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]carbamato de ter-butilo (1,00 g, 3 mmol, 1,0 *eq*) en dioxano (2 ml) se le agregó HCl/dioxano (10 ml). La mezcla se agitó a 25 °C durante 12 h. La mezcla se filtró y se concentró para obtener el compuesto 295j (85,0 mg) como un aceite amarillo. El compuesto 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-cloro-3-metilbenzonitrilo (745 mg) se obtuvo como un sólido blanco se utilizó en el siguiente paso sin purificación adicional.

[001250] LC-MS: MS (ESI$^+$): t_R = 0,509 min, m/z = 293,1 [M + H$^+$]

[001251] A una solución de cloruro de 2-cloropirimidina-5-carbonilo (495 mg, 3 mmol, 1,1 *eq*) en DCM (10 ml) se le agregó DIPEA (987 mg, 8 mmol, 1,30 ml, 3,0 *eq*) a 0 °C, y luego se agregó 4-(3-amino-2,2,4,4-tetrametilciclobutoxi)-2-cloro-3-metilbenzonitrilo (745 mg). La mezcla resultante se agitó a 25 °C durante 1 h. La mezcla se diluyó con agua (5,0 ml) y se extrajo con tolueno (3,0 ml x 3). Las fases orgánicas combinadas se lavaron con salmuera (20 ml), se secaron en Na_2SO_4 anhidro, se filtraron y se concentraron. La mezcla se trituró con PE: EA=0: 1 (20 ml) a 25 °C durante 0,5 h. El compuesto 2-cloro-N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (230 mg, 477 µmol, 19 % de rendimiento en dos pasos) se obtuvo como un sólido blanco.

[001252] LC-MS: MS (ESI$^+$): t_R = 0,684 min, m/z = 433,1 [M + H$^+$]

[001253] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,92 (s, 1H), 7,40 (d, **J** = 8,8 Hz, 1H), 6,51 (d, J = 8,8 Hz, 1H), 6,11 (d, J = 7,6 Hz, 1H), 4,12 (d, J = 8,4 Hz, 1H), 4,04 (s, 3H), 2,32 (s, 3H).

[001254] A una solución de 2-cloro-N-[3-(3-cloro-4-ciano-2-metilfenoxi)-2,2,4,4-tetrametilciclobutil]pirimidina-5-carboxamida (60 mg, 125 µmol, 1,0 *eq*) y 1-[1-[1-[(3,3-dimetil-4-piperidil)metil]-4-piperidil]-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-5-il]etanona (75 mg, 125 µmol, 1,0 *eq*) en NMP (0,5 ml) se agregó DIPEA (49 mg, 376 µmol, 65 µl, 3,0 *eq*). La mezcla se agitó a 25 °C durante 12 h. La mezcla se filtró y se concentró para obtener el compuesto 295j (85,0 mg) como un aceite amarillo. El residuo se purificó mediante HPLC preparativa

(columna: Phenomenex Luna C18 150*25mm*10um; fase móvil: [H_2O (0,225 % FA)-ACN]; gradiente: 34 %-64 % B durante 10,0 min). El compuesto 2-[4-[[4-[5-acetil-3-[7-metil-6-(1-metilpirazol-4-il)-3,4-dihidro-2H-quinolin-1-il]-6,7-dihidro-4H-pirazolo[4,3-c]piridin-1-il]-1-piperidil]metil]-3,3-dimetil-1-piperidil]-N-[3-(3-cloro-4-ciano-2-metil-fenoxi)-2,2,4,4-tetrametil-ciclobutil]pirimidina-5-carboxamida (62,78 mg, 62,00 µmol, 49,51 % de rendimiento) se obtuvo como un sólido blanco.

