Industria y Comercio
SUPERINTENDENCIA

Radicación	16 72744 0000 0000	2016-03-22 17:03:45	
Trámite	11	PCT-PATENTE DE INVENCION CAPITULOS I Y II	
Evento	378	FASE NACIONAL INCLUIDO CAPITULO I	
Actuación	411	PRESENTACION	Folios: 4
Dependencia	2020	DIRECCION DE NUEVAS CREACIONES	
Pago #1	28058	$ 988000	

DIRECCIÓN DE NUEVAS CREACIONES SOLICITUD FASE NACIONAL - PCT

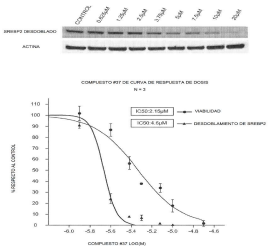


FIG. 1

1	**Titulo de la Invención**(200 caractares o espacios máximos)			
COMPUESTOS HETEROCICLICOS Y METODOS DE USO				
2	**Datos del Solicitante**			
	Nombre:	MEDIVATION TECHNOLOGIES, INC.	**Dirección Electrónica:**	sic@castellanosyco.co
	Dirección:	525 Market Street, 36th Floor, San Francisco, CA 94105, ESTADOS UNIDOS DE AMERICA	**Domicilio/País de constitución:**	ESTADOS UNIDOS DE AMERICA - CALIFORNIA - SAN FRANCISCO
	Identificación: ☐ CEDULA DE CIUDADANIA ☐ CEDULA DE EXTRANJERIA ☒ EMPRESA EXTRANJERA ☐ NIT ☐ PASAPORTE **Número:** 4095530-			
3	**Solicitantes**			

	Apellidos - Nombres o Razón Social	Tipo	Identificación
1.	MEDIVATION TECHNOLOGIES, INC.	NN	4095530

4	Datos del Inventor			
	Nombre:	SARVAJIT CHAKRAVARTY	**Dirección Electrónica:**	sic@castellanosyco.co
	Dirección:	c/o Medivation Technologies, Inc., 525 Market Street, 36th Floor, San Francisco, California 94105, ESTADOS UNIDOS DE AMERICA	**Domicilio/País de constitución:**	ESTADOS UNIDOS DE AMERICA - CALIFORNIA - SAN FRANCISCO

Identificación:

- ☐ CEDULA DE CIUDADANIA
- ☐ CEDULA DE EXTRANJERIA
- ☐ EMPRESA EXTRANJERA
- ☐ NIT
- ☐ PASAPORTE
- ☒ No Aplica

Número: -

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6	Datos Inventor(es)

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7	Datos del Representante Legal / Apoderado		
Nombre:	MARGARITA CASTELLANOS ABONDANO	**Dirección Electrónica:**	sic@castellanosyco.co
Dirección:	CALLE 94A 7A 09	**Domicilio/País de constitución:**	COLOMBIA - BOGOTA D.C. - BOGOTA D.C.

Identificación:

☒ CEDULA DE CIUDADANIA ☐ CEDULA DE EXTRANJERIA
☐ EMPRESA EXTRANJERA ☐ NIT
☐ PASAPORTE

Número: 39779654-

Presentación de Poder

Año de Radicación	
Número de Radicación	

8	**Datos Solicitud: PCT / WO**		
Número Solicitud:	PCT/US2014/053215	**Fecha Solicitud:**	28/08/2014
Número Publicacion:	WO 2015/031650	**Fecha Publicacion:**	05/03/2015

9	**Declaraciones de prioridad**	☒ SI ☐ NO

	(33) País de origen	**Codigo del país**	**(31) No. Solicitud**	**(32) Fecha**
1.	INDIA	IN	2816/MUM/2013	28/08/2013
2.	INDIA	IN	3497/MUM/2013	04/11/2013

10	**Reivindicaciones**			
Número reivindicaciones:	38	**Pago Reivindicaciones:**	Si	

11 Reducción de tasas.

Declaro que carezco de medios económicos para presentar la solicitud de patente.

☐ SI ☒ NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolucón vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

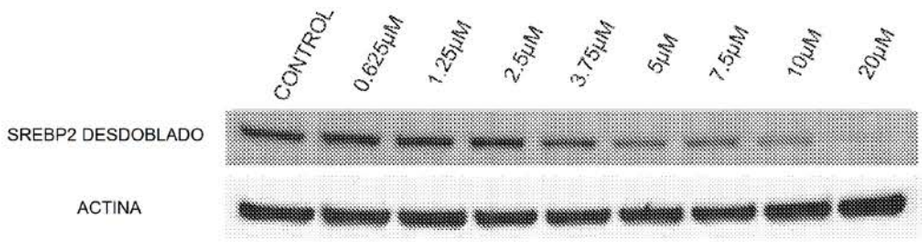
☐ Micro, pequeñas y medianas empresas
☐ Universidades públicas o privadas
☐ Entidades sin ánimo de lucro

Debe aportar los documentos que se indican en el numeral 17 de anexos

12 Documentos Anexos

☒ Reivindicaciones
☒ Descripción
☐ Dibujos y/o Figuras
☒ Resumen

☐ Certificado Depósito Material Biológico
☐ Uso de Conocimiento tradicional
☐ Listado de secuencias
☒ Artes finales 12 x 12 cm
☐ Poderes, si fuere el caso
☐ Copia de la primera solicitud si se reivindica prioridad
☐ Traducción simple de la primera solicitud, si se reivindica prioridad
☒ Otros Anexos


CONTROL
0.625μM
1.25μM
2.5μM
3.75μM
5μM
7.5μM
10μM
20μM
SREBP2 DESDOBLADO
ACTINA

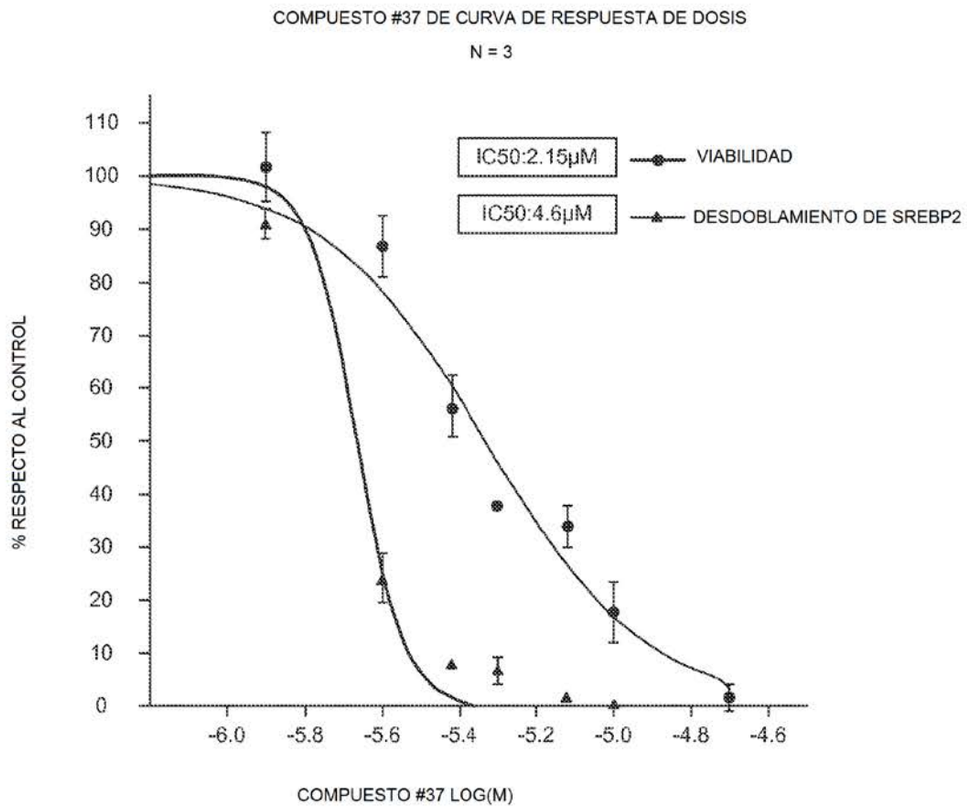

COMPUESTO #37 DE CURVA DE RESPUESTA DE DOSIS
N = 3
IC50:2.15μM
VIABILIDAD
IC50:4.6μM
DESDOBLAMIENTO DE SREBP2
% RESPECTO AL CONTROL
110
100
90
80
70
60
50
40
30
20
10
0
-6.0
-5.8
-5.6
-5.4
-5.2
-5.0
-4.8
-4.6
COMPUESTO #37 LOG(M)

FIG. 1

COMPUESTOS HETEROCÍCLICOS Y MÉTODOS DE USO

REFERENCIA CRUZADA A LAS SOLICITUDES RELACIONADAS

Esta solicitud reivindica la prioridad a la Solicitud de Patente India No. 2816/MUM/2013 presentada el 28 de Agosto de 2013, y Solicitud de Patente India No. 3497/MUM/2013 presentada el 4 de Noviembre de 2013.

CAMPO DE LA INVENCIÓN

Esta descripción en general se refiere a terapéuticos para el tratamiento de trastornos hiperpropiferativos, trastornos metabólicos y pancreatitis.

ANTECEDENTES DE LA INVENCIÓN

Las principales proteínas que se unen al elemento regulatorio de esterol (SREBPs) son los principales factores de transcripción que regulan la biosíntesis del colesterol, ácido graso y triglicéridos. Estos controlan la expresión de genes cruciales involucrados en la lipogénesis y absorción. La inhibición de la trayectoria de SREBP puede reducir la biosíntesis del lípido y puede ser así una estrategia para tratar enfermedades metabólicas, tales como diabetes tipo II, resistencia a la insulina, hígado graso y ateroesclerosis [Xiao, et al. *Acta Biochim. Biophys. Sin* (2013) 45:1, pp 2-10]. En mamíferos, se conocen tres isoformas de SREBP, designadas como SREBP-1a, SREBP-1c, y SREBP-2. La SREBP-1a controla un amplio intervalo de objetivos de SREBP que incluyen

la producción de ácidos grasos, triglicéridos, fosfolípidos y colesterol. La SREBP-1c preferencialmente activa genes del metabolismo de ácido graso y triglicéridos, mientras que la SREBP-2 preferencialmente activa genes del metabolismo del colesterol, ambos han sido estudiados en modelos de humano y ratones [Horton, et al. *J. Clin. Invest*. (2002) 109:9, pp 1125-1131], así como también *Drosophila* [Rawson. *Nature Rev. Mol. Cell Biol*. (2003) 4:8, pp 631-640].

En estudios recientes también se ha presentado una sobrerregulación entre los enlaces de la síntesis de lípido y cáncer de próstata [Suburu, et al. *Prostaglandins Other Lipid Mediat*. (2012) 98:0, pp 1-10]. El cambio metabólico del metabolismo catabólico a anabólico es una huella de células cancerígenas. Muchos cánceres requieren síntesis de ácidos grasos y otros lípidos tales como colesterol y los andrógenos son implicados en el cáncer de próstata. La SREBP-1c es el principal regulador transcripcional de enzimas en la trayectoria de la síntesis de ácido graso, y su expresión puede ser estimulada por andrógenos y el factor de crecimiento epidérmico (EGF) en células cancerígenas en la próstata. La sobreexpresión de SREBP-1c es suficiente para provocar tumorigenicidad e invasión de células cancerígenas de la próstata. La SREBP-1 puede también incrementar la expresión de NOX5, un productor predominante de especies de oxígeno reactivo (ROS) y regulador del crecimiento de células cancerígenas de

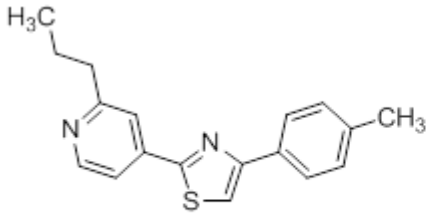
la próstata [Brar, et al. *Am. J. Physiol. Cell Physiol*. (2003) 285:2, pp C353-369; Huang, et al. *Mol. Cancer Res*. (2012) 10:1, pp 133-142; Huang, et al. *Cancer Research* (2012) 72:8, SUPPL. 1; Huang, et al. *Mol. Cancer Res*. (2014) 13:4, pp 855-866].

La SREBP-2, regula la síntesis de andrógeno, también es por sí misma regulada por andrógenos, demostrando un circuito de retroalimentación directa para la regulación de la producción de andrógenos. La expresión de SREBP-2 se incrementa durante el progreso de la enfermedad y es significantemente mayor después de la castración. Este factor de transcripción también carece de su inhibición de retroalimentación en células cancerígenas de la próstata, implicando un papel para la síntesis de colesterol y andrógeno en cáncer de la próstata [Eberle, et al. *Biochimie* (2004) 86:11, pp 839-848; Ettinger, et al. *Cancer Res*. (2004), 64:6, pp2212-2221; Chen, et al. *Int. J. Cancer* (2001), 91:1, pp 41-45].

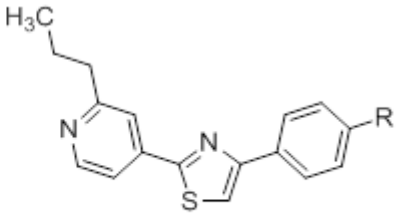
El bloqueo de las funciones de SREBP ligadas a las enfermedades descritas del mismo, representa un importante procedimiento terapéutico para limitar la síntesis de lípido/colesterol en la producción de membrana lo cual ocurre en enfermedades metabólicas y en el progreso de cáncer, así como también en patogénesis viral [Naar, et al. *Clin. Lipidol.* (2012) 7:1, pp 27-36]. Los terapéuticos de molécula pequeña afectan los reguladores metabólicos tales como mTOR, AMPK o SIRT1, incluyendo Rapamicina, Metformina, o Resveratrol,

respectivamente, pueden afectar la actividad transcripcional de SREBPs. Recientemente, se han encontrado dos moléculas pequeñas sin esterol, fatostatina y betulina para inhibir el procesamiento de SREBP [Kamisuki, et al. *Chem. Biol*. (2009) 16:8, pp 882-892; Tang, et al. *Cell. Metab*. (2011) 13:1, pp 44-56]. Se han presentado métodos para el tratamiento de cánceres que tienen una mutación p53, tales como células de cáncer de mama, usando inhibidores de SREBP [Freed-Pastor, et al. *PCT. Publication* WO2013-110007A1].

Recientemente se han descrito análogos de fosfatina como terapéuticos potenciales para el tratamiento de trastornos metabólicos [Uesugi, et al. *Patente Estadounidense No*. 8,207,196]. Los compuestos clave presentados en la presente se basan alrededor de la Fórmula X:



Fatostatina



Fórmula X

en donde R es H, F, Cl, Br, OBz, OH, OCH_3, OCH_2CO_2Me, OCH_2CO_2H, NH_2, NHiPr, $NHCOCH_3$, $NHSO_2Me$, NH[bencilo], NH[ciclopropilo], NH[tercbutiloxicarbonilo], NH[ciclohexilo], NH[tosilo], NH[quinolin-8-ilo], y NH[tiofen-2-ilo]. En particular, un compuesto (FGH10019), el derivado de metansulfonamida de fatostatina anterior en donde R es $NHSO_2Me$,

ha sido descrito como un candidato principal [Kamisuki, et al. *J. Med. Chem.* (2011) 54:13, pp 4923-4927].

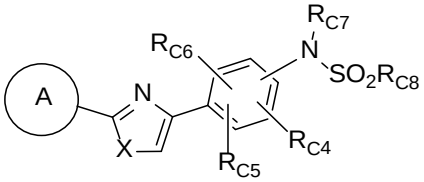
BREVE DESCRIPCIÓN DE LA INVENCIÓN

Esta descripción se refiere en general a terapéuticos para el tratamiento de trastornos proliferativos, trastornos metabólicos y pancreatitis. Esta descripción proporciona compuestos y métodos para usar estos compuestos para tratar trastornos hiperproliferativos benignos y malignos, así como también trastornos metabólicos y pancreatitis, como se describe a continuación. Los compuestos de la invención pueden también encontrar uso en el tratamiento de cáncer.

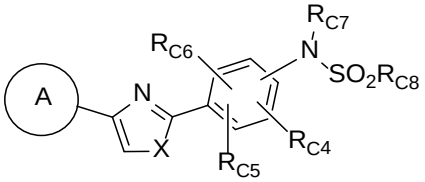
Presentados en la presente están nuevos compuestos que portan una porción de perhaloalquilosulfonamida. Tales compuestos, además de portar inhibidores de SREBP muy efectivos, son también inesperadamente muy biodisponibles *in vivo*. Los compuestos heteroaromáticos que portan grupos sulfonamida son propensos a varios estados iónicos, con base a los valores pKa inherentes. Cuando se colocan en solución acuosa, pueden existir en formas neutral, zwitteriónica o aniónica dependiente del pH de esta solución. Cada una de estas formas puede tener solubilidad dramáticamente diferente, y requiere estudios de formulación farmacéuticos complejos para maximizar su exposición *in-vivo*. Estos estudios pueden necesitar dispersiones sólidas, micronizaciones, coprecipitación, selección de sal, emulsificadores de lípido,

cosolventes, portadores en complejos, excipientes mejoradores de solubilidad y similares, cada uno de los cuales presentan sus propios desafíos, requerimientos de recursos e imprevisibilidad [véase, por ejemplo, Julémont, et al. *J. Med. Chem*. (2004) 47:27, pp6749-6759; Anand, et al. *Publicación de Patente Estadounidense* US2014-128431A1; Patel, et al. *Publicación de PCT* WO2000-072884]. Las perhaloalquilosulfonamidas tienen, en general, un pKa inferior y alta acidez con relación a alquilosulfonamidas no fluoradas, con un potencial para formar el anión a pH fisiológico, dependiendo de la funcionalidad restante en la molécula. Esta imprevisibilidad de cómo los compuestos que contienen perhaloalquilosulfonamida pueden ser formulados como farmacéuticos típicamente los hacen pocos atractivos al experto químico en medicina. Como se presentan en la presente, la alta biodisponibilidad de los compuestos de la invención se atribuye a valores pKa inesperadamente bajos encontrados para los compuestos, proporcionándoles características para aplicaciones terapéuticas.

En algunas modalidades, los compuestos descritos en la presente caen dentro de las fórmulas (Ia) o (Ib):



(Ia)



(Ib)

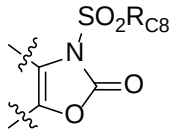
o una sal del mismo farmacéuticamente aceptable, en donde:

A es cualquiera de:

i. un arilo o heteroarilo, cada uno tiene solamente un anillo, sustituido con 1, 2, o 3 sustituyentes seleccionados del grupo que consiste de halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_6, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, hidroxialquilo lineal o ramificado C_1-C_6, alcoxi lineal o ramificado C_1-C_3, cicloalquilometilo C_3-C_6, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -OBn, -CO_2H, -CO_2-alquilo, -NR10R11, y -CONR10R11; o

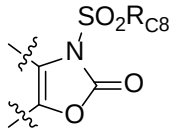
ii. un arilo o heteroarilo, cada uno tiene más de un anillo, opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados del grupo que consiste de halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_6, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, hidroxialquilo lineal o ramificado C_1-C_6, alcoxi lineal o ramificado C_1-C_3, cicloalquilometilo C_3-C_6, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -CH_2OH, -OBn, -CO_2H, -CO_2-alquilo, -NR10R11, y -CONR10R11;

Cada R_{C4}, R_{C5}, y R_{C6}, es independientemente hidrógeno, halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, alcoxi lineal o ramificado C_1-C_3, -CO_2H, -CONR10R11, o -$NHCONH_2$; o se toman con R_{C7} para formar la porción



;

R_{C7} es hidrógeno, alquilo lineal o ramificado C_1-C_6, hidroxialquilo lineal o ramificado C_1-C_6, -$(CR_{9a}R_{9b})_mNR10R11$, -CO_2-alquilo, -$(CR_{9a}R_{9b})_mO$-alquilo, -$(CR_{9a}R_{9b})_mOPO_3Na_2$, -$(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$-alquilo, -$(CR_{9a}R_{9b})_mO(C=O)$-alquilo, -$(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$-alquilo, –$(C=O)CH=CH_2$, -$SO_2R_{C8'}$; o se toman con uno de R_{C4}, R_{C5} o R_{C6} para formar la porción



;

R_{C8} es un perhalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

$R_{C8'}$ es un alquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo

de halógeno;

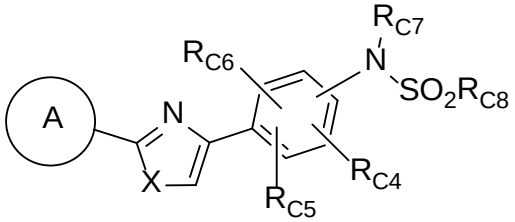
Cada **R_{9a}** y **R_{9b}**, en donde está presente, es independientemente hidrógeno o alquilo lineal o ramificado C_1-C_6;

R10 y **R11** son independientemente hidrógeno, -SO_2**$R_{C8'}$**, alquilo lineal o ramificado C_1-C_6, alquenilo lineal o ramificado C_2-C_6, cicloalquilo C_3-C_6, o cicloalquenilo C_3-C_6; o son tomados junto con el N al cual están unidos para formar un heterociclo C_3-C_6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, una $1\lambda^6$,2-tiazolidin-1,1-diona, una $1,2\lambda^6$,3-oxatiazolidin-2,2-diona, o una $1\lambda^6$,2,5-tiadiazolidin-1,1-diona;

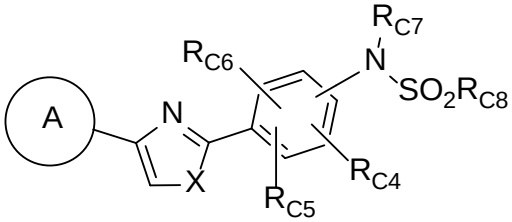
X es un heteroátomo seleccionado de S, O; o N**R_B** en donde **R_B** es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6; y

cada ***m*** y ***n*** es 1, 2 o 3.