[001255] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,61 (s, 1H), 7,53 - 7,35 (m, 3H), 7,35 - 6,84 (m, 1H), 6,37 (s, 1H), 5,87 (d, J = 8,4 Hz, 1H), 4,79 (d, **J** = 12,8 Hz, 1H), 4,42 (br s, 1H), 4,26 - (m, 1H), 3,93 - 3,81 (m, 1H), 3,74 - 3,52 (m, 1H), 3,04 (br s, 1H), 2,94 - 2,60 (m, 1H), 2,40 (d, J = 10,8 Hz, 1H), 2,27 - 2,12 (m, 1H), 2,10 -3,25 (m, 1H), 2,08 - 1,92 (m, 1H), 1,92 - 1,80 (m, 1H), 1,56 - 1,42 (m, 1H), 1,38 - 1,26 (m, 1H), 1,18 (d, J = 11,6 Hz, 3H), 0,98 (d, J = 6,6 Hz, 3H).

LC-MS: MS (ESI^+): t_R = 2,575 min, m/z = 995,8 [M + H^+]

Ejemplo A-1: Solución oral

[001256] Para preparar una composición farmacéutica para administración oral, se agrega una cantidad suficiente de un compuesto de fórmula (I) o (II), o una sal farmacéuticamente aceptable de este, al agua (con solubilizantes opcionales, tampones opcionales y excipientes enmascaradores del sabor) para proporcionar una solución de 20 mg/ml.

Ejemplo A-2: Comprimido oral

[001257] Se prepara un comprimido mezclando entre un 20 y un 50 % en peso de un compuesto de fórmula (I) o (II), o una sal farmacéuticamente aceptable de este, entre un 20 y un 50 % en peso de celulosa microcristalina, entre un 1 y un 10 % en peso de hidroxipropilcelulosa poco sustituida y entre un 1 y un 10 % en peso de estearato de magnesio u otros excipientes apropiados. Los comprimidos se preparan mediante compresión directa. El peso total de los comprimidos se mantiene entre 100 y 500 mg.

Ejemplo A-3: Cápsula oral

[001258] Para preparar una composición farmacéutica para administración oral, se mezclan de 10 a 500 mg de un compuesto de fórmula (I) o (II), o una sal farmacéuticamente aceptable de este, con almidón u otra mezcla de polvo adecuada. La mezcla se incorpora a una unidad de dosificación oral, como una cápsula de gelatina dura, que es apta para la administración oral.

[001259] En otra realización, se colocan de 10 a 500 mg de un compuesto de fórmula (I) o (II), o una sal farmacéuticamente aceptable de este, en una cápsula de tamaño 4 o en una cápsula de tamaño 1 (hipromelosa o gelatina dura) y se cierra la cápsula.

Ejemplo B-1: Ensayo de formación de complejo ternario

Preparación de placas de 96 pocillos recubiertas con anticuerpos anti-AR de ratón

[001260] Placas MaxiSorp negras: recubrir con 50 µL de anticuerpo AR de ratón diluido 1/50 (Anticuerpo monoclonal (AR 441 de Thermo Fisher); diluido en solución salina tamponada con fosfato (PBS). Gire el líquido hasta el fondo de los pozos, si es necesario. Incubar durante la noche a 4 °C. Al día siguiente, lavar 3 veces con 200 µL de TBST. Bloquear con 200 µL de tampón de bloqueo (BSA al 5 % en TBST) a temperatura ambiente durante 2 horas (BSA: A4503 o A2153 de Sigma). Lave los platos 3 veces con TBST. Las placas están listas para los lisados.

Preparación de lisados tratados con dimerizador

[001261] Cultivar las células en placas de 96 pocillos a una concentración de 50.000 células VCaP por pocillo durante al menos 3 días. Placa con suero fetal bovino tratado con carbón activado Omega al 5 % en un volumen total de 200 µL. Tratar con la solución bifuncional durante 1,5 horas añadiendo 1 µL de la solución madre 200x en DMSO. Medio/compuesto de aspiración. Agregue y mezcle con pipeta 70 µL de tampón de lisis AlphaLisa 1x a cada pocillo (Perkin Elmer, AlphaLISA SureFire Ultra, diluido en agua). Al añadir el tampón de lisis para romper las células, pipetee hacia arriba y hacia abajo. Dejar que la lisis proceda durante 30 min a 4 °C.