En algunas modalidades, compuestos descritos en la presente caen dentro de las fórmulas (IIa) o (IIb):



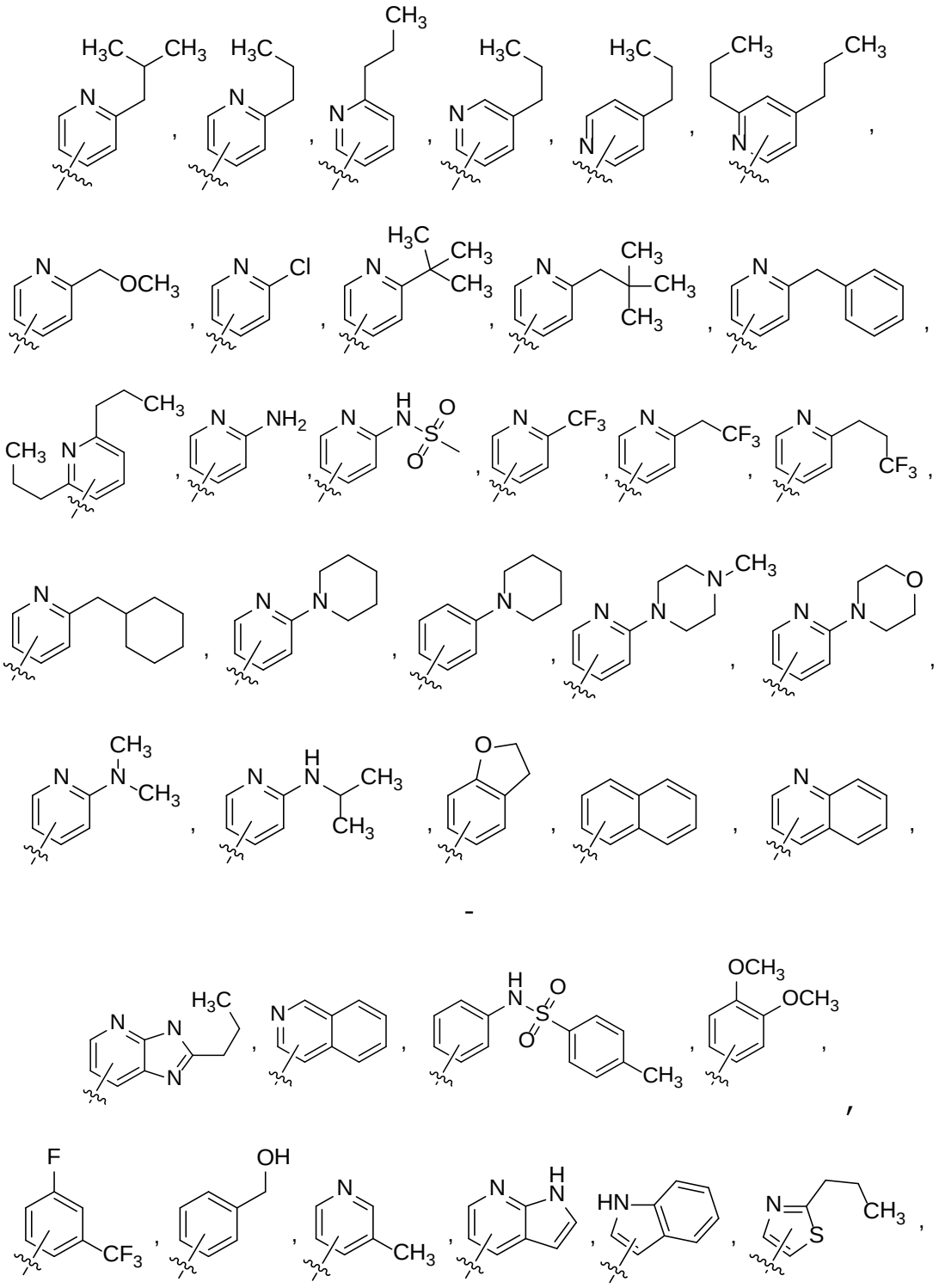
(IIa)



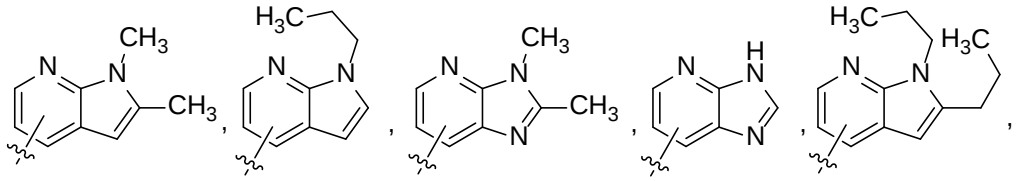
(IIb)

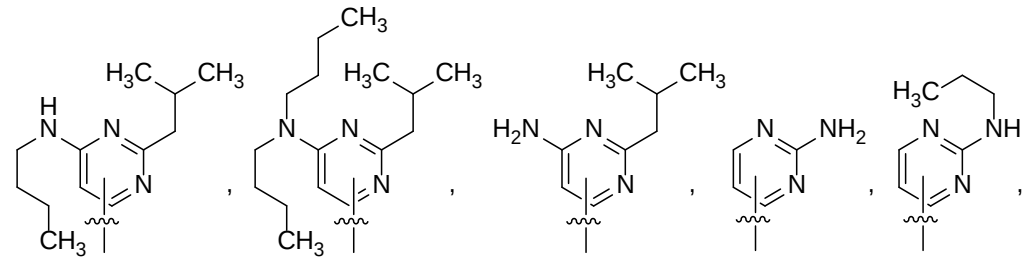
o una sal del mismo farmacéuticamente aceptable, en donde:

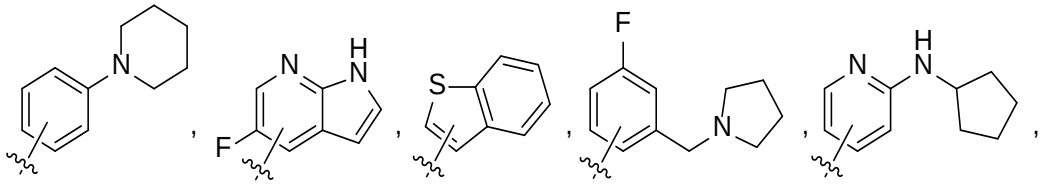
A es una porción seleccionada del grupo que consiste de:

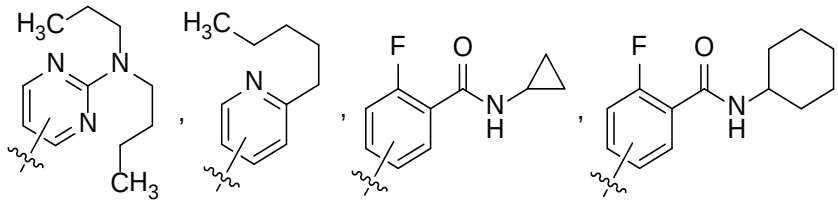


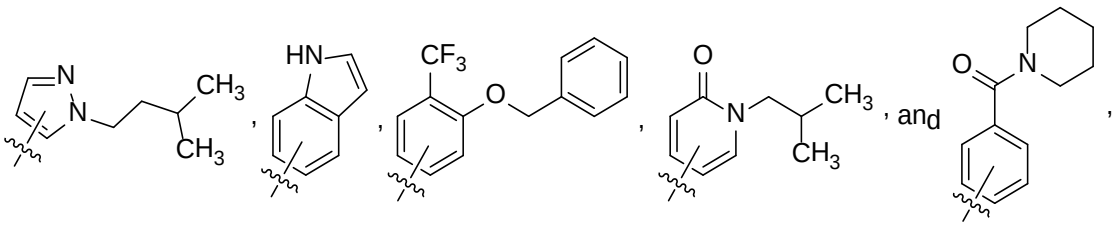
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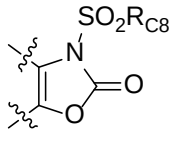






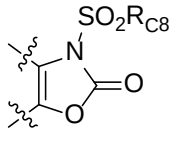
en donde el anillo que contiene X está unido al anillo A en cualquier posición disponible en el anillo , y

Cada **R_{C4}**, **R_{C5}**, y **R_{C6}**, es independientemente hidrógeno, halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, alcoxi lineal o ramificado C_1-C_3, -CO_2H, -CON**R10R11**, o -$NHCONH_2$; o se toman con **R_{C7}** para formar la porción



;

R_{C7} es hidrógeno, alquilo lineal o ramificado C_1-C_6, hidroxialquilo lineal o ramificado C_1-C_6, -(C**R_{9a}****R_{9b}**)$_m$N**R10R11**, -CO_2-alquilo, -(C**R_{9a}****R_{9b}**)$_m$O-alquilo, -(C**R_{9a}****R_{9b}**)$_m$OPO_3Na_2, -(C**R_{9a}****R_{9b}**)$_m$O(C**R_{9a}****R_{9b}**)$_n$O-alquilo, -(C**R_{9a}****R_{9b}**)$_m$O(C=O)-alquilo, -(C**R_{9a}****R_{9b}**)$_m$O(C**R_{9a}****R_{9b}**)$_n$O(C=O)-alquilo, –(C=O)CH=CH_2, -SO_2**$R_{C8'}$**; o se toman con uno de **R_{C4}**, **R_{C5}** o **R_{C6}** para formar la porción



;

R_{C8} es un perhalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

$R_{C8'}$ es un alquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo

de halógeno;

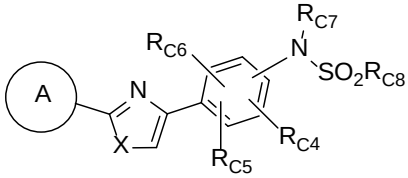
Cada **R_{9a}** y **R_{9b}**, en donde está presente, es independientemente hidrógeno o alquilo lineal o ramificado C_1-C_6;

R10 y **R11** son independientemente hidrógeno, -SO_2**$R_{C8'}$**, alquilo lineal o ramificado C_1-C_6, alquenilo lineal o ramificado C_2-C_6, cicloalquilo C_3-C_6, o cicloalquenilo C_3-C_6; o son tomados junto con el N al cual están unidos para formar un heterociclo C_3-C_6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, una 1λ^6,2-tiazolidin-1,1-diona, una 1,2λ^6,3-oxatiazolidin-2,2-diona, o una 1λ^6,2,5-tiadiazolidin-1,1-diona;

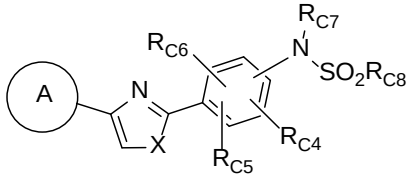
X es un heteroátomo seleccionado de S, O; o N**R_B** en donde **R_B** es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6; y

Cada ***m*** y ***n*** es 1, 2 o 3.

En algunas modalidades, compuestos descritos en la presente caen dentro de las fórmulas (IIa) o (IIb):



(IIa)

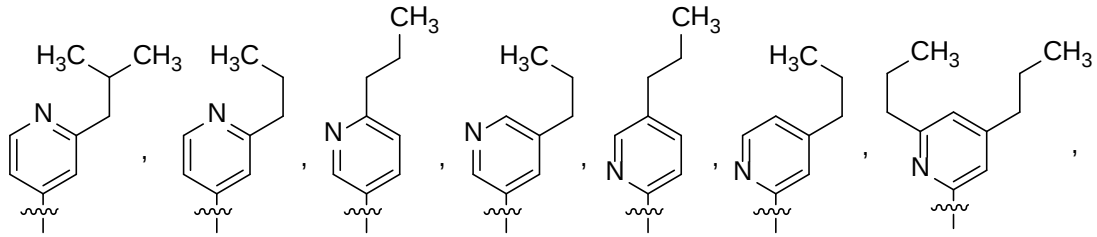


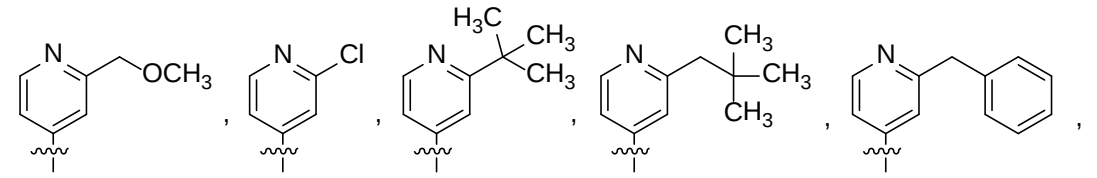
(IIb)

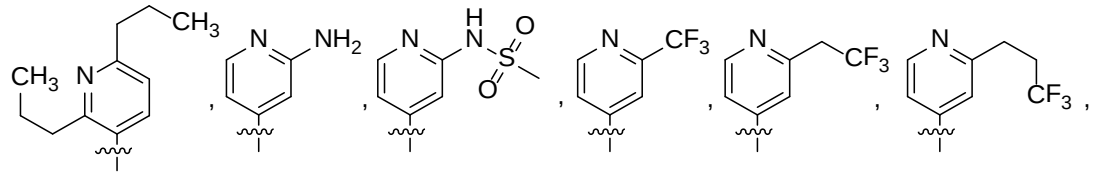
o una sal del mismo farmacéuticamente aceptable, en donde:

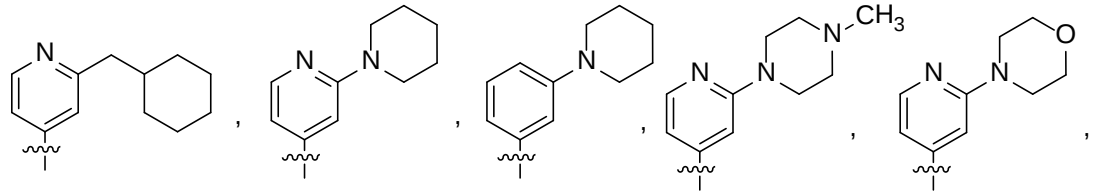
A es una porción seleccionada del grupo que consiste

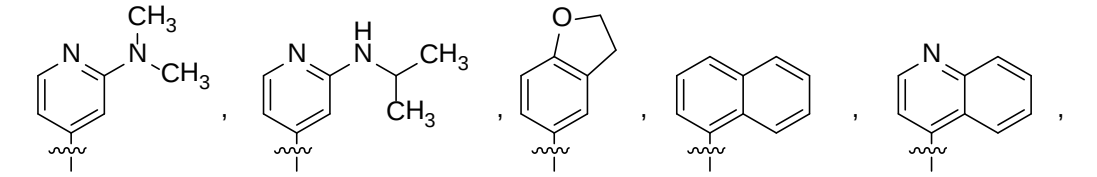
de:

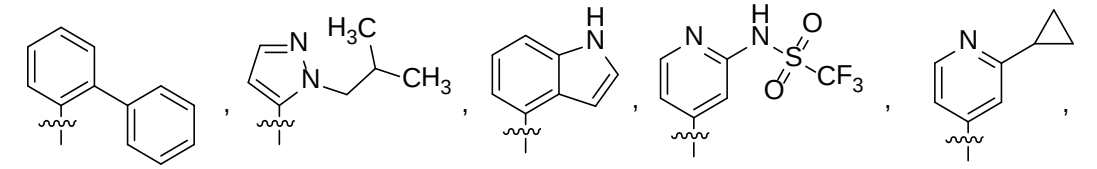


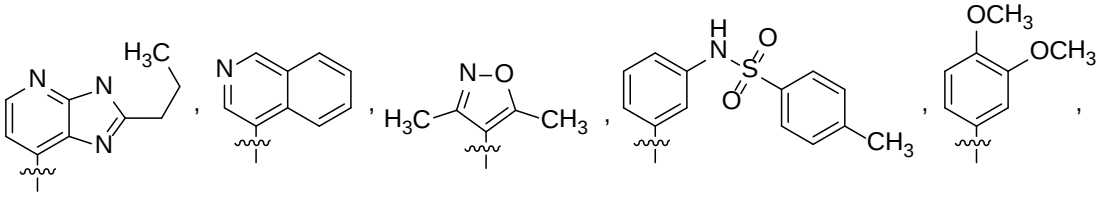


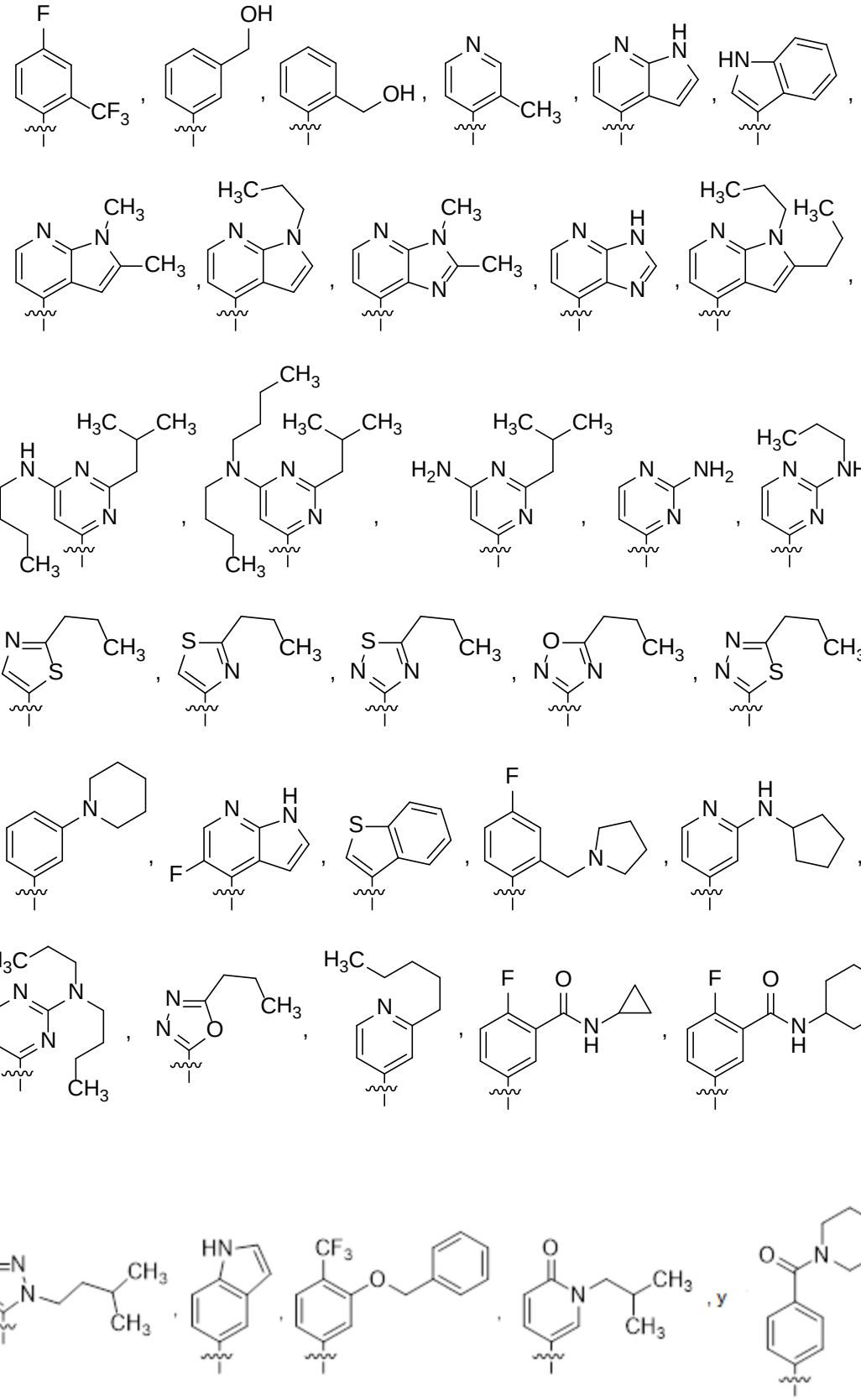








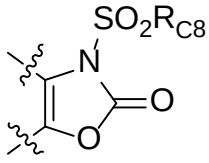




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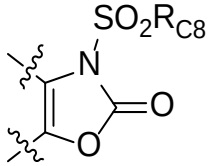
;

Cada **R_{C4}**, **R_{C5}**, y **R_{C6}**, es independientemente hidrógeno, halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, alcoxi lineal o ramificado C_1-C_3, -CO_2H, -CON**R10R11**, o -$NHCONH_2$; o se toman con **R_{C7}** para formar la porción



;

R_{C7} es hidrógeno, alquilo lineal o ramificado C_1-C_6, hidroxialquilo lineal o ramificado C_1-C_6, -(C**R_{9a}R$_{9b}$**)$_m$N**R10R11**, -CO_2-alquilo, -(C**R_{9a}R$_{9b}$**)$_m$O-alquilo, -(C**R_{9a}R$_{9b}$**)$_m$$OPO_3Na_2$, -(C**$R_{9a}R_{9b}$**)$_m$O(C**$R_{9a}R_{9b}$**)$_n$O-alquilo, -(C**$R_{9a}R_{9b}$**)$_m$O(C=O)-alquilo, -(C**$R_{9a}R_{9b}$**)$_m$O(C**$R_{9a}R_{9b}$**)$_n$O(C=O)-alquilo, –(C=O)$CH=CH_2$, -$SO_2$**$R_{C8'}$**; o se toman con uno de **R_{C4}**, **R_{C5}** o **R_{C6}** para formar la porción



;

R_{C8} es un perhalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

$R_{C8'}$ es un alquilo C_1-C_6 lineal o ramificado, un

perhaloalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

Cada $\mathbf{R_{9a}}$ y $\mathbf{R_{9b}}$, en donde está presente, es independientemente hidrógeno o alquilo lineal o ramificado C_1-C_6;

R10 y **R11** son independientemente hidrógeno, $-SO_2\mathbf{R_{C8'}}$, alquilo lineal o ramificado C_1-C_6, alquenilo lineal o ramificado C_2-C_6, cicloalquilo C_3-C_6, o cicloalquenilo C_3-C_6; o son tomados junto con el N al cual están unidos para formar un heterociclo C_3-C_6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, una $1\lambda^6$,2-tiazolidin-1,1-diona, una 1,$2\lambda^6$,3-oxatiazolidin-2,2-diona, o una $1\lambda^6$,2,5-tiadiazolidin-1,1-diona;

X es un heteroátomo seleccionado de S, O; o $N\mathbf{R_B}$ en donde $\mathbf{R_B}$ es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6; y

Cada ***m*** y ***n*** es 1, 2 o 3.

En un aspecto, se describen compuestos de la invención en la Tabla 1, tales como un compuesto seleccionado del grupo que consiste de los compuestos Nos. 1 a 152; o una

sal, solvato, profármaco o N-óxido del mismo farmacéuticamente aceptable.

Se proporciona adicionalmente una composición farmacéutica, que comprende un compuesto de las Fórmulas (Ia), (Ib), (IIa), o (IIb), o cualquiera de las variaciones descritas en la presente, o una sal del mismo, y un portador o excipiente farmacéuticamente aceptable.

Se proporciona adicionalmente un kit, que comprende un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquiera de las variaciones descritas en la presente, o una sal del mismo, e instrucciones para su uso.

Se proporcionan adicionalmente métodos para el tratamiento de uno o más de lo siguiente: trastornos hiperproliferativos, trastornos metabólicos y/o pancreatitis en individuos en necesidad del mismo, tales como humanos, que comprenden administrar a un individuo en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de las Fórmulas (Ia), (Ib), (IIa), o (IIb), o cualquiera de las variaciones descritas en la presente, o una sal del mismo farmacéuticamente aceptable.

Se proporcionan adicionalmente métodos para el tratamiento de cualquier enfermedad o condición para la cual la modulación de SREBP se cree que será o es beneficial, que comprenden administrar a un individuo en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de las

Fórmulas (Ia), (Ib), (IIa), o (IIb), o cualquiera de las variaciones descritas en la presente, o una sal del mismo farmacéuticamente aceptable.

BREVE DESCRIPCIÓN DE LAS FIGURAS

Figura 1. Curvas de manchado Western y respuesta a la dosis, con valores IC_{50}, del compuesto #37 en células HepG2: viabilidad celular y Desdoblamiento de SREBP-2.

Figura 2. Es una gráfica que muestra el efecto del compuesto #37 en un injerto heterólogo LnCap en humano.

Figura 3. Datos IC_{50} del panel de línea celular para el compuesto #37.

Figura 4A. Parámetros de farmacocinética para el compuesto #37 (ratón).

Figura 4B. Parámetros de farmacocinética para el compuesto #37 (perro).