3) ELISA sándwich

[001262] Transfiera 50 µL de lisado a placas MaxiSorp recubiertas con anticuerpos y posteriormente bloqueadas con BSA. Se agitó durante 1 minutos a temperatura ambiente. Retire los lisados. Lavar 3 veces con TBST. Agregue 75 µL de anticuerpo CBP o p300 de conejo a cada pocillo (diluido 1:5000 en tampón de bloqueo (5 % BSA en TBST). Anticuerpo CBP: (D6C5) mAb de conejo n.° 7389; anticuerpo p300: (D8Z4E) mAb de conejo n.° 86377. Incubar durante la noche a 4 °C. Lavar 3 veces con 300 µL de TBST, cada vez en agitador durante 5-10 min. Preparar anticuerpo de cabra anti-conejo conjugado con HRP (dilución 1/100K en tampón de bloqueo). Número de catálogo de Invitrogen: 32260. Añadir 75 µL de anticuerpo de cabra anti-conejo conjugado con HRP. Incubar a temperatura ambiente durante 1 hora. Retire la mezcla de anticuerpos HRP. Lave de 7 a 8 veces con TBST, agitando durante 10 minutos cada vez. En los lavados posteriores, procure que los pocillos se desborden para que no quede HRP residual adherido a las paredes del pocillo. Prepare y añada 75 µL/pocillo de solución de sustrato quimiofluorescente QuantaRed Enhance HRP. Lea inmediatamente la fluorescencia en el BMG ClarioStar (ej.: 570/em 585) y repita la lectura a los 5 y 15 minutos.

[001263] Los resultados del ensayo de formación del complejo ternario se muestran en la Tabla 2.

Tabla 2

Compuesto	Complejo ternario promedio* (nM)	Compuesto	Complejo ternario promedio* (nM)	Compuesto	Complejo ternario promedio* (nM)
1	A	**44**	D	**77**	A
3	D	**45**	D	**78**	A
4	D	**46**	A	**79**	A
5	D	**48**	D	**82**	A
6	D	**49**	D	**83**	A
8	D	**50**	A	**84**	A
9	A	**51**	A	**85**	A
10	D	**53**	A	**86**	D
11	C	**54**	D	**87**	A
12	B	**55**	D	**89**	A
13	B	**56**	A	**90**	A
15	C	**57**	D	**91**	D
18	A	**58**	D	**92**	D
19	A	**59**	D	**93**	D
20	A	**60**	D	**94**	C
21	B	**64**	A	**95**	B
22	A	**65**	A	**96**	A
24	A	**66**	A	**97**	A
25	B	**69**	A	**98**	A
26	A	**70**	A	**99**	A
27	A	**71**	A	**100**	A
28	A	**72**	A	**101**	A
41	A	**74**	A	**102**	A
42	A	**75**	D	**103**	A
43	D	**76**	A	**104**	A

Compuesto	Complejo ternario promedio* (nM)
105	A
106	A
107	A
108	A
109	A
111	A
112	A
113	A
114	A
115	A
116	D
117	B
118	D
119	A
120	A
122	A
127	A
128	D
129	A
131	A
135	A
136	A
137	A
138	A
139	D
140	A
141	A
142	A

Compuesto	Complejo ternario promedio* (nM)
143	A
144	A
150	B
152	D
155	A
157	A
158	B
160	D
161	C
162	A
163	A
167	A
169	A
170	A
171	A
172	A
173	A
174	A
175	A
176	A
177	A
178	A
179	A
180	A
185	A
186	A
188	A
193	D

Compuesto	Complejo ternario promedio* (nM)
209	C
212	C
213	D
214	A
215	A
216	A
217	A
218	D
219	B
220	A
221	B
222	A
223	A
224	A
225	A
226	A
227	A
228	B
229	B
230	C
231	C
232	C
233	B
234	B
235	A
236	D
237	A
238	C

Compuesto	Complejo ternario promedio* (nM)
239	A
240	B
241	B
242	D
243	D
244	B
245	A
246	A
247	A
248	A
249	A
250	A
251	A
252	A
253	A
254	A
255	A
256	A
257	A
258	B
259	B
263	A
264	A
265	A
267	B
268	A
271	A
273	A

Compuesto	Complejo ternario promedio* (nM)
274	A
275	A
277	A
278	A
280	A
282	A
284	A
286	D
287	B
288	A
289	A
292	A
293	A
294	A
295	A
296	A
299	A
302	A
304	A
305	A
307	B
308	A
309	A
310	A
313	A
314	A
317	A
318	A

Compuesto	Complejo ternario promedio* (nM)
319	A
320	A
321	A
322	A
323	A
324	A
325	A
326	A
327	A
329	A
331	A
332	A
333	D
334	A
335	A
336	A
337	A
338	A
339	A
340	A
341	A
342	A
343	A
344	A
345	A
346	A
347	A
348	A

Compuesto	Complejo ternario promedio* (nM)
349	A
350	A
356	A
357	A
360	A
362	A
363	A
364	A
367	A
369	A
370	A
371	A
372	A
373	A
374	A
375	A
376	A
377	B
378	B
379	B
380	B
381	A
382	A
383	A
384	A
385	A
386	A
387	A

Compuesto	Complejo ternario promedio* (nM)
388	A
389	A
390	A
391	A
392	A
395	A
396	A
397	B
398	B
399	B
400	A
401	A
402	A
403	D
404	A
405	C
406	B
407	C
408	D
410	D
412	D
413	A
414	A
415	B
416	B
422	A
424	A
425	A

Compuesto	Complejo ternario promedio* (nM)
426	A
428	A
431	A
432	A
433	A
434	A
435	A
437	A
440	A
441	A
442	A
443	A
444	A
446	A
447	A
448	A
449	A
450	A
451	A
452	A
453	A
455	A
456	A
457	A
458	A
459	A
460	A
461	A

Compuesto	Complejo ternario promedio* (nM)
462	A
463	A
464	A
465	A

Compuesto	Complejo ternario promedio* (nM)
466	A
467	A
468	A
469	A

Compuesto	Complejo ternario promedio* (nM)
470	B
471	A
472	A
473	A

*A es <1 nM; B es >1 nM y ≤10 nM; C es >10 nM y ≤100 nM; D es activo y >100 nM.

Ejemplo B-2: Ensayo celular NanoBRET

[001264] Los reactivos para el ensayo de interacción NanoBRET™ Histona H3,3/CBP-BD y los reactivos para la transfección FuGENE® HD se adquirieron de Promega. El compuesto de referencia SGC-CBP-30 fue adquirido en MedChem Express. La línea celular HEK293 se adquirió de American Type Culture Collection (Manassas, VA). Las células HEK293 se cultivaron en medio EMEM suplementado con 10 % de FBS, 100 µg/ml de penicilina y 100 µg/ml de estreptomicina. Los cultivos se mantuvieron a 37°C en una atmósfera humidificada de 5 % CO_2 y 95 % aire.

[001265] Las células HEK293 se transfectaron con 2 µg de ADN del vector de fusión Histona H3,3-HaloTag más 0,05 µg del vector de fusión CBP-BD-NanoLuc. Las células transfectadas se trataron con el ligando NanoBRET™ 618 y los compuestos de prueba (a partir de 1 µM, 10 dosis con dilución triple) o con el compuesto de referencia SGC-CBP-30 (a partir de 10 µM, 10 dosis con dilución triple) durante 22 horas. La interacción celular histona H3,3/CBP-BD se midió mediante el ensayo NanoBRET. Los ajustes de curvas se realizaron únicamente cuando el porcentaje de señal NanoBret a la concentración más alta de compuestos fue inferior al 55 %.

[001266] Los resultados del ensayo de escisión se muestran en la Tabla 3.