Figura 5. Gráfica que muestra el efecto del compuesto #37 en un injerto heterólogo MDA-MB-453 humano *in vivo*.

FIGS. 6A-B. Gráfica que muestra el efecto del compuesto #37 en un injerto heterólogo de LNCaP humano *in vivo*: **Figura 6A**, muestra el volumen de tumor en tres concentraciones. **Figura 6B**, muestra las veces de cambio del volumen de tumor a varias dosis.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Definiciones

Para uso en la presente, a menos que se indique

claramente de otra forma, el uso de los términos “un”, “uno” y similares se refiere a uno o más.

Como se usa en la presente, se hace referencia a “aproximadamente” un valor o parámetro en la presente que incluye (y describe) modalidades que se dirigen a este valor o parámetro *per se*. Por ejemplo, la descripción que se refiere a “aproximadamente X” incluye la descripción de “X”.

“Alquilo” se refiere a, e incluye, estructuras de hidrocarburo univalentes lineales o ramificadas y combinaciones de las mismas. Grupos alquilo particulares son aquellos que tiene 1 a 6 átomos de carbono (un “alquilo C_1-C_6”). Cuando un residuo alquilo que tiene un número específico de carbonos es nombrado, todos los isómeros geométricos que tiene este número de carbonos están destinados a ser abarcados y descritos; así, por ejemplo, “butilo” se entiende que incluye *n*-butilo, *sec*-butilo, *iso*-butilo, y *terc-butilo*; “propilo” incluye *n*-propilo e isopropilo. Este término es ejemplificado por grupos tales como metilo, *t*-butilo, *n*-heptilo, octilo, y similares.

“Alquenilo” se refiere a un grupo hidrocarburo insaturado que tiene al menos un sitio de insaturación olefínica (*es decir*, que tiene al menos una porción de la fórmula C=C) y preferiblemente que tiene de 2 a 10 átomos de carbono y más preferiblemente 2 a 8 átomos de carbono. Ejemplos de alquenilo incluyen pero no se limitan a etenilo “–CH=CH_2”,

$-CH_2-CH=CH-CH_3$ y $-CH=CH-CH=CH_2$.

"Alquinilo" se refiere a un grupo hidrocarburo insaturado que tiene al menos un sitio de insaturación acetilénica (*es decir*, que tiene al menos una porción de la fórmula C≡C) y preferiblemente que tiene de 2 a 10 átomos de carbono y más preferiblemente 2 a 8 átomos de carbono y similares. Ejemplos de alquinilo incluyen pero no se limitan a etinilo "-C≡CH", $-CH_2-C\equiv C-CH_3$ y -C≡C-C≡CH.

"Cicloalquilo" se refiere a, e incluye, estructuras de hidrocarburo univalentes cíclicas. El cicloalquilo puede consistir de un anillo, tal como ciclohexilo, o anillos múltiples, tales como adamantilo. Un cicloalquilo que comprende más de un anillo puede ser fusionado, espiro o puenteado, o combinaciones de los mismos. Un cicloalquilo preferido es un hidrocarburo cíclico saturado que tiene de 3 a 13 átomos de carbono anulares. Un cicloalquilo más preferido es un hidrocarburo cíclico saturado que tiene de 3 a 6 átomos de carbono anulares (un "cicloalquilo C_3-C_6"). Ejemplos de grupos cicloalquilo incluyen adamantilo, decahidronaftalenilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y similares.

"Cicloalquenilo" se refiere a un grupo hidrocarburo insaturado dentro de un cicloalquilo que tiene al menos un sitio de insaturación olefínica (*es decir*, que tiene al menos una porción de la fórmula C=C). El cicloalquenilo puede

consistir de un anillo, tal como ciclohexilo, o anillos múltiples, tales como norbornenilo. Un cicloalquenilo más preferido es un hidrocarburo cíclico insaturado que tiene de 3 a 8 átomos de carbono anulares (un “cicloalquenilo C_3-C_8”). Ejemplos de grupos cicloalquenilo incluyen ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, y similares.

“Heterociclo”, “heterocíclico”, o “heterociclilo” se refiere a un grupo no aromático saturado o insaturado que tiene un anillo único o anillos condensados múltiples, y que tiene de 1 a 10 átomos de carbono anulares y de 1 a 4 heteroátomos anulares, tales como nitrógeno, azufre u oxígeno, y similares. Un heterociclo que comprende más de un anillo, puede ser fusionado, espiro o puenteado, o cualquier combinación de los mismos. En sistemas de anillo fusionados, uno o más de los anillos pueden ser arilo o heteroarilo. Un heterociclo que tiene más de un anillo en donde al menos un anillo es aromático puede ser conectado a la estructura precursora en cualquiera de una posición de anillo no aromático o en una posición de anillo aromático. En una variación, un heterociclo que tiene más de un anillo en donde al menos un anillo es aromático se conecta a la estructura precursora en una posición de anillo no aromático.

“Arilo” como se usa en la presente se refiere a un grupo carbocíclico aromático insaturado que tiene un anillo único *(por ejemplo,* fenilo) o anillos condensados múltiples

(por ejemplo, naftilo o antrilo) tales anillos condensados mayores pueden no ser aromáticos. El grupo arilo puede ser opcionalmente sustituido independientemente con uno o más sustituyentes descritos en la presente. Grupos arilo particulares son aquellos que tiene de 6 a 14 (es decir, el anillo) átomos de carbono anulares (un "arilo C_6-C_{14}"). Un grupo arilo que tiene más de un anillo, en donde al menos un anillo no es aromático puede ser conectado a la estructura precursora en cualquiera de una posición de anillo aromático o en una posición de anillo no aromático. En una variación, un grupo arilo que tiene más de un anillo, en donde al menos un anillo no es aromático se conecta a la estructura precursora en una posición de anillo aromático.

"Heteroarilo" como se usa en la presente se refiere a un grupo cíclico aromático insaturado que tiene de 1 a 14 átomos de carbono anulares (es decir, anillo) y al menos un heteroátomo anular, que incluye, pero no se limita a heteroátomos tales como nitrógeno, oxígeno y azufre. Un grupo heteroarilo puede tener un anillo único (por ejemplo, piridilo, furilo) o anillos condensados múltiples (por ejemplo, indolizinilo, benzotienilo) tales anillos condensados mayores pueden no ser aromáticos. El grupo heteroarilo puede ser opcionalmente sustituido independientemente con uno o más sustituyentes descritos en la presente. Grupos heteroarilo particulares son de 5- a 14-elementos del anillo que tienen 1

a 12 (es decir, anillo) átomos de carbono anulares y 1 a 6 heteroátomos anular (es decir, anillo) seleccionados independientemente de nitrógeno, oxígeno y azufre; 5- a 10-elementos del anillo que tienen 1 a 8 átomos de carbono anulares y 1 a 4 heteroátomos anulares seleccionados independientemente de nitrógeno, oxígeno y azufre; y anillo de 5-,6- o 7-elementos que tiene 1 a 5 átomos de carbono anulares y 1 a 4 heteroátomos anulares seleccionados independientemente de nitrógeno, oxígeno y azufre. En una variación, heteroarilo incluye anillo de 5-, 6- o 7-elementos monocíclicos aromáticos que tiene de 1 a 6 átomos de carbono anulares y 1 a 4 heteroátomos anulares seleccionados independientemente de nitrógeno, oxígeno y azufre. En otra variación, heteroarilo incluye anillos aromáticos policíclicos que tienen de 1 a 12 átomos de carbono anulares y 1 a 6 heteroátomos anulares seleccionados independientemente de nitrógeno, oxígeno y azufre. Un grupo heteroarilo que tiene más de un anillo en donde al menos un anillo no es aromático puede ser conectado a la estructura precursora en cualquiera de una posición de anillo aromático o en una posición de anillo no aromático. En una variación, un grupo heteroarilo que tiene más de un anillo en donde al menos un anillo no es aromático se conecta a la estructura precursora en una posición de anillo aromático.

“Alcoxi” se refiere al grupo alquilo-O-, el cual incluye, por medio de ejemplo, metoxi, etoxi, n-propoxi, iso-

propoxi, n-butoxi, terc-butoxi, sec-butoxi, n-pentoxi, n-hexoxi, 1,2-dimetilbutoxi, y similares.

"Hidroxialquilo" se refiere al grupo alquilo-OH, el cual incluye, por medio de ejemplo, hidroximetilo, 1-hidroxietilo, 2-hidroxietilo, 1-hidroxiprop-1-ilo, 2-hidroxiprop-2-ilo, 3-hidroxipropilo, 4-hidroxibutilo, 5-hidroxipentilo, 6-hidroxihexilo, y similares.

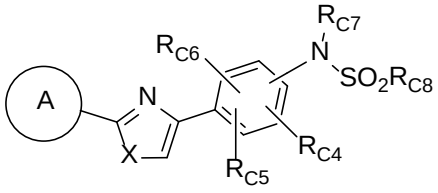
"Halógeno" se refiere a elementos de las series del Grupo 17 que tienen número atómico 9 a 85. Grupos halo preferidos incluyen los radicales de flúor, cloro, bromo y yodo. En donde un residuo es sustituido con más de un halógeno, puede ser referido usando un prefijo que corresponde al número de porciones de halógeno unidos, por ejemplo, dihaloarilo, dihaloalquilo, trihaloarilo etc. se refieren a arilo y alquilo sustituido con dos ("di") o tres ("tri") grupos halo, los cuales pueden ser, pero no necesariamente son el mismo halógeno; así 4-cloro-3-fluorofenilo está dentro del alcance de dihaloarilo. Un grupo alquilo en el cual cada H es reemplazado con un grupo halógeno es referido como un "perhaloalquilo." Un grupo alquenilo en el cual cada H es reemplazado con un grupo halógeno es referido como un "perhaloalquenilo." Un grupo alquinilo en el cual cada H es reemplazado con un grupo halógeno que es referido como un "perhaloalquinilo." Un grupo perhaloalquilo preferido es trifluoroalquilo ($-CF_3$). De manera similar, "perhaloalcoxi" se

refiere a un grupo alcoxi en el cual halógeno toma el lugar de cada H en el hidrocarburo que forma la porción alquilo del grupo alcoxi. Un ejemplo de un grupo perhaloalcoxi es trifluorometoxi (–OCF_3).

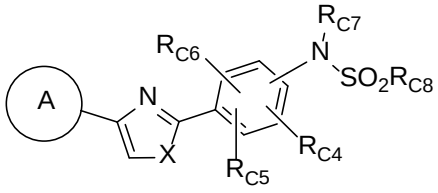
Cualquiera y todos estereoisómeros, que incluyen isómeros geométricos (isómeros *cis/trans* o *E/Z*), tautómeros, sales, N-óxidos, y solvatos de los compuestos descritos en la presente se pueden usar en los métodos descritos. Esta descripción también proporciona métodos para elaborar tales compuestos.

Compuestos

En algunas modalidades, los compuestos descritos en la presente caen dentro de las fórmulas (Ia) o (Ib):



(Ia)



(Ib)

o una sal del mismo farmacéuticamente aceptable, en donde:

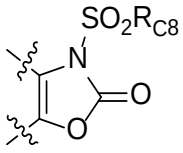
A es cualquiera de:

i. un arilo o heteroarilo, cada uno tiene solamente un anillo, sustituido con 1, 2, o 3 sustituyentes seleccionados del grupo que consiste de halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_6, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, hidroxialquilo lineal o ramificado C_1-C_6, alcoxi lineal o ramificado C_1-C_3, cicloalquilometilo C_3-C_6, -$(CH_2)_mCF_3$, =O, -

CH_2OCH_3, -OBn, $-CO_2H$, $-CO_2$-alquilo, -N**R10R11**, y -CON**R10R11**; o

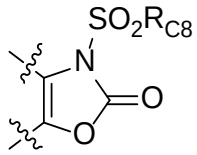
ii. un arilo o heteroarilo, cada uno tiene más de un anillo, opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados del grupo que consiste de halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_6, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, hidroxialquilo lineal o ramificado C_1-C_6, alcoxi lineal o ramificado C_1-C_3, cicloalquilometilo C_3-C_6, -$(CH_2)_mCF_3$, =O, $-CH_2OCH_3$, $-CH_2OH$, -OBn, $-CO_2H$, $-CO_2$-alquilo, -N**R10R11**, y -CON**R10R11**;

Cada $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, y $\mathbf{R_{C6}}$, es independientemente hidrógeno, halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, alcoxi lineal o ramificado C_1-C_3, $-CO_2H$, -CON**R10R11**, o $-NHCONH_2$; o se toman con $\mathbf{R_{C7}}$ para formar la porción



;

$\mathbf{R_{C7}}$ es hidrógeno, alquilo lineal o ramificado C_1-C_6, hidroxialquilo lineal o ramificado C_1-C_6, -$(C\mathbf{R_{9a}R_{9b}})_mN$**R10R11**, -$CO_2$-alquilo, -$(C\mathbf{R_{9a}R_{9b}})_m$O-alquilo, -$(C\mathbf{R_{9a}R_{9b}})_mOPO_3Na_2$, -$(C\mathbf{R_{9a}R_{9b}})_mO(C\mathbf{R_{9a}R_{9b}})_n$O-alquilo, -$(C\mathbf{R_{9a}R_{9b}})_m$O(C=O)-alquilo, -$(C\mathbf{R_{9a}R_{9b}})_mO(C\mathbf{R_{9a}R_{9b}})_n$O(C=O)-alquilo, –(C=O)$CH=CH_2$, $-SO_2\mathbf{R_{C8'}}$; o se toman con uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ o $\mathbf{R_{C6}}$ para formar la porción



;

R_{C8} es un perhalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

$R_{C8'}$ es un alquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

Cada **R_{9a}** y **R_{9b}**, en donde está presente, es independientemente hidrógeno o alquilo lineal o ramificado C_1-C_6;

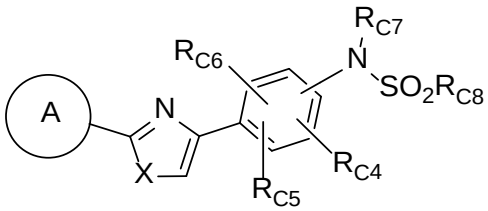
R10 y **R11** son independientemente hidrógeno, -SO_2**$R_{C8'}$**, alquilo lineal o ramificado C_1-C_6, alquenilo lineal o ramificado C_2-C_6, cicloalquilo C_3-C_6, o cicloalquenilo C_3-C_6; o son tomados junto con el N al cual están unidos para formar un heterociclo

C_3-C_6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, una $1\lambda^6$,2-tiazolidin-1,1-diona, una 1,$2\lambda^6$,3-oxatiazolidin-2,2-diona, o una $1\lambda^6$,2,5-tiadiazolidin-1,1-diona;

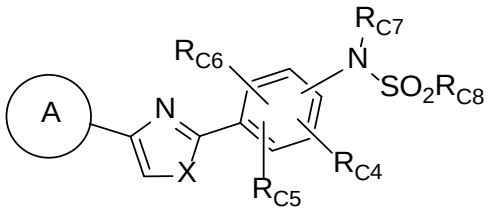
X es un heteroátomo seleccionado de S, O; o N$\mathbf{R_B}$ en donde $\mathbf{R_B}$ es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6; y

Cada ***m*** y ***n*** es 1, 2 o 3.

En algunas modalidades, compuestos descritos en la presente caen dentro de las fórmulas (IIa) o (IIb):



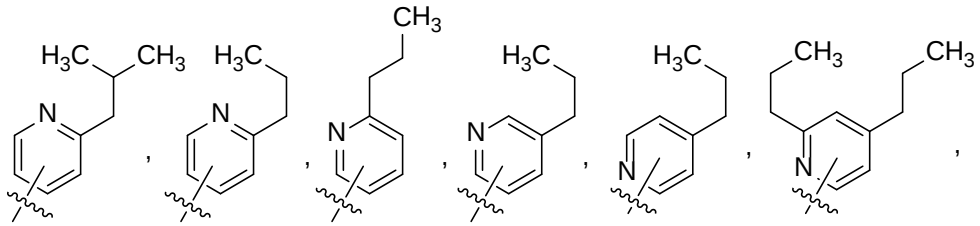
(IIa)

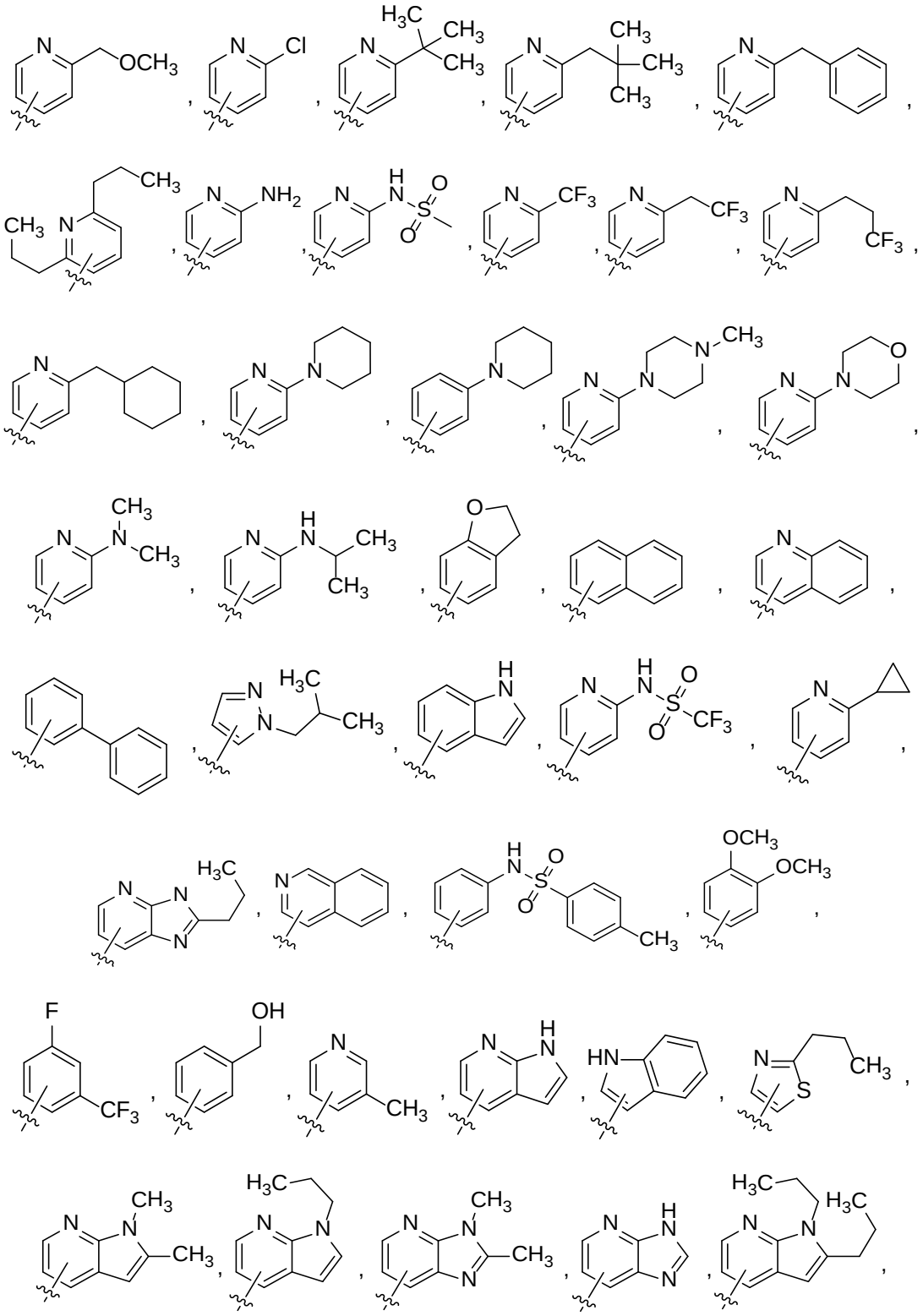


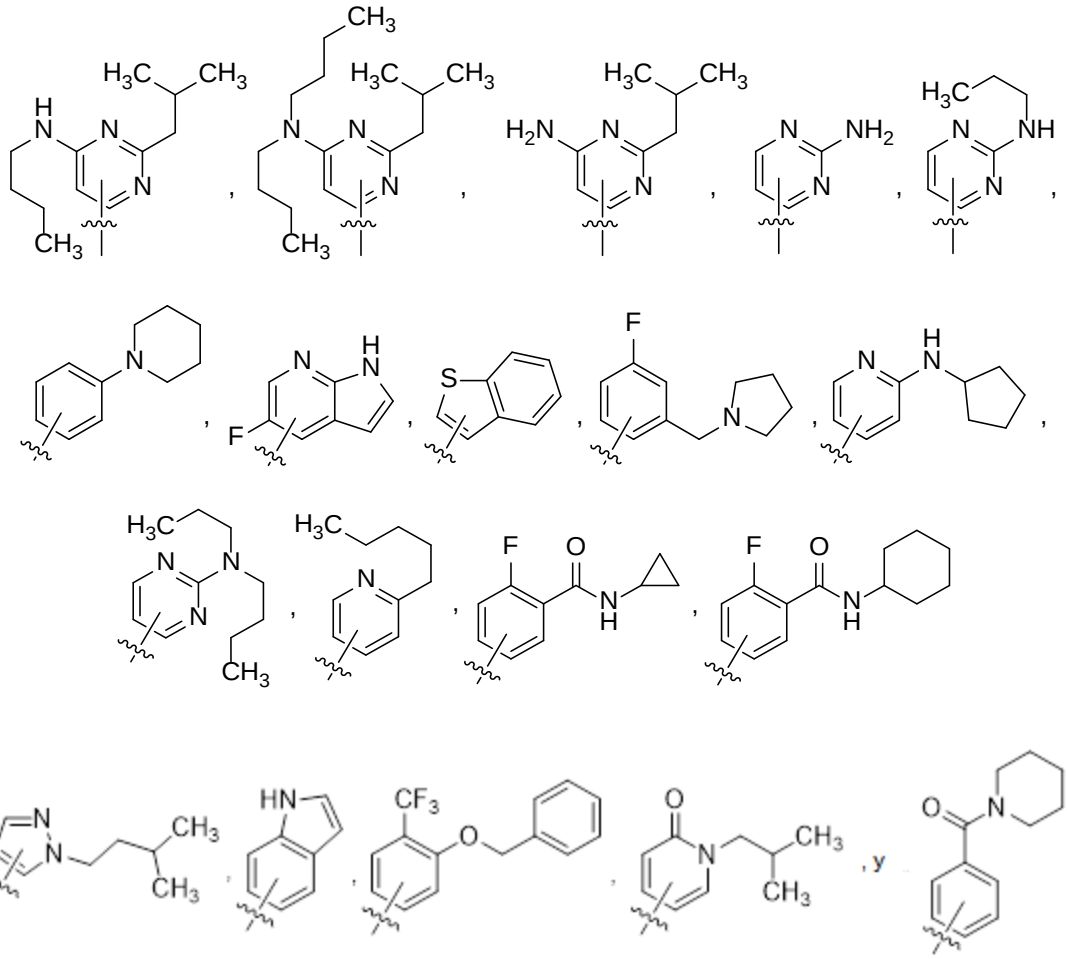
(IIb)

o una sal del mismo farmacéuticamente aceptable, en donde:

A es una porción seleccionada del grupo que consiste de:

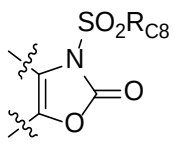






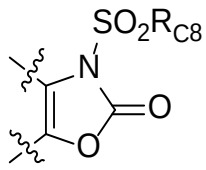
en donde el anillo que contiene X está unido al anillo A en cualquier posición disponible en el anillo A;

Cada **R_{C4}**, **R_{C5}**, y **R_{C6}**, es independientemente hidrógeno, halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, alcoxi lineal o ramificado C_1-C_3, -CO_2H, -CON**R10R11**, o -$NHCONH_2$; o se toman con **R_{C7}** para formar la porción



;

$\mathbf{R_{C7}}$ es hidrógeno, alquilo lineal o ramificado C_1-C_6, hidroxialquilo lineal o ramificado C_1-C_6, -($C\mathbf{R_{9a}R_{9b}}$)$_m$N**R10R11**, -CO_2-alquilo, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O-alquilo, -($C\mathbf{R_{9a}R_{9b}}$)$_m$$OPO_3Na_2$, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O($C\mathbf{R_{9a}R_{9b}}$)$_n$O-alquilo, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O(C=O)-alquilo, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O($C\mathbf{R_{9a}R_{9b}}$)$_n$O(C=O)-alquilo, –(C=O)$CH=CH_2$, -$SO_2\mathbf{R_{C8'}}$; o se toman con uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ o $\mathbf{R_{C6}}$ para formar la porción



;

$\mathbf{R_{C8}}$ es un perhalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

$\mathbf{R_{C8'}}$ es un alquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

Cada $\mathbf{R_{9a}}$ **y** $\mathbf{R_{9b}}$, en donde está presente, es

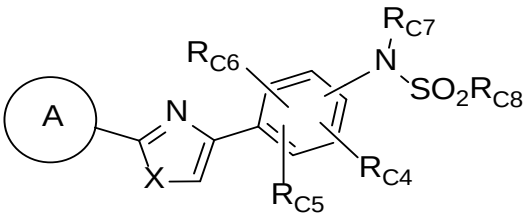
independientemente hidrógeno o alquilo lineal o ramificado C_1-C_6;

R10 y **R11** son independientemente hidrógeno, -SO_2**$R_{C8'}$**, alquilo lineal o ramificado C_1-C_6, alquenilo lineal o ramificado C_2-C_6, cicloalquilo C_3-C_6, o cicloalquenilo C_3-C_6; o son tomados junto con el N al cual están unidos para formar un heterociclo C_3-C_6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, una $1\lambda^6$,2-tiazolidin-1,1-diona, una $1,2\lambda^6$,3-oxatiazolidin-2,2-diona, o una $1\lambda^6$,2,5-tiadiazolidin-1,1-diona;

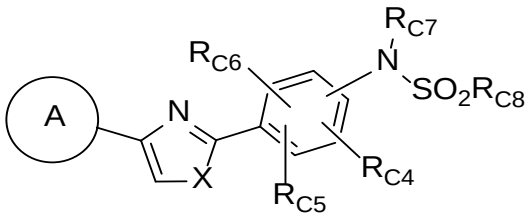
X es un heteroátomo seleccionado de S, O; o N**R_B** en donde **R_B** es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6; y

Cada ***m*** y ***n*** es 1, 2 o 3.

En algunas modalidades, compuestos descritos en la presente caen dentro de las fórmulas (IIa) o (IIb):



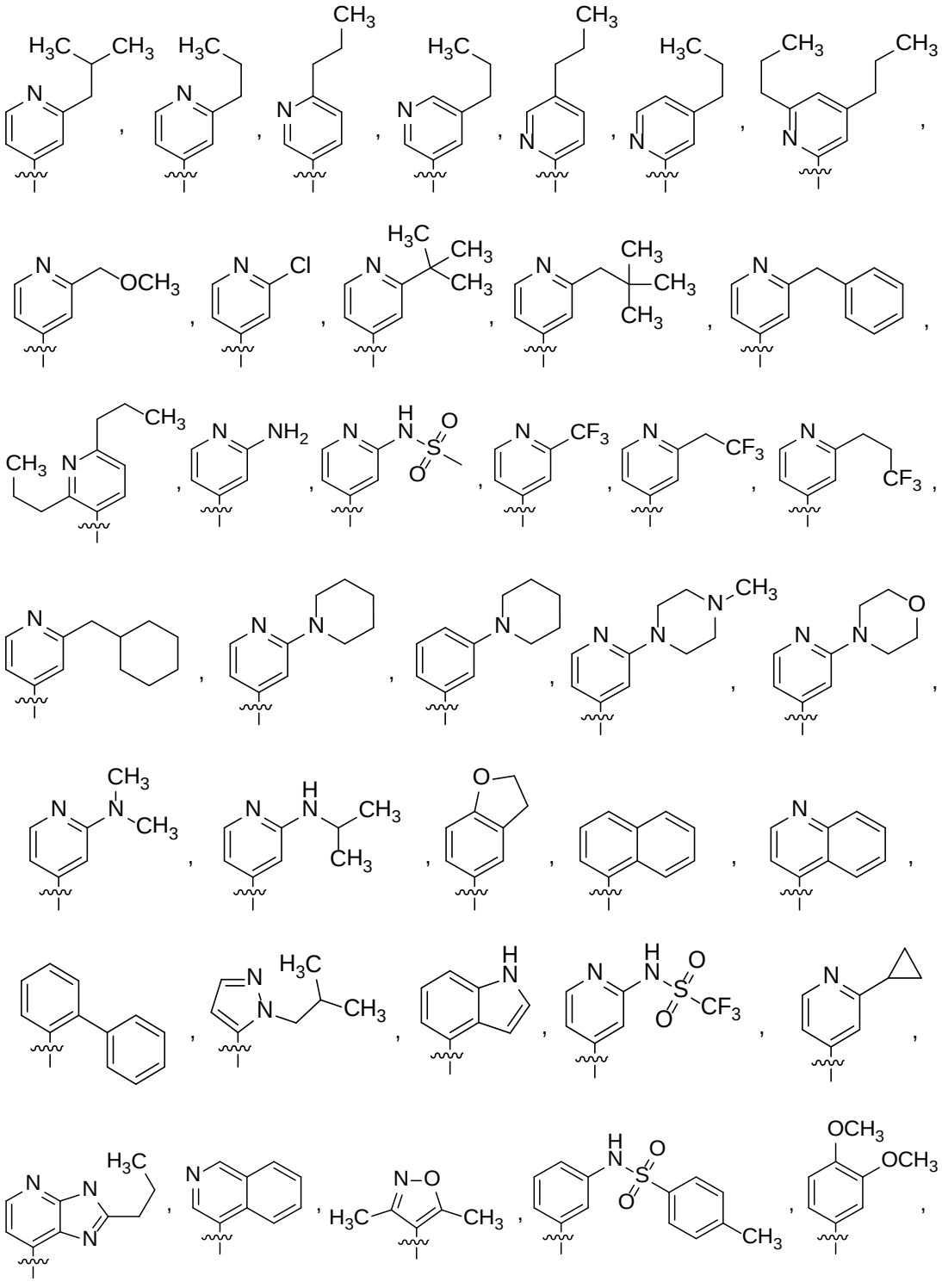
(IIa)

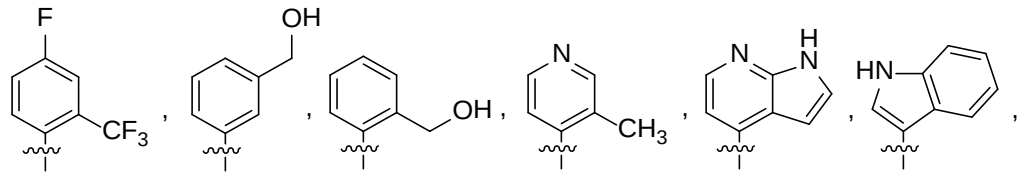


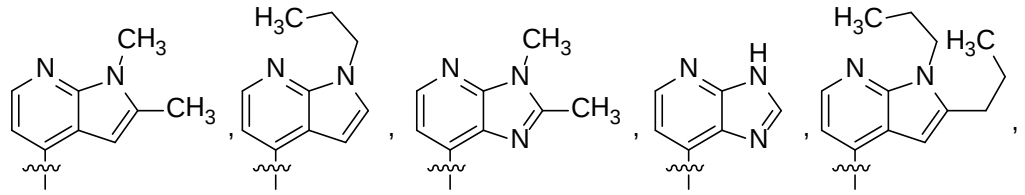
(IIb)

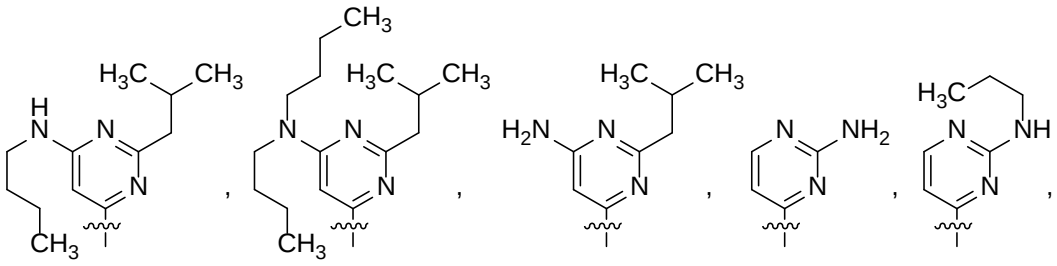
o una sal del mismo farmacéuticamente aceptable, en donde:

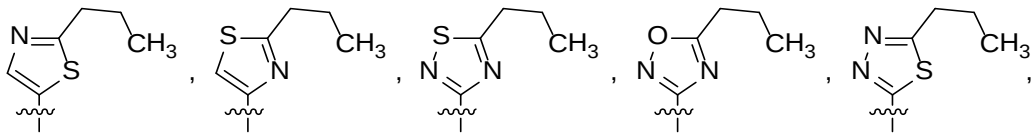
A es una porción seleccionada del grupo que consiste de:

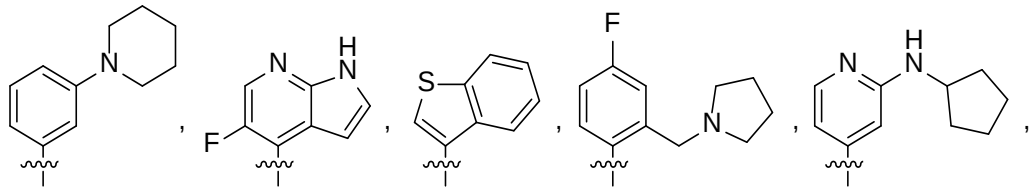


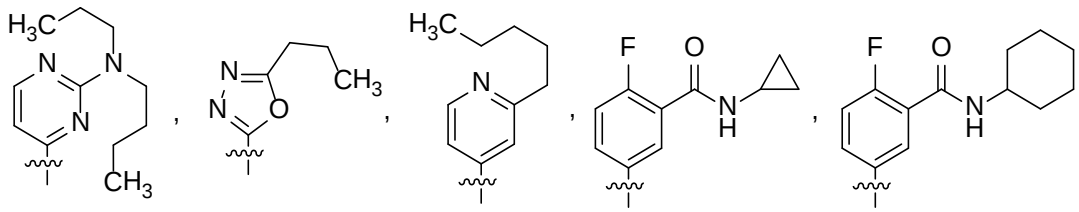


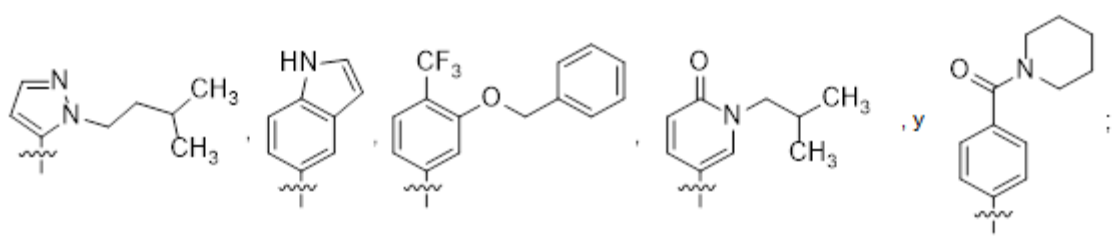






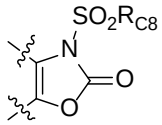






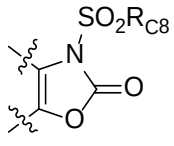
Cada R_{C4}, R_{C5}, y R_{C6}, es independientemente hidrógeno,

halógeno, CN, CF_3, OH, alquilo lineal o ramificado C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_6, cicloalquenilo C_3-C_6, alcoxi lineal o ramificado C_1-C_3, -CO_2H, -CON**R10R11**, o -$NHCONH_2$; o se toman con $\mathbf{R_{C7}}$ para formar la porción



;

$\mathbf{R_{C7}}$ es hidrógeno, alquilo lineal o ramificado C_1-C_6, hidroxialquilo lineal o ramificado C_1-C_6, -(C$\mathbf{R_{9a}R_{9b}}$)$_m$NR10R11, -CO_2-alquilo, -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O-alquilo, -(C$\mathbf{R_{9a}R_{9b}}$)$_m$$OPO_3Na_2$, -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O(C$\mathbf{R_{9a}R_{9b}}$)$_n$O-alquilo, -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O(C=O)-alquilo, -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O(C$\mathbf{R_{9a}R_{9b}}$)$_n$O(C=O)-alquilo, –(C=O)CH=CH_2, -$SO_2\mathbf{R_{C8'}}$; o se toman con uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ o $\mathbf{R_{C6}}$ para formar la porción



;

$\mathbf{R_{C8}}$ es un perhalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

$\mathbf{R_{C8'}}$ es un alquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o

ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno;

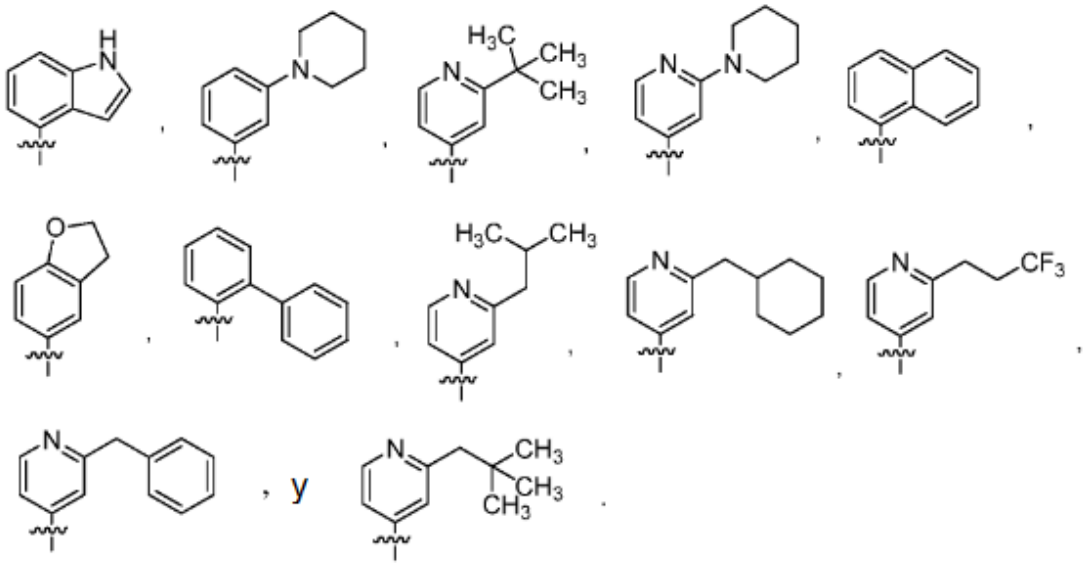
Cada $\mathbf{R_{9a}}$ **y** $\mathbf{R_{9b}}$, en donde está presente, es independientemente hidrógeno o alquilo lineal o ramificado C1-C6;

R10 y **R11** son independientemente hidrógeno, $-SO_2\mathbf{R_{C8'}}$, alquilo lineal o ramificado C_1-C_6, alquenilo lineal o ramificado C_2-C_6, cicloalquilo C_3-C_6, o cicloalquenilo C_3-C_6; o son tomados junto con el N al cual están unidos para formar un heterociclo C_3-C_6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, una $1\lambda^6$,2-tiazolidin-1,1-diona, una 1,$2\lambda^6$,3-oxatiazolidin-2,2-diona, o una $1\lambda^6$,2,5-tiadiazolidin-1,1-diona;

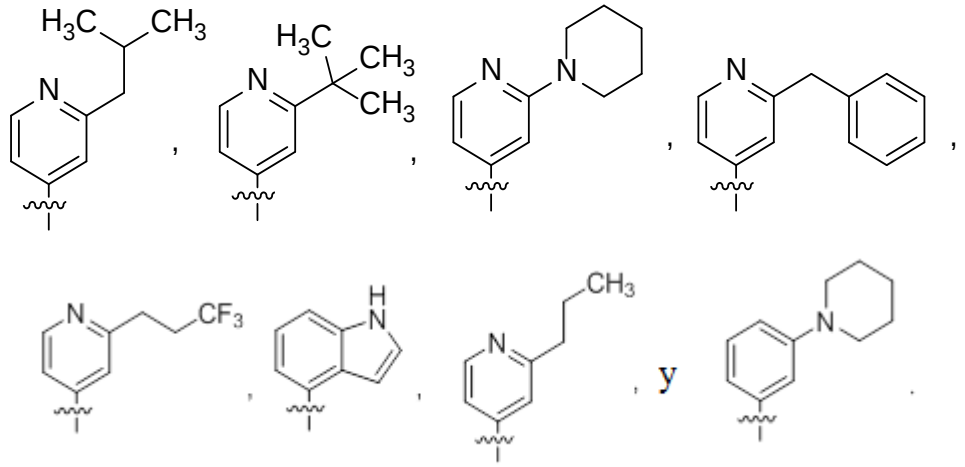
X es un heteroátomo seleccionado de S, O; o $N\mathbf{R_B}$ en donde $\mathbf{R_B}$ es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6; y

Cada ***m*** y ***n*** es 1, 2 o 3.

En algunas variaciones de Fórmulas (IIa) o (IIb), A es una porción seleccionada del grupo que consiste de:



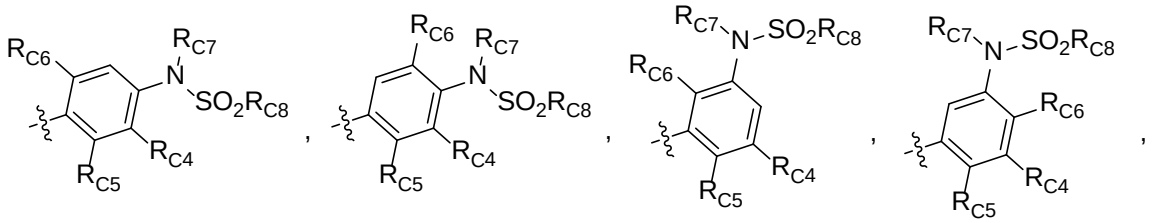
En algunas variaciones de Fórmulas (IIa) o (IIb), A es una porción seleccionada del grupo que consiste de:

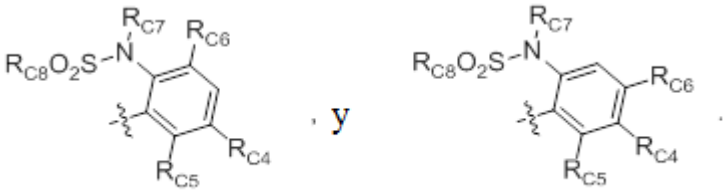


En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), X es S. En algunas variaciones, X es O. En algunas variaciones, X es NR_B, en donde R_B es hidrógeno. En algunas variaciones, X es NR_B, en donde R_B es un alquilo C_1-C_6 lineal o ramificado. En estas variaciones, R_B es un alquilo lineal C_1-C_6 seleccionado de metilo, etilo, n-propilo, n-butilo, n-

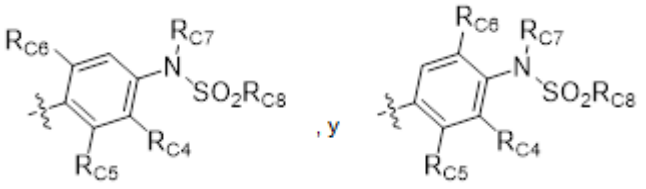
pentilo o n-hexilo. En variaciones particulares, $\mathbf{R_B}$ es metilo. En algunas variaciones, $\mathbf{R_B}$ es un alquilo ramificado C_1-C_6 seleccionado de iso-propilo, iso-pentilo, y terc-butilo.

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), el anillo fenilo que contiene los grupos $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, y $\mathbf{-NR_{C7}SO_2R_{C8}}$, es una porción seleccionada de:



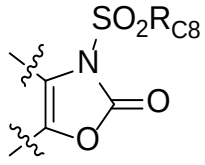


En variaciones particulares de Fórmulas (Ia), (Ib), (IIa) o (IIb), el anillo fenilo que contiene los grupos $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, y $\mathbf{-NR_{C7}SO_2R_{C8}}$, es una porción seleccionada de:



En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), uno o más de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$, es hidrógeno. En algunas variaciones, uno o más de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$, es halógeno. En algunas variaciones, uno o más de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$, es CN. En algunas

variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es CF_3. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es OH. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es alquilo lineal o ramificado C_1-C_3. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es alquenilo C_2-C_3. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es alquinilo C_2-C_3. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es cicloalquilo C_3-C_6. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es cicloalquenilo C_3-C_6. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es alcoxi lineal o ramificado C_1-C_3. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es $-CON(CH_3)_2$. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es $-CO_2H$. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es $-CONH_2$. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es $-NHCONH_2$. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, es–$CONHCH_3$. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6}, se toman con R_{C7} para formar la porción

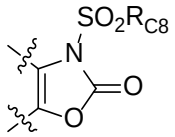


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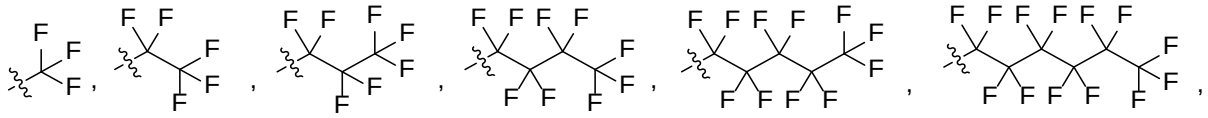
En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), uno de R_{C4}, R_{C5} y R_{C6} es hidrógeno. En algunas variaciones, dos de R_{C4}, R_{C5} y R_{C6} son hidrógeno. En algunas variaciones, cada R_{C4}, R_{C5} y R_{C6} es hidrógeno. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6} es metoxi. En algunas variaciones, uno o más de R_{C4}, R_{C5} y R_{C6} es OH.