Tabla 3

Compuesto	IC_{50} (M)
GNE-781	1,23E-10
Compuesto 109	1,0E-06
SGC-CBP-30	6,09E-07

Transfección para el ensayo de interacción de la histona H3,3/CBP-BD con NanoBRET™

1. Cultive las células HEK293 adecuadamente antes del ensayo.
2. Retire el medio de cultivo del matraz de cultivo celular mediante aspiración, realice la tripsinización y deje que las células se disocien del fondo del matraz.
3. Neutralizar la tripsina usando medio de cultivo celular, contar las células para estimar la densidad y resuspender a una densidad final de 4×10^5 células/ml en medio de cultivo celular.
4. Coloca 2 ml de células en cada pocillo de una placa de seis pocillos.
5. Dejar que las células se adhieran y se recuperen durante la noche a 37 °C, 5 % de CO_2.
6. Prepare una mezcla de transfección que contenga las siguientes cantidades de ADN: 2 µg de Histona H3,3-HaloTag 0,05 µg de NanoLuc-CBP-BD
7. Agregue 100 µl de Opti-MEM® I Reduced Serum Medium, sin rojo de fenol, a la mezcla de transfección y mezcle bien.
8. Añada 8 µl del reactivo de transfección FuGENE® HD e incube a temperatura ambiente durante 10 minutos.
9. Añadir la mezcla de transfección a los pocillos con células adheridas y expresar las proteínas durante 24 horas a 37 °C, 5 % de CO_2.
Reimplantación de células HEK293 transfectadas en placas de múltiples pocillos y adición del ligando HaloTag® NanoBRET™ 618
1. En una placa de seis pocillos, retire el medio de cultivo de cada pocillo y lave con 1 ml de PBS. Desechar.
2. Agregue tripsina-EDTA al 0,25 % e incube a temperatura ambiente hasta que las células se desprendan del fondo del pocillo.
3. Agregue medio de cultivo celular para neutralizar la tripsina, mezcle para recolectar y resuspender las células, y transfiera la suspensión celular a un tubo cónico de 15 ml.
4. Centrifugue las células a 125 × g durante 5 minutos. Deseche el medio de cultivo celular y resuspenda en un volumen igual de medio de ensayo (Medio Opti-MEM® I con suero reducido, sin rojo de fenol + 4 % de FBS).
5. Contar para estimar la densidad celular y ajustar la densidad a 2×10^5 células/ml en el medio de ensayo.
6. Divida las células en dos grupos y agregue el ligando HaloTag® NanoBRET™ 618 o el vehículo DMSO de la siguiente manera: Muestras experimentales (+ ligando): Agregue 1 µl de ligando HaloTag® NanoBRET™ 618 0,1 mM por mililitro de células (concentración final de 100 nM). Controles sin aceptor (– ligando): Añadir 1 µl de DMSO por mililitro de células (concentración final de DMSO del 0,1 %). Aplique los compuestos

a la placa de 384 pocillos con Echo 550.

7. Para las mediciones de NanoBRET™ con o sin tratamiento con el compuesto, dispense 25 µl de cada grupo de células preparadas en el paso 6 por duplicado para alcanzar las concentraciones de prueba finales requeridas (comenzando en 1 o 10 µM, 10 dosis con dilución de 3 veces).

8. Incubar las placas a 37 °C, 5 % CO_2 durante 22 horas.

Agregar sustrato NanoBRET™ Nano-Glo® y tomar medidas NanoBRET™

1. Prepare una solución 5X de sustrato NanoBRET™ Nano-Glo® en medio Opti-MEM® I con suero reducido, sin rojo de fenol.

2. Agregue el sustrato a las células y agite la placa durante 30 segundos para mezclar.

3. Mida la emisión del donante (460 nm) y la emisión del aceptor (600 nm) dentro de los 10 minutos posteriores a la adición del sustrato utilizando un lector multietiqueta Envision 2104.

Cálculos NanoBRET™

1. Para generar los valores brutos de la relación NanoBRET™, divida el valor de emisión del aceptor (por ejemplo, 600 nm) entre el valor de emisión del donante (por ejemplo, 460 nm) para cada muestra.

2. Determinar la proporción media de NanoBRET™ para cada conjunto de muestras: muestras experimentales con el ligando HaloTag®NanoBRET™ 618 y muestras de control sin aceptor.

3. Se trazaron las curvas de IC50 y se calcularon los valores de IC50 utilizando el programa GraphPad Prism, basándose en una ecuación sigmoidal de dosis-respuesta.