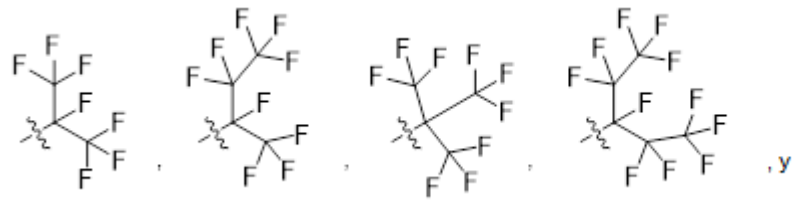
En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es halógeno. En algunas variaciones, dos de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ son halógeno. En algunas variaciones cada $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es halógeno. En algunas variaciones, uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es hidrógeno, y los restantes dos de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ son halógeno. En algunas variaciones, dos de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ son hidrógeno, y los restantes uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es halógeno. En algunas variaciones, $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ are cada halógeno. En algunas modalidades, uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es flúor, cloro o bromo. En algunas modalidades, dos de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ son flúor, cloro o bromo. En algunas modalidades, uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es cloro. En algunas modalidades, uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es cloro y uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ y $\mathbf{R_{C6}}$ es bromo. En algunas modalidades, $\mathbf{R_{C4}}$ es cloro. En algunas modalidades, $\mathbf{R_{C5}}$ es cloro. En algunas modalidades, $\mathbf{R_{C4}}$ es bromo. En algunas modalidades, $\mathbf{R_{C5}}$ es bromo.

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), $\mathbf{R_{C7}}$ es hidrógeno. En algunas variaciones, $\mathbf{R_{C7}}$ es alquilo lineal o ramificado C_1-C_6. En algunas variaciones, $\mathbf{R_{C7}}$ es hidroxialquilo lineal o ramificado C_1-C_6. En algunas variaciones, $\mathbf{R_{C7}}$ es -(C$\mathbf{R_{9a}R_{9b}}$)$_m$N**R10R11**. En algunas variaciones, $\mathbf{R_{C7}}$ es -CO_2-alquilo. En algunas variaciones, $\mathbf{R_{C7}}$ es -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O-alquilo. En algunas variaciones, $\mathbf{R_{C7}}$ es -(C$\mathbf{R_{9a}R_{9b}}$)$_m$OPO_3Na_2. En algunas variaciones, $\mathbf{R_{C7}}$ es -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O(C$\mathbf{R_{9a}R_{9b}}$)$_n$O-alquilo. En algunas variaciones, $\mathbf{R_{C7}}$ es -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O(C=O)-alquilo. En algunas

variaciones, $\mathbf{R_{C7}}$ es -(C$\mathbf{R_{9a}R_{9b}}$)$_m$O(C$\mathbf{R_{9a}R_{9b}}$)$_n$O(C=O)-alquilo. En algunas variaciones, $\mathbf{R_{C7}}$ es –(C=O)CH=CH$_2$. En algunas variaciones, $\mathbf{R_{C7}}$ es -SO$_2$$\mathbf{R_{C8'}}$. En algunas variaciones, $\mathbf{R_{C7}}$ se toman con uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ o $\mathbf{R_{C6}}$ para formar la porción  .

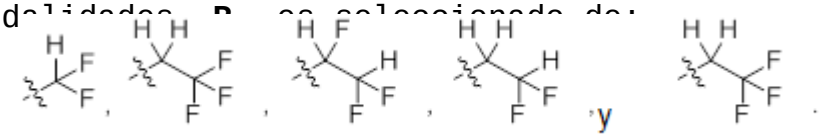
En todas las modalidades, $\mathbf{R_{C8}}$ es un perhalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno. En algunas modalidades, $\mathbf{R_{C8}}$ es un perhalquilo C_1-C_6 lineal o ramificado. En algunas modalidades, el perhalquilo C_1-C_6 es un perfluoroalquilo C_1-C_6. En algunas modalidades, el perfluoroalquilo C_1-C_6 es seleccionado de





En modalidades preferidas, el perfluoroalquilo C_1-C_6

es $-CF_3$. En algunas modalidades, $\mathbf{R_{C8}}$ es un alquilo C_1-C_6 lineal o ramificado que tiene al menos dos átomos de halógenos. En algunas modalidades, $\mathbf{R_{C8}}$ es seleccionado de:

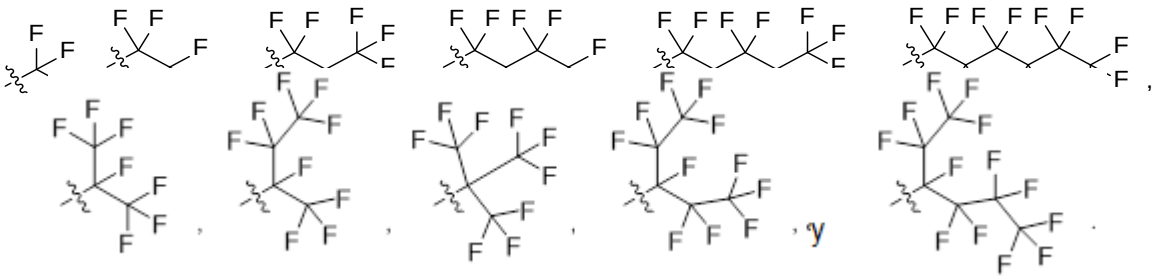


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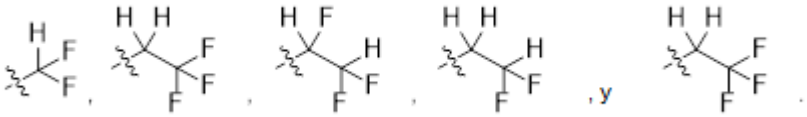
En algunas modalidades, $\mathbf{R_{C8}}$ es un perhaloalquilo C_2-C_6 lineal o ramificado. En algunas modalidades, $\mathbf{R_{C8}}$ es un perhaloalquinilo C_2-C_6 lineal o ramificado. En algunas modalidades, $\mathbf{R_{C8}}$ es un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno. En algunas modalidades, $\mathbf{R_{C8}}$ es un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno. En algunas modalidades, $\mathbf{R_{C8}}$ es o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno.

En algunas modalidades, $\mathbf{R_{C8'}}$ es un alquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_1-C_6 lineal o ramificado, un perhaloalquilo C_2-C_6 lineal o ramificado, un perhaloalquinilo C_2-C_6 lineal o ramificado, un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno. En algunas modalidades, $\mathbf{R_{C8'}}$ es un perhalquilo C_1-C_6 lineal o ramificado. En algunas modalidades, el perhalquilo C_1-C_6 es un perfluoroalquilo C_1-C_6. En algunas

modalidades, el perfluoroalquilo C_1-C_6 es seleccionado de



En modalidades preferidas, el perfluoroalquilo C_1-C_6 es $-CF_3$. En algunas modalidades, $\mathbf{R_{C8'}}$ es un alquilo C_1-C_6 lineal o ramificado que tiene al menos dos átomos de halógenos. En algunas modalidades, $\mathbf{R_{C8'}}$ es seleccionado de:



En algunas modalidades, $\mathbf{R_{C8'}}$ es un perhaloalquilo C_2-C_6 lineal o ramificado. En algunas modalidades, $\mathbf{R_{C8'}}$ es un perhaloalquinilo C_2-C_6 lineal o ramificado. En algunas modalidades, $\mathbf{R_{C8'}}$ es un alquilo C_1-C_6 lineal o ramificado que tiene al menos un átomo de halógeno. En algunas modalidades, $\mathbf{R_{C8'}}$ es un alquenilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno. En algunas modalidades, $\mathbf{R_{C8'}}$ es o un alquinilo C_2-C_6 lineal o ramificado que tiene al menos un átomo de halógeno.

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), tanto $\mathbf{R_{9a}}$ como $\mathbf{R_{9b}}$ son hidrógeno. En algunas modalidades, $\mathbf{R_{9a}}$ es hidrógeno, y $\mathbf{R_{9b}}$ es alquilo lineal o

ramificado C_1-C_6. En algunas modalidades, tanto **R_{9a}** como **R_{9b}** son alquilo lineal o ramificado C_1-C_6. En algunas modalidades, **R_{9a}** es hidrógeno, y **R_{9b}** es metilo.

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), uno o ambos de **R10** y **R11** son hidrógeno. En algunas variaciones, uno o ambos de **R10** y **R11** son $-SO_2$**$R_{C8'}$**. En algunas variaciones, uno o ambos de **R10** y **R11** son alquilo lineal o ramificado C_1-C_6. En algunas variaciones, uno o ambos de **R10** y **R11** are Alquenilo lineal o ramificado C_2-C_6. En algunas variaciones, uno o ambos de **R10** y **R11** son cicloalquilo C_3-C_6. En algunas variaciones, uno o ambos de **R10** y **R11** son cicloalquenilo C_3-C_6.

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), **R10** y **R11** son tomados junto con el N al cual están unidos para formar un heterociclo C_3-C_6. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar a pirrolidin-2-ona o pirrolidin-3-ona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar a piperidin-2-ona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar a piperidin-3-ona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar a piperidin-4-ona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar una oxazolidinona. En algunas variaciones, **R10** y **R11** son tomados

junto con el N al cual están unidos para formar una oxazinanona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar una imidazolidinona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar a tetrahidropirimidin-2(1H)-ona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar una $1\lambda^6$,2-tiazolidin-1,1-diona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar una 1,$2\lambda^6$,3-oxatiazolidin-2,2-diona. En algunas variaciones, **R10** y **R11** son tomados junto con el N al cual están unidos para formar una $1\lambda^6$,2,5-tiadiazolidin-1,1-diona

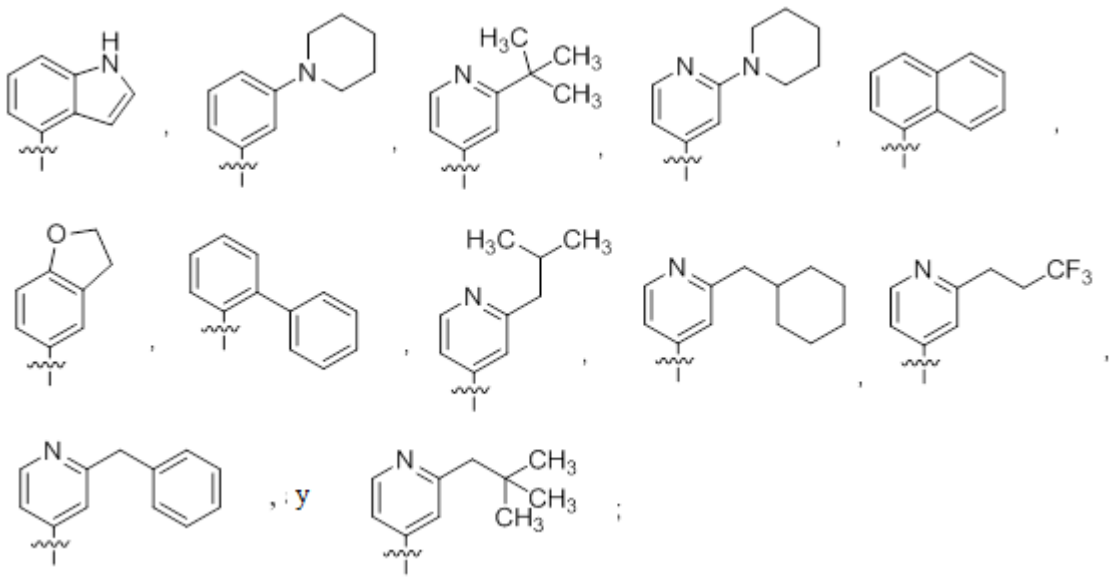
En algunas variaciones, el compuesto es de fórmula (Ia) o (IIa), en donde **X** es un heteroátomo seleccionado de S, O; o N$\mathbf{R_B}$ en donde $\mathbf{R_B}$ es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6. En algunas variaciones, X es S. En algunas variaciones, X es O. En algunas variaciones, X es N$\mathbf{R_B}$ en donde $\mathbf{R_B}$ es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6. En algunas variaciones, X es N$\mathbf{R_B}$ en donde $\mathbf{R_B}$ es un alquilo lineal o ramificado C_1-C_6. En algunas variaciones, X es N$\mathbf{R_B}$ en donde $\mathbf{R_B}$ es cicloalquilo C_3-C_6.

En algunas variaciones, el compuesto es de fórmula (Ib) o (IIb), en donde **X** es un heteroátomo seleccionado de S, O; o N$\mathbf{R_B}$ en donde $\mathbf{R_B}$ es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6. En algunas variaciones, X es S.

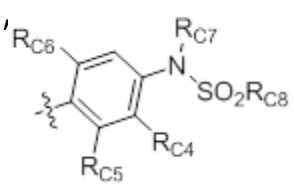
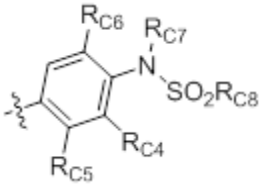
En algunas variaciones, X es O. En algunas variaciones, X es NR_B en donde R_B es hidrógeno, un alquilo lineal o ramificado C_1-C_6, o un cicloalquilo C_3-C_6. En algunas variaciones, X es NR_B en donde R_B es un alquilo lineal o ramificado C_1-C_6. En algunas variaciones, X es NR_B en donde R_B es cicloalquilo C_3-C_6.

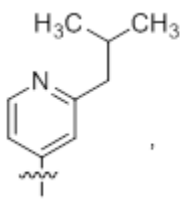
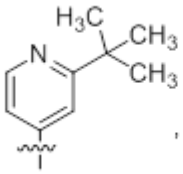
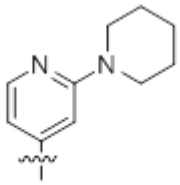
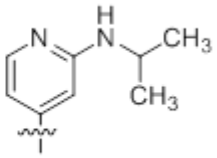
En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), tanto ***m*** como ***n*** son 1. En algunas variaciones, ***m*** es 1 y ***n*** es 2. En algunas variaciones, ***m*** es 1 y ***n*** es 3. En algunas variaciones, ***m*** es 2 y ***n*** es 1. En algunas variaciones, tanto ***m*** como ***n*** son 2. En algunas variaciones, ***m*** es 2 y ***n*** es 3. En algunas variaciones, ***m*** es 3 y ***n*** es 1. En algunas variaciones, ***m*** es 3 y ***n*** es 2. En algunas variaciones, tanto ***m*** como ***n*** son 3.

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o

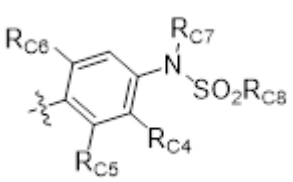
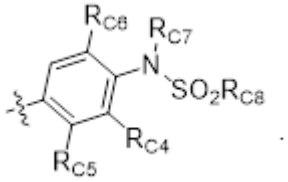


X es S, y el anillo fenilo que contiene los grupos

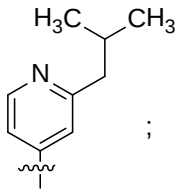
R_{C4}, R_{C5}, R_{C6},  y  :cionada de:

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb)    y  ;

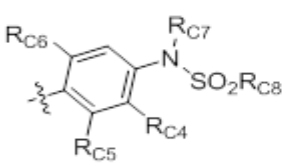
X es S, y el anillo fenilo que contiene los grupos R_{C4}, R_{C5}, R_{C6}, y $-NR_{C7}SO_2R_{C8}$, es una porción seleccionada de

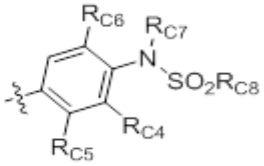
 y 

En algunas variaciones de Fórmulas (Ia), (Ib), (IIa) o (IIb), A es

 ;

X es S; el anillo fenilo que contiene los grupos R_{C4}, R_{C5}, R_{C6}, y $-NR_{C7}SO_2R_{C8}$, es seleccionado de

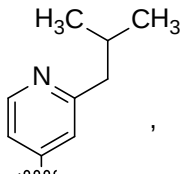


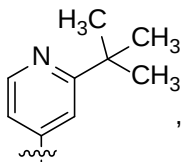
, y


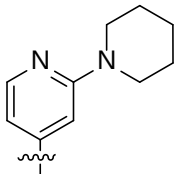
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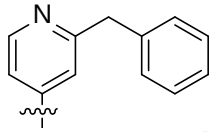
en donde **R_{C4}**, **R_{C5}**, y **R_{C6}** son hidrógeno o halógeno; **R_{C7}** es hidrógeno; y **R_{C8}** es perfluoroalquilo. En algunas variaciones **R_{C8}** es $-CF_3$.

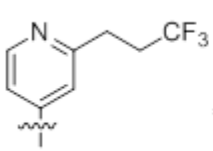
En algunas variaciones, el compuesto es de Fórmula (Ia), en donde A es una porción seleccionada de

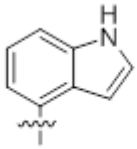


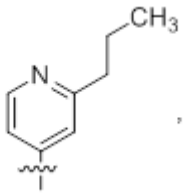
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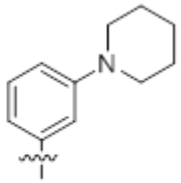
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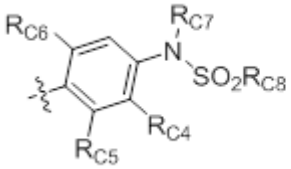
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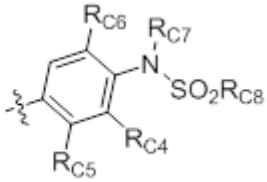
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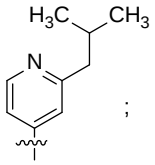
X es S, y el anillo fenilo que contiene los grupos **R_{C4}**, **R_{C5}**, **R_{C6}**, y **$-NR_{C7}SO_2R_{C8}$**, es una porción seleccionada de



, y


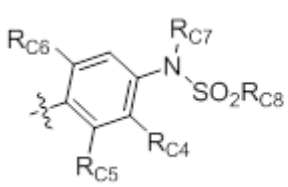
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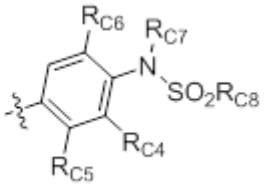
En variaciones particulares, el compuesto es de Fórmula (Ia), en donde A es



;

X es S; el anillo fenilo que contiene los grupos **R_{C4}**, **R_{C5}**, **R_{C6}**, y **$-NR_{C7}SO_2R_{C8}$**, es seleccionado de



, y


;

en donde **R_{C4}**, **R_{C5}**, y **R_{C6}** son hidrógeno o halógeno; **R_{C7}** es hidrógeno y **R_{C8}** es perfluoroalquilo. En algunas variaciones, **R_{C8}** es $-CF_3$.

Se pretende y se entenderá que cada y cada variación de A, **R_{C4}**, **R_{C5}**, **R_{C6}**, **R_{C7}**, **R_{C8}**, **$R_{C8'}$**, **R_{9a}**, **R_{9b}**, **R10**, **R11**, **X**, ***m***, y ***n***, en donde está presente, se describen por las Fórmulas (Ia) y (Ib), se pueden combinar con cada variación de A, **R_{C4}**, **R_{C5}**, **R_{C6}**, **R_{C7}**, **R_{C8}**, **$R_{C8'}$**, **R_{9a}**, **R_{9b}**, **R10**, **R11**, **X**, ***m***, y ***n***, ya que cada combinación es individualmente descrita.

En algunas modalidades, el compuesto se selecciona del grupo que consiste de:

1,1,1-trifluoro-N-(4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(3-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(3-cloro-4-(2-(1-isobutil-1H-pirazol-5-il)tiazol-

4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1,2-dimetil-1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1-propil-1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2,3-dimetil-3H-imidazo[4,5-b]piridin-7-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(3-propil-3H-imidazo[4,5-b]piridin-7-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(3H-imidazo[4,5-b]piridin-7-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1,2-dipropil-1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(6-(butilamino)-2-isobutilpirimidin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(6-(dibutilamino)-2-isobutilpirimidin-4-il)tiazol-4-il)fenil)-1,1,1-

trifluorometansulfonamida;

N-(4-(2-(6-amino-2-isobutilpirimidin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-aminopirimidin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(propilamino)pirimidin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(dibutilamino)pirimidin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2'-propil-2,4'-bitiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,2,4-tiadiazol-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,2,4-oxadiazol-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2'-propil-2,5'-bitiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,3,4-tiadiazol-2-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,3,4-oxadiazol-2-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1-isobutil-6-oxo-1,6-dihidropiridin-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(4-fluoro-3-isobutilfenil)tiazol-4-

il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3,5-dicloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-(trifluorometil)fenil)metansulfonamida;

N-(2-ciclopropil-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-metilfenil)metansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-isopropilfenil)metansulfonamida;

N-(2-etinilo-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-3-etinilo-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-6-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-6-metilfenil)-1,1,1-trifluorometansulfonamida;

N-(4-(4-(2-terc-butilpiridin-4-il)-1-metil-1H-imidazol-2-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(1-metil-2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-3-cloro-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-5-cloro-4-(1-metil-2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(4-(2-terc-butilpiridin-4-il)oxazol-2-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)oxazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(dimetilamino)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-N-(trifluorometilsulfonil)acrilamida;

N-(3-cloro-4-(2-(2-(metilsulfonamido)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(3,3,3-trifluoropropil)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(2-hidroxi-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(2-hidroxi-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-2-hidroxifenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(2-metoxi-4-(2-(2-propilpiridin-

4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-metoxifenil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-2-metoxifenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-3-(trifluorometil)fenil)metansulfonamida;

N-(3-cloro-4-(2-(2-neopentilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

6-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-3-(trifluorometilsulfonil)benzo[d]oxazol-2(3H)-ona;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,2,2,2-pentafluoroetansulfonamida;

1,1,1-trifluoro-N-(2-metoxi-4-{2-[2-(2-metilpropil)piridin-4-il]-1,3-tiazol-4-il}fenil)metansulfonamida;

1,1,1-trifluoro-N-{2-metoxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-{4-[2-(2-terc-butilpiridin-4-il)-1,3-tiazol-4-il]-2-metoxifenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-bencilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-aminopiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-metansulfonamidopiridin-4-il)-

1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-{2-hidroxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(3,3,3-trifluoropropil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(4-{2-[2-(2,2-dimetilpropil)piridin-4-il]-1,3-tiazol-4-il}-2-metoxifenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-trifluorometansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(4-(piperidin-1-carbonil)fenil)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[1-(3-metilbutil)-1H-pirazol-5-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{4-[5-(2-terc-butilpiridin-4-il)tiofen-3-il]-3-clorofenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(ciclohexilometil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(naftalen-1-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-6-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(4-{2-[3-(benciloxi)-4-(trifluorometil)fenil]-1,3-tiazol-4-il}-3-clorofenil)-1,1,1-

trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-fenilofenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(isoquinolin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(4-metilpiperazin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(dimetil-1,2-oxazol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-[4-(2-cloro-4-trifluorometansulfonamidofenil)-1,3-tiazol-2-il]fenil}-4-metilbencen-1-sulfonamida;

N-{3-cloro-4-[2-(3,4-dimetoxifenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(trifluorometil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2,3-dihidro-1-benzofuran-5-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(piperidin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(3-metilpiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(piperidin-1-il)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{5-fluoro-1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-{4-[2-(1-benzotiofen-3-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(pirrolidin-1-ilmetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(ciclopentilamino)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-3-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(quinolin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-cloropiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-hidroxietil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-(2-oxopirrolidin-1-il)etil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-il)etil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-(2-oxoimidazolidin-1-il)etil)metansulfonamida;

N-(2-bromo-4-(2-(2-(piperidin-1-il)piridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

acetato de 2-(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)etilo;

(2-(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)etoxi)metilacetato;

N-{4-[2-(2-tert-butilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-N-(2-{[4-(3-clorofenil)-2-oxo-1,3,2λ^5-dioxafosfinan-2-il]oxi}etil)-1,1,1-trifluorometansulfonamida;

(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)metilacetato;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(metoximetil)metansulfonamida;

N-{4-[2-(2-tert-butilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-N-({[4-(3-clorofenil)-2-oxo-1,3,2λ^5-dioxafosfinan-2-il]oxi}metil)-1,1,1-trifluorometansulfonamida;

4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenilo(trifluorometilsulfonil)carbamato de metilo;

(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)metilfosfato de sodio;

1-(N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometilsulfonamido)etilisobutirato;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-il)etil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-hidroxietil)metansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-(2-(pirrolidin-1-il)etil)metansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-N-(2-(dietilamino)etil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-N-(2-(dimetilamino)etil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(3-fluoro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-(2-hidroxietil)metansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-metilmetansulfonamida;

1,1,1-trifluoro-N-(3-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(2-bromo-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-metil-N-(4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(2-butilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida

1,1,1-trifluoro-N-(4-(2-(2-(metoximetil)piridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(4,6-dipropilpiridin-2-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(4-propilpiridin-2-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(2,6-dipropilpiridin-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-(ciclohexilometil)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-3-metoxifenil)metansulfonamida;

N-(3-cloro-4-(2-(2-((trifluorometilsulfonil)metil)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propil-3H-imidazo[4,5-b]piridin-7-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

5-(4-(2-cloro-4-(trifluorometilsulfonamido)fenil)tiazol-2-il)-N-ciclopropil-2-fluorobenzamida;

5-(4-(2-cloro-4-(trifluorometilsulfonamido)fenil)tiazol-2-il)-N-ciclohexilo-2-fluorobenzamida;

N-(4-(2-(1H-indol-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(3-(piperidin-1-il)fenil)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(piperidin-1-il)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-terc-butilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-cloro-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-5-cloro-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida; y

N-(2-bromo-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida.

En algunas modalidades, el compuesto se selecciona del grupo que consiste de:

1,1,1-trifluoro-N-(4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(3-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(3-cloro-4-(2-(1-isobutil-1H-pirazol-5-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(2-metoxi-4-{2-[2-(2-metilpropil)piridin-4-il]-1,3-tiazol-4-il}fenil)metansulfonamida;

1,1,1-trifluoro-N-{2-metoxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-{4-[2-(2-terc-butilpiridin-4-il)-1,3-tiazol-4-il]-2-metoxifenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-bencilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-aminopiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-metansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-{2-hidroxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(3,3,3-trifluoropropil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(4-{2-[2-(2,2-dimetilpropil)piridin-4-il]-1,3-tiazol-4-il}-2-metoxifenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-trifluorometansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(4-(piperidin-1-carbonil)fenil)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[1-(3-metilbutil)-1H-pirazol-5-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{4-[5-(2-terc-butilpiridin-4-il)tiofen-3-il]-3-

clorofenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(ciclohexilometil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(naftalen-1-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-6-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(4-{2-[3-(benciloxi)-4-(trifluorometil)fenil]-1,3-tiazol-4-il}-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-fenilofenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(isoquinolin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(4-metilpiperazin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(dimetil-1,2-oxazol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-[4-(2-cloro-4-trifluorometansulfonamidofenil)-1,3-tiazol-2-il]fenil}-4-metilbencen-1-sulfonamida;

N-{3-cloro-4-[2-(3,4-dimetoxifenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(trifluorometil)fenil]-

1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2,3-dihidro-1-benzofuran-5-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(piperidin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(3-metilpiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(piperidin-1-il)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{5-fluoro-1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-{4-[2-(1-benzotiofen-3-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(pirrolidin-1-ilmetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(ciclopentilamino)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-3-il)-1,3-tiazol-4-

il]fenil}-1,1,1-trifluorometansulfonamida; y

N-(3-cloro-4-(2-(quinolin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida.

En algunas modalidades, el compuesto se selecciona del grupo que consiste de:

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-bencilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(3,3,3-trifluoropropil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(piperidin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida; y

N-(3-cloro-4-{2-[3-(piperidin-1-il)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida.

En algunas modalidades, el compuesto es el compuesto #37: N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida.

Los compuestos descritos a continuación no están

destinados para ser limitantes; más bien, estas modalidades y variaciones están planeadas para proporcionar ejemplos de compuestos dentro del alcance de Fórmulas (Ia), (Ib), (IIa) o (IIb).

Los compuestos representativos son presentados en la Tabla 1.

Tabla 1

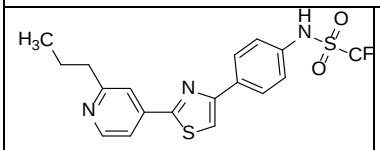
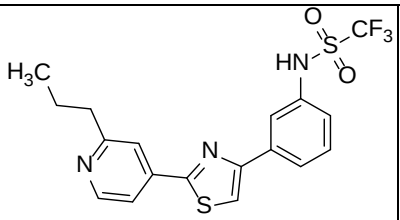
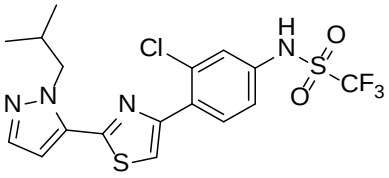
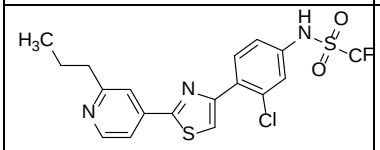
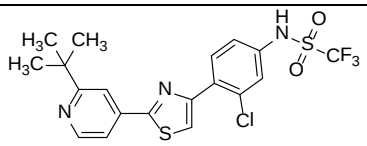
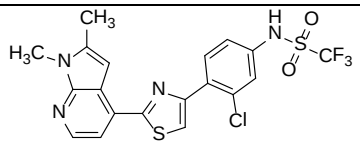
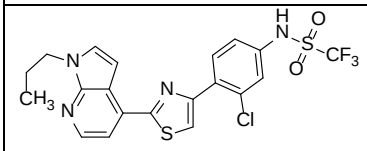
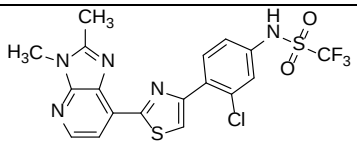
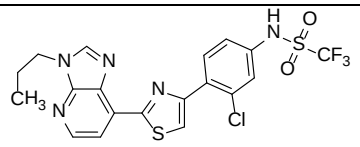
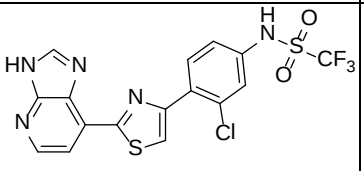
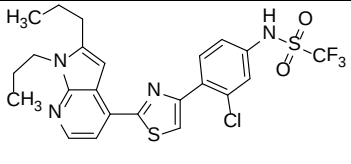
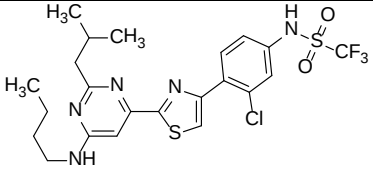
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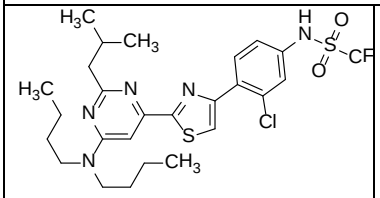
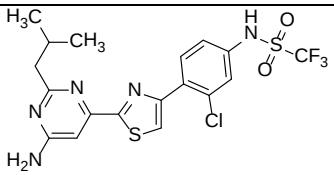
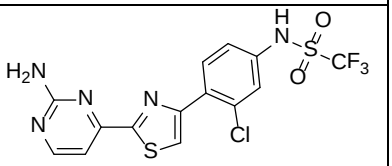
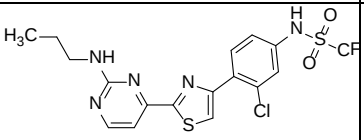
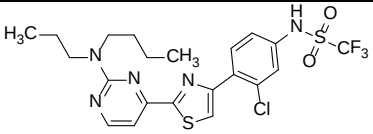
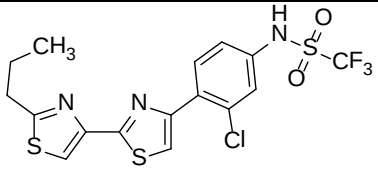
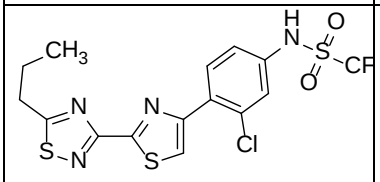
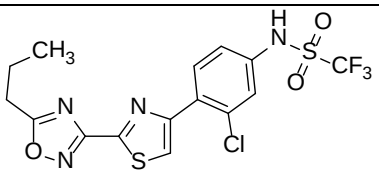
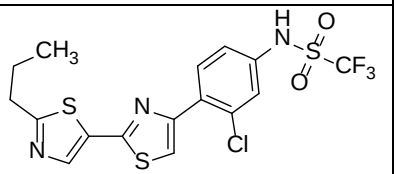
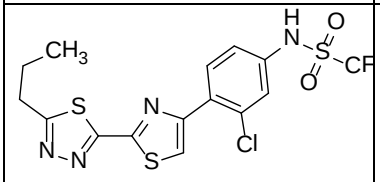
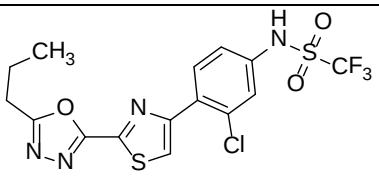
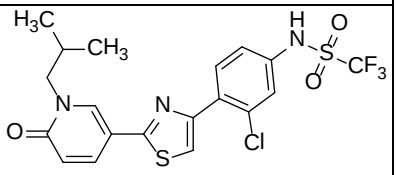
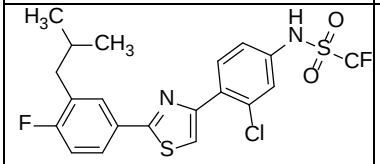
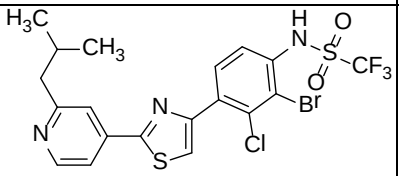
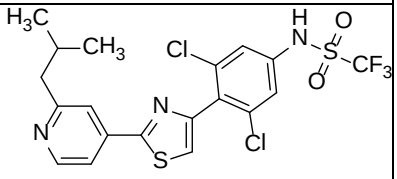
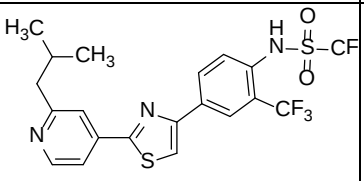
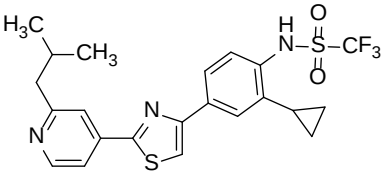
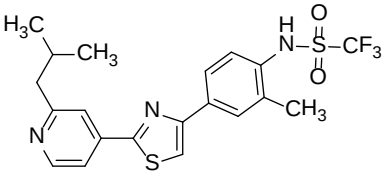
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Tabla 1

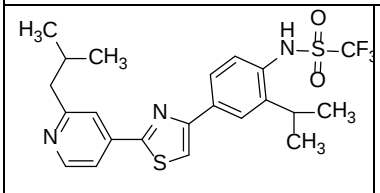
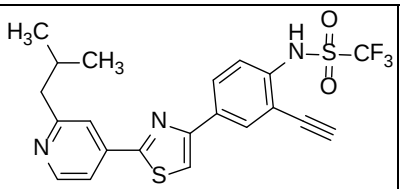
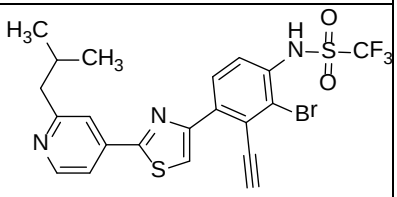
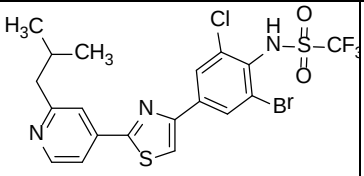
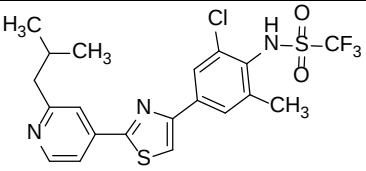
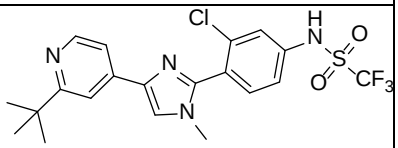
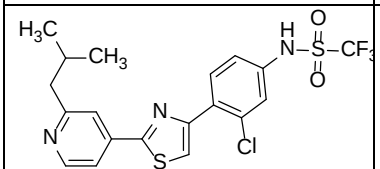
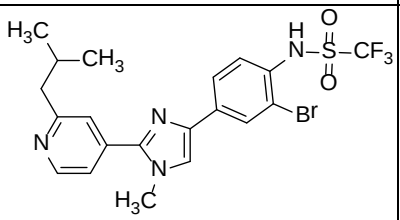
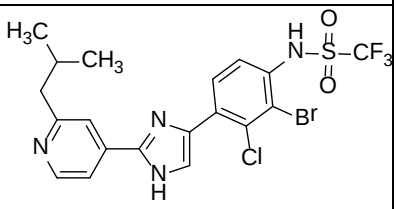
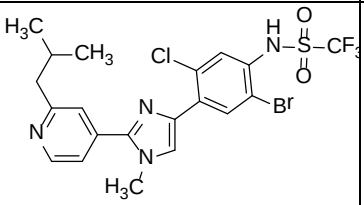
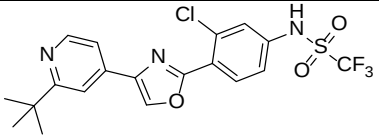
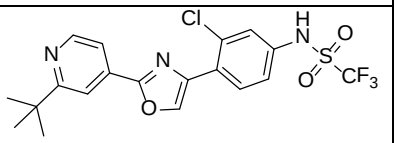
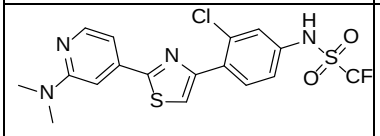
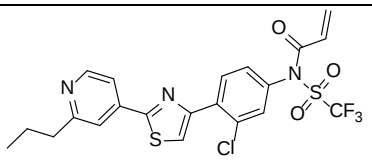
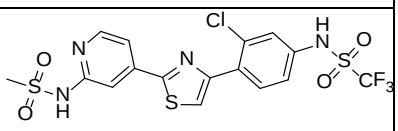
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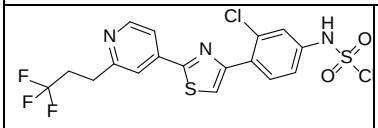
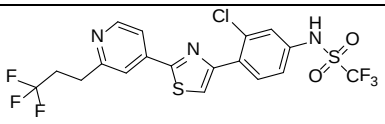
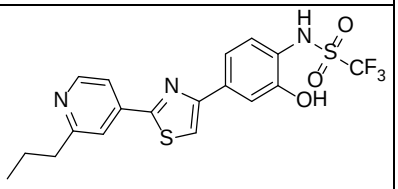
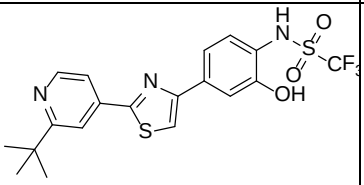
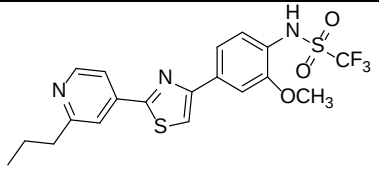
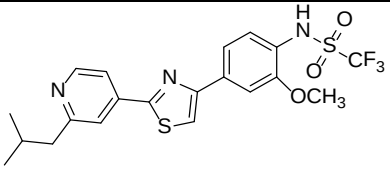
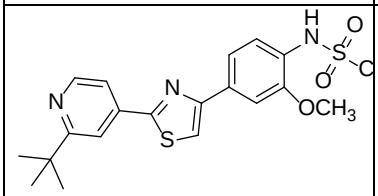
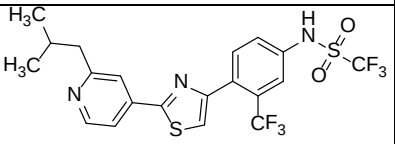
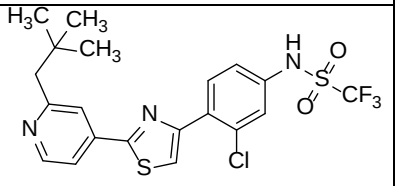
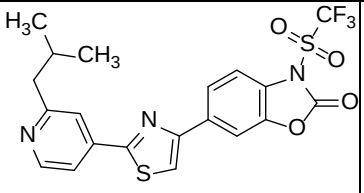
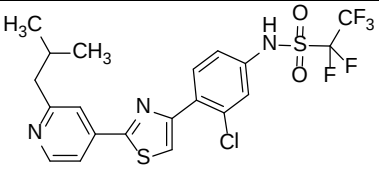
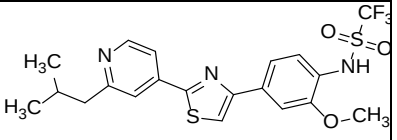
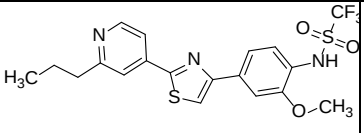
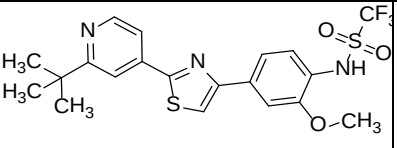
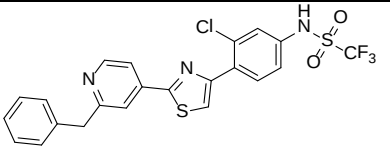
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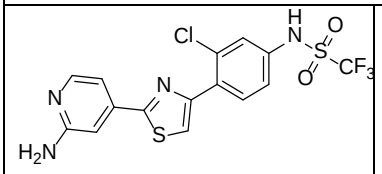
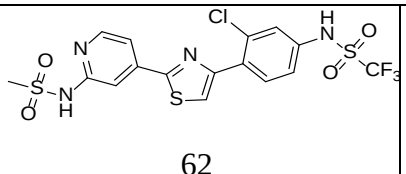
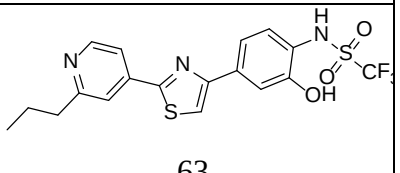
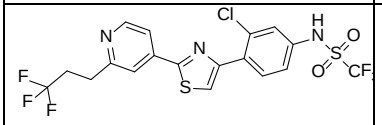
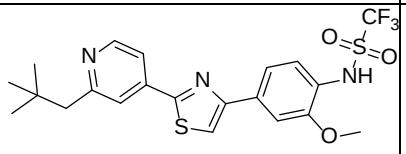
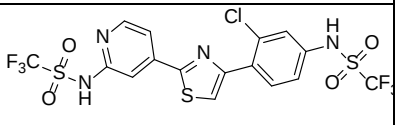
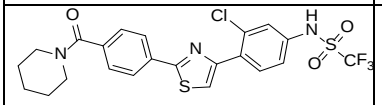
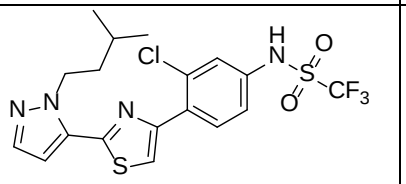
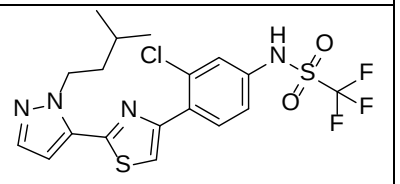
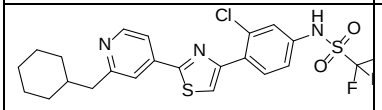
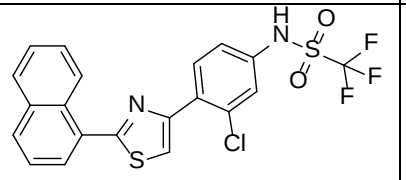
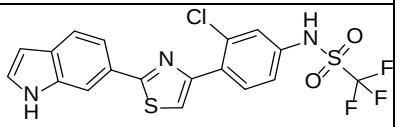
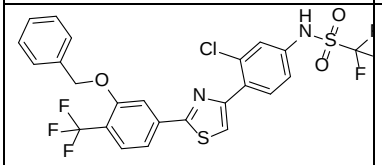
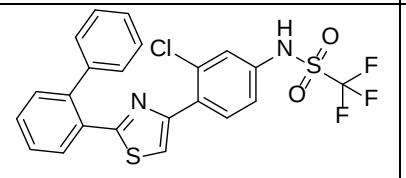
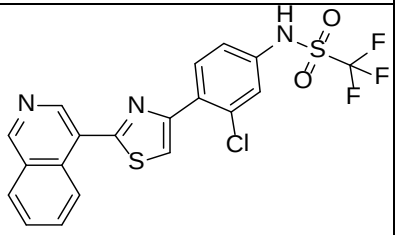
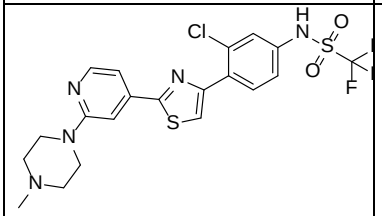
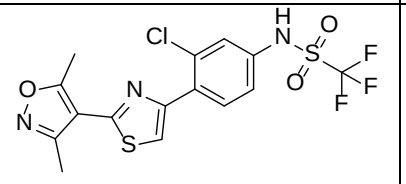
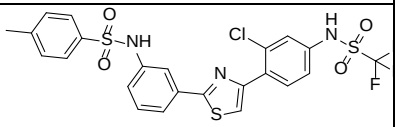
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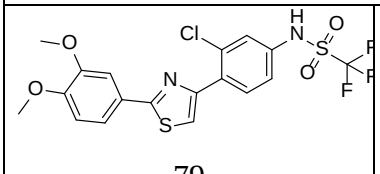
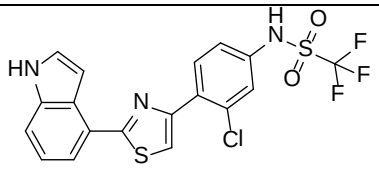
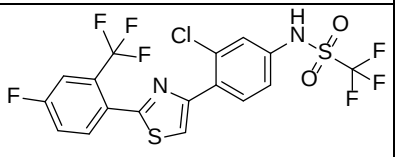
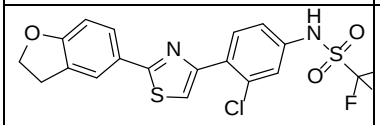
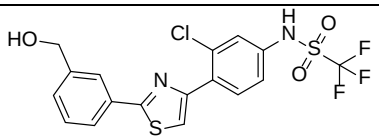
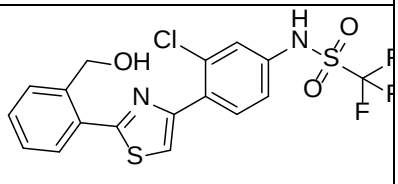
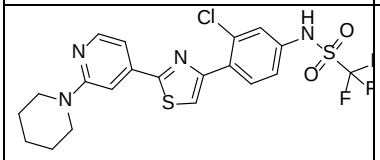
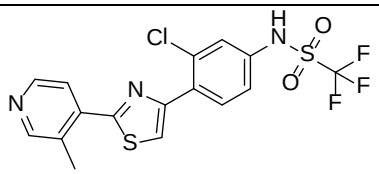
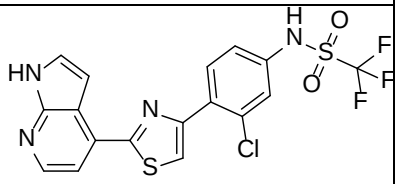
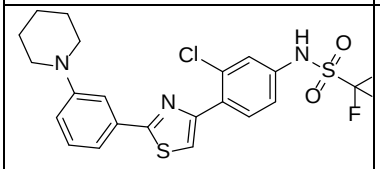
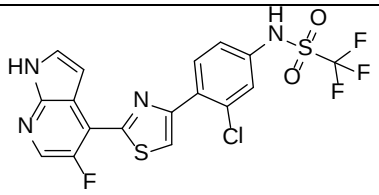
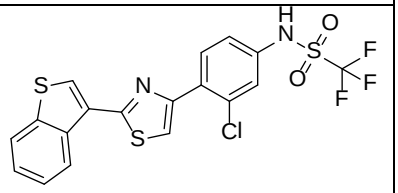
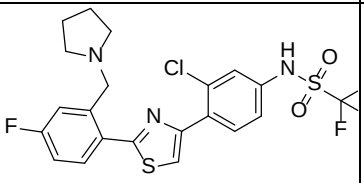
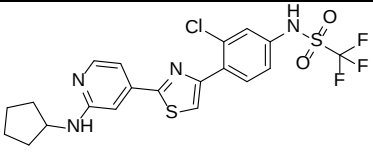
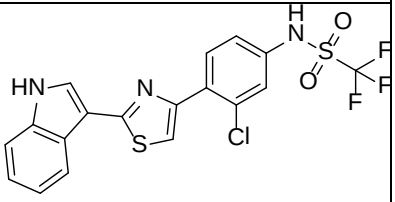
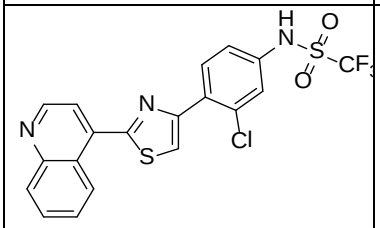
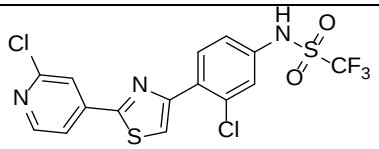
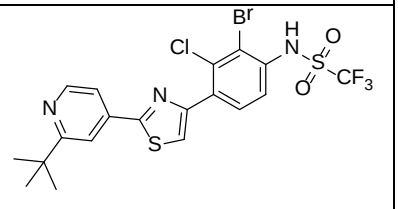
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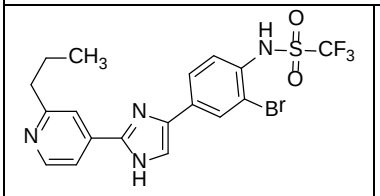
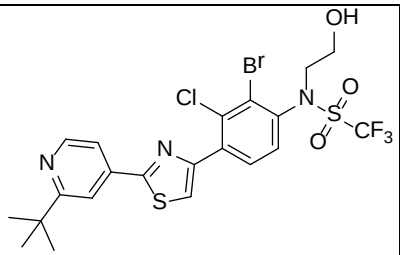
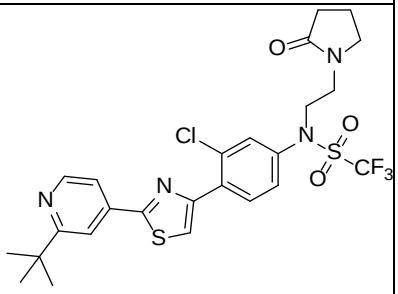
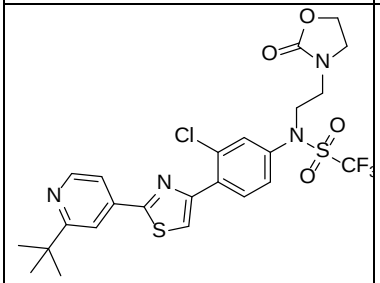
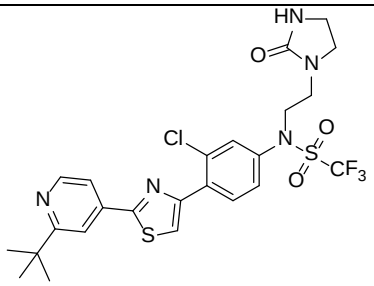
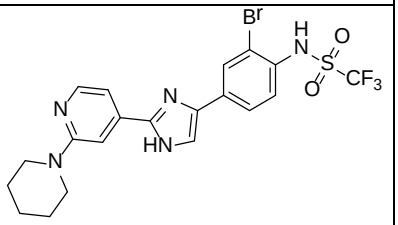
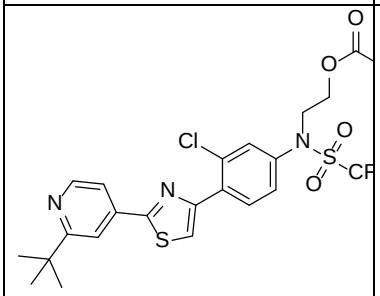
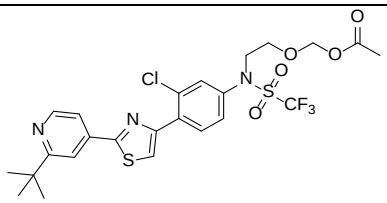
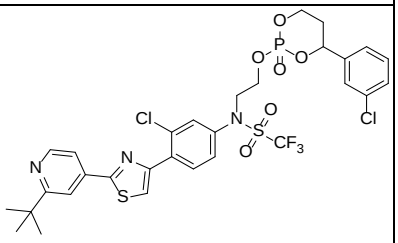
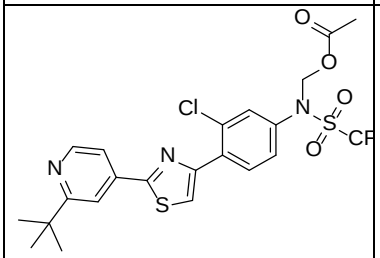
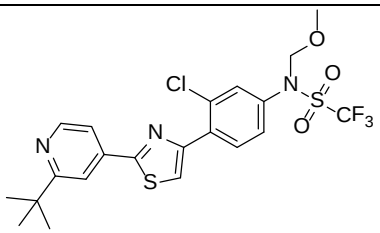
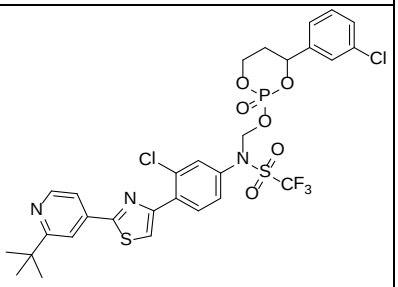
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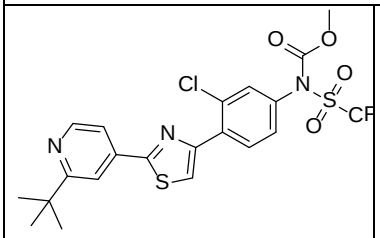
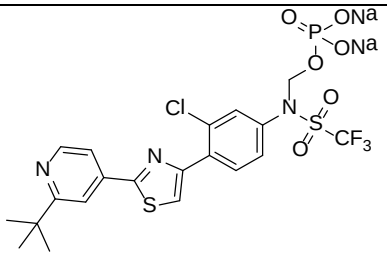
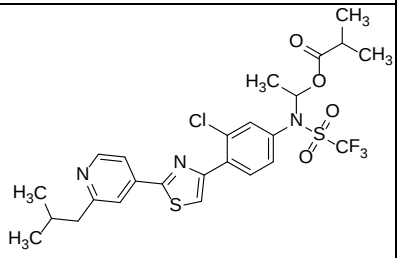
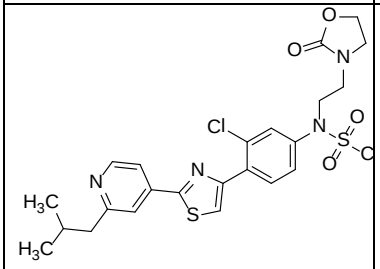
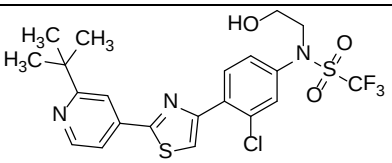
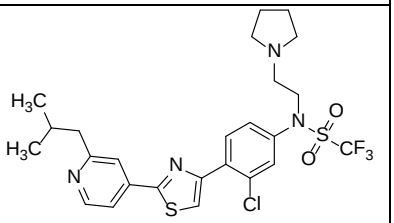
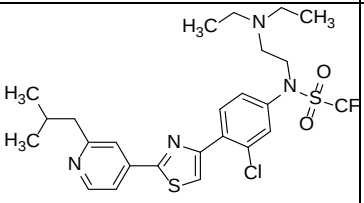
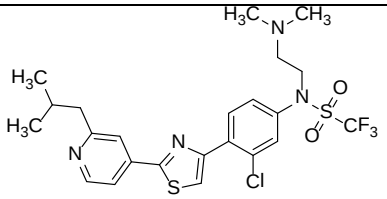
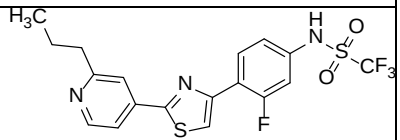
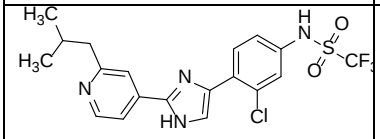
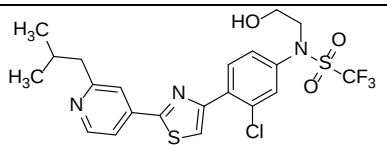
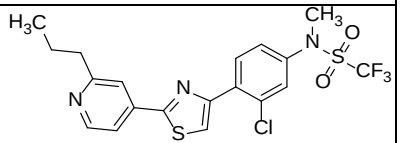
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Tabla 1