Ejemplo B-3: Ensayo de inhibición del crecimiento de VCaP

[001267] Las células VCaP (ATCC Cat#CRL-2876) se siembran a una densidad de $1x10^4$ células por pocillo en una placa de cultivo de 96 pocillos de plástico blanco (Thermo Scientific Nunc Cat#165306) en 100 µL de medio DMEM sin rojo de fenol (Gibco Cat#21063-029) con 5 % de CSS (Omega Scientific Cat#FB-04). Las placas de cultivo se devuelven a la incubadora (37 °C/5 % CO2) durante 72 horas antes del tratamiento. Justo antes del tratamiento, se añadieron 100 µL de DMEM/5 %CSS sin rojo de fenol y 60 pM de R1881 (Sigma Cat#R0908-10mg) a cada pocillo de las placas de cultivo (concentración final de R1881 = 30 pM). Se añadieron compuestos (200X) a cada pocillo en un volumen de 1 µL, con diluciones seriadas (1:5) desde 20 µM hasta 2 pM (las concentraciones finales en el pocillo son de 100 nM a 10 fM). Las placas de cultivo se devuelven a la incubadora durante 9 días.

[001268] Tras un período de tratamiento de 9 días, se retiró el medio de cultivo de las

placas de cultivo por inversión y se añadieron 100 µL de reactivo CTG a temperatura ambiente (Promega Cat#G7573) a cada pocillo. Las placas con los cultivos en racimo se colocan en un agitador y se incuban a temperatura ambiente durante 20 minutos. Tras este proceso de agitación/incubación, las placas de cultivo se leen en un luminómetro (BMG ClarioStar). IC_{50} se obtienen graficando los datos de RLU frente a la concentración del compuesto con curvas logísticas de regresión no lineal de 4 parámetros (GraphPad Prism).

[001269] Los resultados del ensayo de inhibición del crecimiento de VCaP se muestran en la Tabla 4.

Tabla 4

Compuesto	IC_{50} (M)	Compuesto	IC_{50} (M)	Compuesto	IC_{50} (M)
1	++	**28**	+	**66**	++
2	+++	**41**	++	**69**	++
3	++++	**42**	+	**70**	++
4	++++	**43**	++++	**71**	+++
5	++++	**44**	++++	**72**	++
7	++	**45**	++++	**74**	+++
9	++	**48**	+++	**75**	++
10	+++	**49**	+++	**76**	+
11	++	**50**	++	**77**	++
12	+++	**51**	++	**78**	+++
13	++	**52**	++	**79**	++
15	++++	**53**	++++	**82**	+
18	++	**54**	+++	**83**	++
19	++	**55**	++++	**84**	+
20	+	**56**	++	**85**	++
21	++	**57**	++++	**87**	++
22	+	**58**	++++	**88**	++
24	++	**59**	++++	**89**	++
25	++	**60**	++++	**90**	++++
26	++	**64**	++	**91**	++++
27	++	**65**	+	**92**	++++

Compuesto	IC_{50} (M)
93	++
94	+++
95	++
96	+
97	+
98	+
99	+
100	+
101	+
102	++
103	++
104	++
105	++
106	+
107	+
108	+
109	+
110	+
114	+
120	+
122	+
127	+
128	++++
129	+
135	+
136	+
139	+
141	+
142	+
144	++

Compuesto	IC_{50} (M)
150	+
152	+
155	++
158	+
164	+
165	+
167	++
168	++
169	+
170	++
171	+
172	+
174	+
175	+
177	++++
178	++
179	++
180	+
185	+
186	++
188	+
190	++++
191	++++
192	+++
194	+++
195	+++
196	+++
197	+++
198	++++
199	++++

Compuesto	IC_{50} (M)
200	++++
201	++++
202	++++
209	+
213	++
214	+++
215	++
216	+
217	++
218	+++
219	++
220	+++
221	+++
222	++
223	+
224	++
225	++
226	+
227	+
228	++
229	++
230	++
231	++
232	++++
233	++++
234	++++
235	++++
236	++++
237	+++
238	++++

Compuesto	IC_{50} (M)
239	+++
240	+++
241	++
242	++
243	++
244	++
245	++
246	++
247	++
248	++
249	++
250	+
251	++
252	++
253	+
254	++
255	++
256	++
257	++
263	+
264	++
265	+
266	++
267	+++
268	++
269	++
270	++
271	++
273	+
274	+