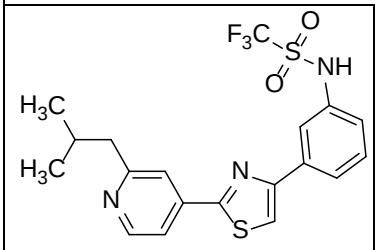
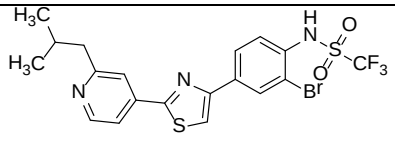
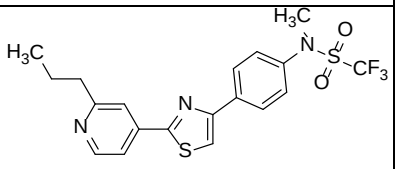
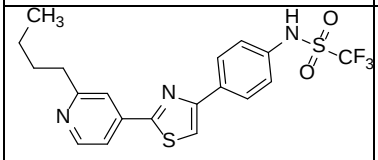
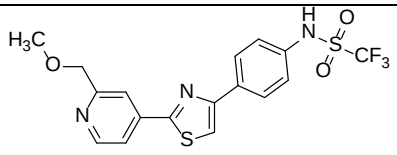
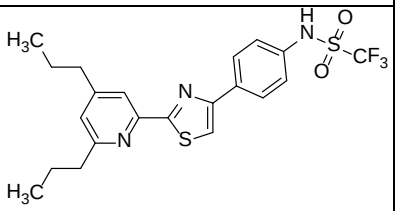
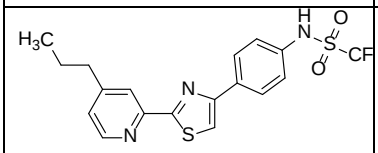
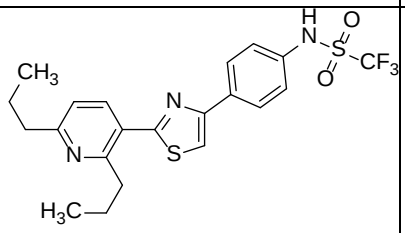
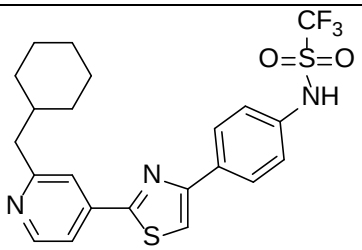
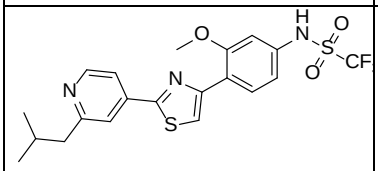
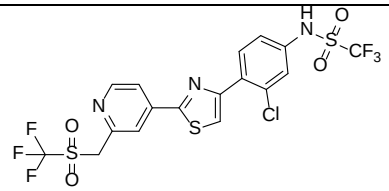
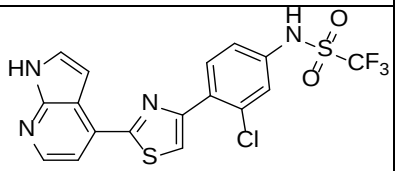
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Tabla 1

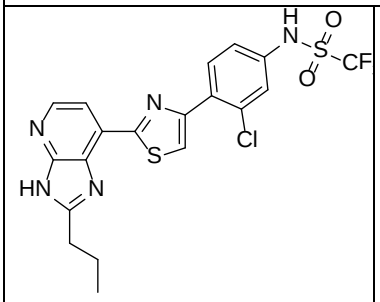
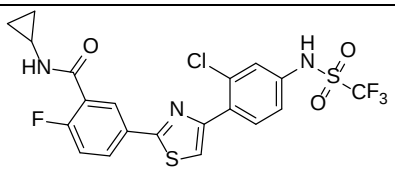
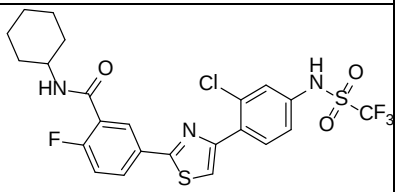
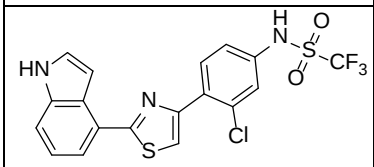
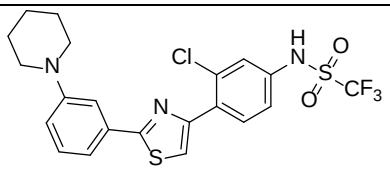
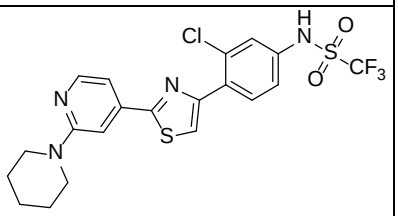
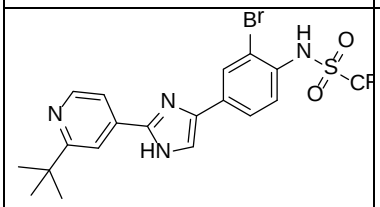
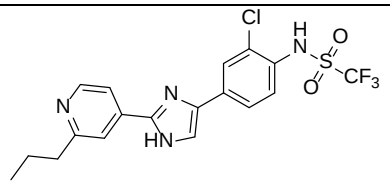
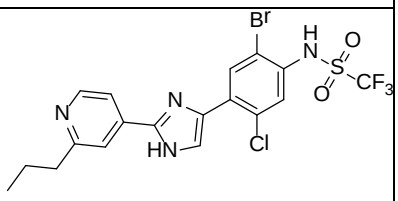
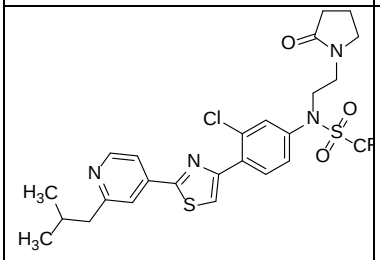
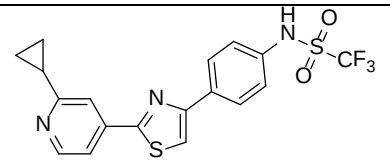
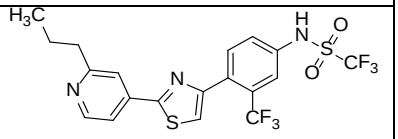
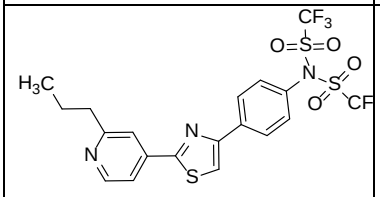
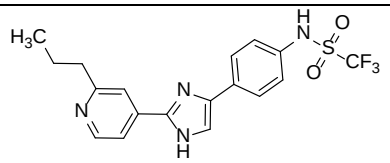
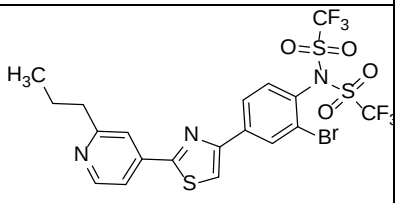
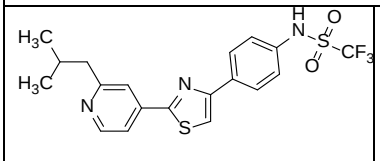
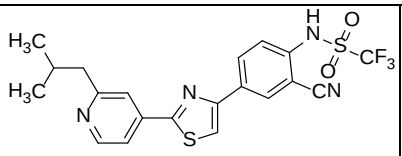
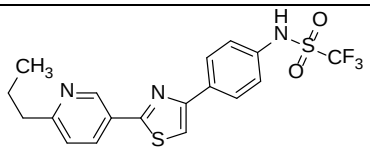
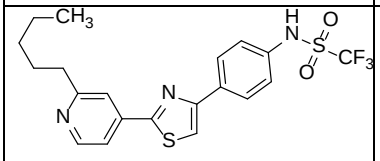
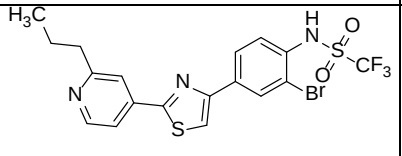
 133	 134	 135
 136	 137	 138
 139	 140	 141
 142	 143	 144
 145	 146	 147

Tabla 1

 148	 149	 150
 151	 152	

En algunas modalidades, el compuesto es 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, o 152.

En algunas modalidades, el compuesto es 1, 2, 3, 4, 5, 37, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85,

86, 87, 88, 89, 90, 91, 92, 93, o 94.

Ejemplos representativos de compuestos detallados en la presente, que incluyen intermediarios y compuestos finales, se describen en la Tabla 1 y en otra parte en la presente. Se entenderá que en un aspecto, cualquiera de los compuestos se puede usar en los métodos detallados en la presente, que incluyen, en donde sea aplicable, compuestos intermediarios que pueden ser aislados y administrados a un individuo.

Los compuestos descritos en la presente pueden ser presentados como sales aún si las sales no están descritas, y se entenderá que las composiciones y métodos proporcionados en la presente abarcan todas las sales y solvatos de los compuestos descritos en la presente, así como también la forma no salina y no solvato del compuesto, como se entiende bien por el experto en la técnica. En algunas modalidades, las sales de los compuestos proporcionados en la presente son sales farmacéuticamente aceptables.

En una modalidad, el compuesto es una sal farmacéuticamente aceptable de un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, o una sal del mismo farmacéuticamente aceptable.

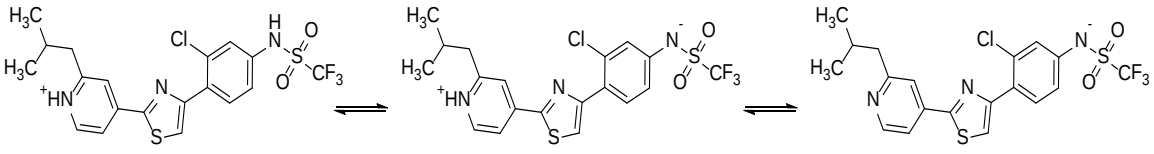
En algunas modalidades, ciertos compuestos presentados en la presente se consideran ser formas de “profármaco” de otros compuestos en la presente. Los profármacos son derivados precursores que, después de la

administración a un paciente, sufren del metabolismo *in-vivo* tal como, por ejemplo, hidrólisis para liberar la forma activa del compuesto – el compuesto 'precursor'. La forma misma del profármaco es ya sea inactiva o menos activa que el precursor. Los profármacos son diseñados para mejorar la biodisponibilidad o para mejorar la administración selectiva a órganos particulares, tales como el hígado [véase, por ejemplo, Erion, et al. *PNAS* (2007) 104:39, pp 15490-15495; Erion, et al. *J. Pharmacol. Exp. Ther.* (2005) 312:2, pp 554-560; Meyer, et al. *Publicación de Patente Estadounidense 2006-0281695A1*]. Los compuestos proporcionados en la presente tales como, por ejemplo, compuestos nos. 106-111 pueden ser considerados formas de profármaco del compuesto "precursor" no. 5. En algunas modalidades, se proporcionan las formas de profármaco de los compuestos presentados en la presente. Procedimientos convencionales para la selección y preparación de derivados de profármacos adecuados se describe por ejemplo, en *"Design of Profármacos"*, ed. H. Bundgaard, Elsevier, 1985; Beaumont; K. et al. *Curr. Drug Metab*. (2003) 4, pp 461-485; Mizen, L, et al. *Pharm. Biotechnol*. (1998) 11, pp 345-365. Además de los profármacos, la invención proporciona las sales, ésteres, amidas, y otras formas protegidas o derivatizadas de los compuestos descritos.