Compuesto	IC_{50} (M)
275	+
277	+
284	+
286	+++
287	+++
288	+
289	+
292	++
293	++
294	++
296	++
297	+++
298	++++
299	++
300	+
301	+
302	+
304	++
305	+
306	+++
308	+
309	++
310	+
313	++
317	+
318	+
319	+
320	++
321	+
322	+

Compuesto	IC_{50} (M)
323	+
324	+
325	++
327	++
329	+
331	++
332	+
333	+
334	++
335	++
336	+++
337	++
338	++
339	+
341	++
342	++
343	++
347	+
348	+
349	+
350	+
356	+
357	+
360	+
362	+
363	+
364	+
369	+
371	+
372	+

Compuesto	IC_{50} (M)
373	+
374	++
375	++
376	++
377	+++
378	+++
379	+++
380	+++
383	++
384	+
385	++
386	++
387	++
388	++
389	+
390	++
392	++
395	++
396	++
397	++++
398	+++
399	+++
401	++
402	+
406	+++
410	++++
412	++++
415	+++
432	+
442	+

Compuesto	IC_{50} (M)
443	+
444	++
446	++
447	++
448	++
449	++
450	++
451	++
455	++
458	++
459	++
460	+
461	+
462	+
464	+
465	++
466	++
468	++
471	++
472	++
473	++

** ++++ es IC_{50} activo y > 1E-7; +++ es 1E-7 ≤ IC_{50} > 1E-9; ++ es 1E-9 ≤ IC_{50} > 1E-10; + es IC_{50} ≤ 1E-10

Ejemplo B-4: Ensayo de inhibición del crecimiento de células HEK-293

[001270] Las células HEK-293 (ATCC Cat#CRL-1573) se siembran a una densidad de $3x10^3$ células por pocillo en una placa de cultivo en racimos de 96 pocillos de plástico blanco (Thermo Scientific Nunc Cat#165306) en 200 µL de medio DMEM (ATCC Cat#30-2002) con 10 % de FBS (Gibco Cat#26140-079). Las placas de cultivo se devuelven a la incubadora (37 °C/5 % CO2) durante 24 horas antes del tratamiento. Se añadieron compuestos (200X) a cada pocillo en un volumen de 1 µL, con diluciones seriadas (1:5) desde 2 mM hasta 200 pM (las concentraciones finales en el pocillo son de 10 µM a 1 pM). Las placas de cultivo se devuelven a la incubadora durante 3 días.

[001271] Tras un período de tratamiento de 3 días, se extrajeron 100 µL de medio de cultivo de cada pocillo mediante aspiración y se añadieron 100 µL de reactivo CTG a temperatura ambiente (Promega Cat#G7573) a cada pocillo. Las placas con los cultivos en racimo se colocan en un agitador y se incuban a temperatura ambiente durante 20 minutos. Tras este proceso de agitación/incubación, las placas de cultivo se leen en un luminómetro (BMG ClarioStar). IC_{50} se obtienen graficando los datos de RLU frente a la concentración del compuesto con curvas logísticas de regresión no lineal de 4 parámetros (GraphPad Prism).

[001272] Los resultados del ensayo de inhibición del crecimiento de las células HEK-293 se muestran en la Tabla 5.

Tabla 5

Compuesto	**IC_{50} (µM)**
20	>10
22	>10
28	>10
41	>10
42	>10
57	>10
59	>10
64	>10
65	>10
66	>10

Compuesto	IC_{50} (µM)
69	>10
70	>10
72	>10
74	>10
75	>10
77	>10
79	>10
82	>10
83	>10
84	>10
85	>10
87	>10
90	2,159
91	>10
96	>10
97	>10
98	>10
99	>10
100	>10
101	>10
102	>10
103	>10
104	>10
105	>10
106	>10
107	>10
108	>10
109	>10
110	>10
172	>10

Compuesto	IC_{50} (µM)
263	>1
273	>1
275	>1
327	>1
350	>1
356	>1
360	>1