Como se ha descrito anteriormente, lo(s) pKa(s) inherente(s) de las moléculas se pueden valorar por los métodos

potenciométricos conocidos por el experto en la técnica, típicamente espectrometría UV [véase, por ejemplo, Julémont, et al. *J. Med. Chem.* (2002), 45, pp 5182-5185]. Se pueden usar métodos in silico como una herramienta predictiva, y el software es comercialmente disponible de, por ejemplo, ACD/Labs, Molecular Discovery, ChemAxon, y otros proveedores. Sin estar ligados por teoría, se presenta que los compuestos proporcionados en la presente poseen propiedades fisicoquímicas inesperadas que se presume se originan de la presencia de la porción de trifluorometilsulfonamida y su efecto en la acidez de las estructuras restantes de los compuestos proporcionados como un todo. Los compuestos proporcionados en la presente contienen varios centros ionizables que incluyen, por ejemplo, el átomo de nitrógeno de trifluorometilsulfonamida; el átomo de nitrógeno del anillo tiazol; el átomo de nitrógeno piridina del “anillo A”, etc.

Como un ejemplo para describir la teoría, el compuesto #37 podrá existir en las siguientes formas:

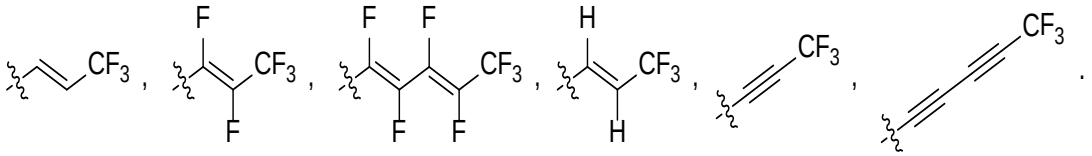


Otras formas ionizadas son concebibles, pero aquellas presentadas en la presente están en una forma protonada; una forma zwiteriónica neutral o interna; y una forma aniónica. Tal forma que podría existir es dependiente del pH de la

solución acuosa o fisiológica en la cual el compuesto es colocado. Valores de pKa calculados del compuesto #37 [proporcionado por I-Lab 2.0 (ACD/Labs, Inc.)] proporcionan dos valores de 3.4 y 5.4. Estos valores son similares a aquellos experimentalmente obtenidos bajo métodos potenciométricos y espectrofotométricos [cortesía de Pion, Inc.], encontrados por ser 3.09 y 5.27. Cuando el grupo CF_3 es reemplazado por un grupo CH_3, los valores de pKa calculados llegaron a ser 5.1 y 7.5 – ambos notablemente mayores. Se postula que la naturaleza más electronegativa del grupo CF3 resulta en la naturaleza altamente acídica del compuesto. Con base en los valores de pKa calculados/medidos de la trifluorometilsulfanamida que contiene los compuestos reivindicados en la presente, es probable que a un pH de 6-8, estos compuestos podrían predominantemente existir en la forma aniónica, con el equilibrio anterior que se encuentra a la derecha de los valores de pH mayores. La forma aniónica proporciona al compuesto, con el equilibrio anterior que se extiende a la derecha a valores de pH mayores. La forma aniónica proporciona al compuesto más acuoso soluble y por lo tanto mejor absorbido. Un estudio de solubilidad [cortesía de Pion, Inc.] mostró solubilidades promedio de 13µg/mL @ pH 6.0, 104µg/mL @ pH 7.0, y >130µg/mL @ pH 8.0. Cundo un compuesto es dosificado oralmente, la mayoría de la absorción ocurre en el intestino en donde el pH varía de 6-8. Por lo tanto, es probable que la

trifluorometilsulfonamida que contiene compuestos reivindicados en la presente podría tener significantemente mejor solubilidad y absorción cuando la dosis oral con relación a la metilsulfonamida con la cual la forma aniónica podría estar presente a una extensión significativamente menor a pH 6-8, comparado con su forma neutral/zwitteriónica).

Ejemplos de grupos perhaloalquilo sulfonamida son presentados en la presente anteriormente. En algunas modalidades, también se proporcionan compuestos que portan grupos perhaloalquenilsulfonamida, grupos perhaloalquenilsulfonamida, o grupos alquilsulfonamida que portan 1 o más átomos de halógenos. Tales compuestos pueden incluir, por ejemplo, lo siguiente:



Sin estar ligados por teoría, se espera que cada uno de estos grupos particulares, y variaciones en la presente, tengan grados variados de electronegatividad, proporcionando cambios sutiles en pKa, y permitiendo una afinación de la acidez para los compuestos de la invención, en donde se requiera por el experto en la técnica.

Sales farmacéuticamente aceptables

Las “Sales farmacéuticamente aceptables” son

aquellas sales las cuales retienen al menos alguna actividad biológica del compuesto libre (no sal) y las cuales puedan ser administradas como fármacos o farmacéuticos a un individuo. Tales sales, por ejemplo, incluyen: (1) sales de adición de ácido, formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares; o formadas con ácidos orgánicos tales como ácido acético, ácido oxálico, ácido propiónico, ácido succínico, ácido maleico, ácido tartárico y similares; (2) sales formadas cuando un protón acídico presente en el compuesto precursor ya sea es reemplazado por un ion de metal, *por ejemplo*, un ion de metal álcali, un ion de metal alcalino térreo, o un ion de aluminio; o coordinadas con una base orgánica. Las bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina y similares. Las bases inorgánicas aceptables incluyen hidróxido de aluminio, hidróxido de calcio, hidróxido de potasio, carbonato de sodio, hidróxido de sodio, y similares. Ejemplos adicionales de sales farmacéuticamente aceptables incluyen aquellas listadas en Berge *et al.*, Pharmaceutical Sales, *J. Pharm. Sci.* 1977 Jan; 66(1):1-19. Sales farmacéuticamente aceptables se pueden preparar *in situ* en el proceso de manufacturación, o haciendo reaccionar separadamente un compuesto purificado descrito en la presente en su forma de ácido o base libre con una base o ácido orgánico o inorgánico adecuado, respectivamente, y aislar

la sal así formada durante la purificación subsecuente. En una modalidad, una sal farmacéuticamente aceptable incluye las formas de adición del solvente o formas cristalinas del mismo, particularmente solvatos o polimorfos. Los solvatos contienen ya sea cantidades estequiométricas o no estequiométricas de un solvente, y son a menudo formados durante el proceso de cristalización. Los hidratos son formados cuando el solvente es agua, o alcoholatos son formados cuando el solvente es alcohol. Los polimorfos incluyen los diferentes arreglos de paquetes de cristal de la misma composición elemental de un compuesto. Los polimorfos usualmente tienen diferentes patrones de difracción de rayos-X, espectro infrarrojo, puntos de fusión, densidad, dureza, forma de cristal, propiedades ópticas y eléctricas, estabilidad, y solubilidad. Varios factores tales como el solvente de recristalización, velocidad de cristalización, y temperatura de almacenaje, pueden causar que domine una forma de cristal única.

Composiciones Farmacéuticas

Un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, típicamente se proporciona en una composición farmacéutica que comprende un portador y/o excipiente farmacéuticamente aceptable. Un portador o excipiente “farmacéuticamente aceptable” es un material que no es biológicamente o de otro modo indeseable, *por ejemplo*, el material puede ser incorporado en una

composición farmacéutica administrada a un individuo sin provocar efectos biológicos indeseables significantes o que interactúa de una manera perjudicial sin cualquiera de los otros componentes de la composición, en donde está contenido. Portadores o excipientes farmacéuticamente aceptables cubren el requerimiento estándar de pruebas de toxicología y manufacturación y se incluyen en la Guía de Ingrediente Inactivos preparada por la administración de Alimentos y Fármacos de los Estados Unidos.

Una composición farmacéutica puede comprender uno o más compuestos de Fórmulas (Ia), (Ib), (IIa) o (IIb) o cualquier variación aquí presentada. En algunas modalidades, una composición farmacéutica además comprende agentes de quimioterapia, como se describe a continuación.

Preferiblemente un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, es oralmente biodisponible. Sin embargo, los compuestos pueden también ser formulados para administración parenteral (por ejemplo, intravenosa).

Un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, se puede usar en la preparación de un medicamento combinando el compuesto o compuestos como un ingrediente activo con un portador farmacéuticamente aceptable, el cual se conoce en la técnica. Dependiendo de la forma terapéutica de la medicación, el

portador puede estar en varias formas. En una variación, la manufactura de un medicamento es para el uso de cualquiera de los métodos descritos en la presente.

Los métodos como se proporcionan en la presente pueden comprender administrar a un individuo una composición farmacológica que contiene una cantidad efectiva de un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, y un portador farmacéuticamente aceptable. La cantidad efectiva del compuesto puede en un aspecto ser una dosis entre aproximadamente 0.01 y aproximadamente 100 mg.

El compuesto puede ser formulado por cualquier ruta de suministro disponible, que incluye una forma de suministro oral, mucosal (*por ejemplo*, nasal, sublingual, vaginal, bucal o rectal), parenteral (*por ejemplo*, intramuscular, subcutánea o intravenosa), tópica o transdérmica. Un compuesto puede ser formulado con portadores adecuados para proporcionar formas de suministro que incluyen, pero no se limitan a, tabletas, capsulas, capsulas (tales como capsulas de gelatina dura o capsulas de gelatina elástica suave), sobres, trociscos, pastilla, gomas, dispersiones, supositorios, ungüentos, cataplasmas (emplasto), pastas, polvos, apósitos, cremas, soluciones, parches, aerosoles (*por ejemplo*, atomizadores o inhaladores nasales), geles, suspensiones (*por ejemplo*, suspensiones líquidas acuosas y no acuosas, emulsiones aceite

en agua o emulsiones líquidas agua en aceite), soluciones y elixires.

Un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, se pueden usar en la preparación de una formulación, tal como una formulación farmacéutica, combinando el compuesto o compuestos como un ingrediente activo con un portador farmacéuticamente aceptable, tal como aquellos mencionados anteriormente. Dependiendo de la forma terapéutica del sistema (*por ejemplo*, parche transdérmico contra tableta oral), el portador puede estar en varias formas. Además, las formulaciones farmacéuticas pueden contener preservativos, solubilizadores, estabilizadores, agentes de re-humectación, emulsionantes, edulcorantes, tintes, ajustadores, sales para el ajuste de presión osmótica, amortiguadores, agentes de recubrimiento o antioxidantes. Las formulaciones que comprenden que el compuesto puede también contener otras sustancias las cuales tienen valiosas propiedades terapéuticas. Las formulaciones farmacéuticas pueden ser preparadas por métodos farmacéuticos conocidos. Las formulaciones adecuadas pueden ser encontradas, *por ejemplo*, en *Remington's Pharmaceutical Scie**nces***, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), el cual es incorporado en la presente por referencia.

Un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, puede ser

administrado a individuos en una forma de composiciones orales en general aceptadas, tales como tabletas, tabletas recubiertas, tabletas de gel en una cubierta dura o suave, emulsiones o suspensiones. Ejemplos de portadores, los cuales se pueden usar para la preparación de tales composiciones, son lactosa, almidón de maíz o sus derivados, talco, estearato o sus sales, *etc*. Portadores aceptables puros, tabletas de gel con cubierta suave son, por ejemplo, aceites vegetales, cera, grasas, polioles semisólidos y líquidos, etcétera. Además, las formulaciones farmacéuticas pueden contener preservativos, solubilizadores, estabilizadores, agentes de re-humectación, emulsionantes, edulcorantes, tintes, ajustadores, sales para el ajuste de presión osmótica, amortiguadores, agentes de recubrimiento o antioxidantes.

Un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, puede ser formulado en una tableta en cualquier forma de dosificación descrita, por ejemplo, un compuesto como se describe en la presente o una sal del mismo farmacéuticamente aceptable puede ser formulado como una tableta de 10 mg.

Un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, puede ser administrado a un individuo de conformidad con un régimen de dosificación efectivo por un periodo de tiempo o duración deseado, tal como al menos aproximadamente un mes, al menos

aproximadamente 2 meses, al menos aproximadamente 3 meses, al menos aproximadamente 6 meses, o al menos aproximadamente 12 meses o más largo, el cual en algunas variaciones puede ser por la duración de la vida del individuo. En una variación, un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, es administrado en un esquema diario o intermitente. El compuesto puede ser administrado a un individuo continuamente (por ejemplo, al menos una vez al día) durante un periodo de tiempo. La frecuencia de dosificación puede también ser menos de una vez al día, *por ejemplo*, aproximadamente una dosificación a la semana. La frecuencia de dosificación puede ser más de una vez al día, *por ejemplo*, dos veces o tres veces al día. La frecuencia de dosificación puede también ser intermitente (*por ejemplo*, la dosificación una vez al día por 7 días seguido por ninguna dosis por 7 días, se repite por cualquier periodo de tiempo 14 días, tal como aproximadamente 2 meses, aproximadamente 4 meses, aproximadamente 6 meses o más). Cualquiera de las frecuencias de dosificación puede emplear cualquiera de los compuestos descritos en la presente junto con cualquiera de las dosificaciones descritas en la presente.

En algunas modalidades, una composición farmacéutica se proporciona como una forma de dosificación unitaria, tal como una tableta, cápsula, o contenedor individualmente empaquetado (*por ejemplo*, una ampolla, jeringa, o vial).

En algunas modalidades, la forma de dosificación unitaria contiene una dosis diaria de un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada. En algunas modalidades, la forma de dosificación unitaria contiene una sub-dosis diaria del compuesto.

En algunas modalidades, la forma de dosificación unitaria contiene una dosis diaria de cada uno de dos o más compuestos de Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada. En algunas modalidades, la forma de dosificación unitaria contiene una sub-dosis diaria de cada uno de dos o más compuestos.

En algunas modalidades, la forma de dosificación unitaria contiene una dosis diaria del compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, y una dosis diaria de cada uno de uno o más agentes quimioterapéuticos. En algunas modalidades, la forma de dosificación unitaria contiene una sub-dosis diaria del compuesto y una sub-dosis diaria de cada uno de uno o más agentes quimioterapéuticos.

En algunas modalidades, la forma de dosificación unitaria contiene una dosis diaria de cada uno de dos o más compuestos de Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, y una dosis diaria de cada uno de uno o más agentes quimioterapéuticos. En algunas modalidades, la forma de dosificación unitaria contiene una sub-dosis diaria

de cada uno de dos o más compuestos y una dosis diaria de cada uno de uno o más agentes quimioterapéuticos.

Kits y Artículos de Manufactura

Esta descripción también proporciona kits y artículos de manufactura que comprende uno o más compuestos de Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, o una composición farmacológica que comprende un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada. Los kits pueden emplear cualquiera de los compuestos descritos en la presente. En una variación, el kit emplea un compuesto descrito en la presente o una sal del mismo farmacéuticamente aceptable.

Los kits en general comprenden envasado adecuado. Los kits pueden comprender uno o más contenedores que comprenden cualquier compuesto descrito en la presente. Cada componente (si existe más de un componente) puede ser envasado en contenedores separados o algunos componentes pueden ser combinados en contendores separados o algunos componentes pueden ser combinados en un contenedor donde se permite la reactividad cruzada y vida útil.

Los kits pueden estar en formas de dosificación unitaria, paquetes de volumen (*por ejemplo*, paquetes de dosis múltiples) o dosis sub-unitarias. Por ejemplo, los kits pueden ser proporcionados que contengan suficientes dosificaciones de un compuesto como se describe en la presente y/o un segundo

compuesto farmacéuticamente activo útil para una enfermedad detallada en la presente para proporcionar tratamiento efectivo de un individuo por un periodo extendido, tal como cualquiera de una semana, 2 semanas, 3 semanas, 4 semanas, 6 semanas, 8 semanas, 3 meses, 4 meses, 5 meses, 7 meses, 8 meses, 9 meses, o más. Los kits pueden incluir también dosis unitaria múltiple de los compuestos o instrucciones para uso y ser envasadas en cantidades suficientes para almacenamiento y uso en farmacias (*por ejemplo*, farmacias de hospitales y farmacias de compuestos).

Los kits pueden incluir opcionalmente una serie de instrucciones, en general instrucciones escritas, aunque medios de almacenamiento electrónico (*por ejemplo*, disquete magnético o disco óptico) que contienen instrucciones también son aceptables, con relación al uso del(los) componente(s) de los métodos descritos. Las instrucciones incluidas con el kit en general incluyen información en cuanto a los componentes y su administración a un individuo.

Usos Terapéuticos

Los compuestos de Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, se pueden usar para tratar trastornos hiperproliferativos. Un “trastorno hiperproliferativo” es un trastorno asociado con algún grado de proliferación anormal de células. Un trastorno hiperproliferativo puede ser benigno (que incluye trastornos

pre-cancerosos) o maligno.

En algunas modalidades, el trastorno hiperproliferativo es benigno, tal como hiperplasia prostática benigna, neurofibromatosis, queratosis actínica, queratosis actínica hipertrófica, queratosis actínica Bowenoide, queratosis arsénica, queratosis de hidrocarburo, queratosis térmica, queratois por radiación, queratosis de cicatriz crónica, queratosis viral, queilitis actínica, enfermedad de Bowen, eritroplaquia de queirat, eritroplaquia oral, leucoplaquia, epitelioma intraepidermal, psoriasis, pólipos, esófago de Barrett, gastritis atrófica, displasia cervical, meningioma benigno, y tumores epiteliales de ovario benignos (*por ejemplo*, adenomas serososo, adenomas mucinosos, tumores de Brenner).

En algunas modalidades, el trastorno hiperproliferativo es maligno, *por ejemplo*, adenocarcinoma, carcinoma de vejiga, carcinoma de mama, carcinoma cervical, colangiocarcinoma, cáncer de CNS (*por ejemplo*, astrocitoma, dendroma, ependimoma, glioma, meningioma maligno, meduloblastoma, neuroblastoma, neuroglioma, oligodendroglioma), cáncer gastrointestinal (*por ejemplo*, carcinoma estromal gastrointestinal, cáncer colorrectal), cáncer de riñón, leucemia (*por ejemplo*, leucemia linfocítica aguda; leucemia mielogenosa aguda; leucemia linfocítica crónica; leucemia mielogenosa crónica), cáncer de hígado (*por*

ejemplo, cáncer hepático, carcinoma hepatocelular), cáncer de pulmón (*por ejemplo*, carcinoma escamoso de pulmón, carcinoma de pulmón de células pequeñas, carcinoma de pulmón de células no pequeñas, mesotelioma), linfoma (*por ejemplo*, linfoma Hodgkin y linfoma no Hodgkin), melanoma, mieloma (*por ejemplo,* mieloma múltiple, plasmacitoma), cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer tiroideo, y cáncer uterino.

En algunas modalidades, el cáncer de mama es AR+, ER+, y Her2+. En algunas modalidades, el cáncer de mama es AR+, ER+, y PR+. En algunas modalidades, el cáncer de mama es AR+, ER+, Her2+, y PR+. En algunas modalidades, el cáncer de mama es AR-, ER+, y Her2+. En algunas modalidades, el cáncer de mama es AR-, ER+, y PR+. En algunas modalidades, el cáncer de mama es AR-, ER+, Her2+, y PR+.

En algunas modalidades, el cáncer de mama es carcinoma ductal *in situ*. En algunas modalidades, el cáncer de mama es carcinoma ductal invasivo. En algunas modalidades, el cáncer de mama es cáncer de mama triple negativo (*por ejemplo*, subtipos del tipo 1 similar al basal (BL1), tipo 2 similar al basal (BL2), inmunomodulador (IM), mesenquimal (M), similar al troncal a mesenquimal (MSL), y receptor del andrógeno luminal (LAR)). En algunas modalidades, el cáncer de mama es cáncer de mama inflamatorio. En algunas modalidades, el cáncer de mama es cáncer de mama relacionado con BRCA1. En algunas

modalidades, el cáncer de mama es cáncer de mama medular, cáncer de mama metaplásico. En algunas modalidades, el cáncer de mama es tipo histológico Especial de cáncer de mama. En algunas modalidades, el cáncer de mama es resistente a terapia endocrina.

En algunas modalidades, el cáncer de próstata es cáncer de próstata sensible a la hormona. En algunas modalidades, el cáncer de próstata es cáncer de próstata resistente a castración.

En algunas modalidades, el cáncer de ovario es un carcinoma epitelial. En algunas modalidades, el cáncer de ovario es un tumor de células germinales. En algunas modalidades, el cáncer de ovario es un tumor estromal de ovario (*por ejemplo*, tumores de células teca-granulosa y tumores de células Sertoli-Leydig).

Los compuestos descritos en la presente también se pueden usar para tratar una variedad de trastornos metabólicos, que incluyen trastornos metabólicos que son mediados por factores genéticos (*por ejemplo*, enfermedad de Niemann-Pick, enfermedad de Fabry, enfermedad de Gaucher, enfermedad de Forbe, enfermedad de Tangier) y factores ambientales (*por ejemplo*, dietas ricas en grasas y/o azúcar). Los compuestos también pueden ser útiles en el tratamiento de complicaciones de enfermedades metabólicas, tales como enfermedad cardiovascular, esteatosis hepática no alcohólica,

hiperlipidemia, y obesidad.

Los compuestos descritos en la presente también se pueden usar para tratar pancreatitis.

Regímenes de Tratamiento

Los compuestos pueden ser administrados solos o en conjunto con otras intervenciones terapéuticas. Los compuestos descritos reducen la síntesis del colesterol y ácidos grasos, los cuales son componentes esenciales de las membranas celulares y división celular; por consiguiente, la administración de un compuesto debe reducir la velocidad de división celular. Estos efectos, acoplados con alteraciones en las trayectorias de señalización celular mediadas por lípidos, inducen muerte celular.

La administración de un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, “en conjunto con” otro terapéutico de intervención, puede incluir cualquiera de los regímenes.

Dosificación y Método de Administración

La dosis de un compuesto administrada a un individuo (tal como un humano) puede variar con el compuesto particular o sal del mismo, el método de administración, y la etapa particular de trastorno hiperproliferativo o metabólico que será tratado. Para propósitos terapéuticos, “dosis efectiva” o “cantidad efectiva”, se refiere a aquella cantidad de cada compuesto activo o agente farmacéutico, solo o en combinación,

que provoca la respuesta biológica o medicinal en un sistema de tejido, animal, o humano que está siendo buscado por un investigador, veterinario, doctor médico, u otro especialista, la cual incluye alivio de los síntomas de la enfermedad o trastorno que será tratado. Para propósitos profilácticos (es decir, prevenir o inhibir el comienzo o progreso de un trastorno), el término “dosis efectiva” o “cantidad efectiva” se refiere a tal cantidad de cada compuesto activo o agente farmacéutico activo, sola o en combinación, que inhibe en un sujeto, el comienzo o progreso de un trastorno conforme es buscado por un investigador, veterinario, doctor médico, u otro especialista, el retardo de tal trastorno es mediado, al menos en parte, por el bloqueo de la función de SREBP. La cantidad debe ser suficiente para producir una respuesta deseable, tal como una respuesta terapéutica o profiláctica contra el trastorno. En algunas modalidades, la cantidad del compuesto o sal del mismo es una cantidad terapéuticamente efectiva. En algunas modalidades, la cantidad del compuesto o sal del mismo es una cantidad profilácticamente efectiva. En algunas modalidades, la cantidad del compuesto o sal del mismo está por debajo del nivel que induce un efecto toxicológico (por ejemplo, un efecto anterior a un nivel clínicamente aceptable de toxicidad) o está en un nivel en donde un efecto secundario potencial puede ser controlado o tolerado cunado la composición es administrada al individuo.

En algunas modalidades, la cantidad del compuesto o sal del mismo es una cantidad suficiente para inhibir el crecimiento y/o proliferación de células cancerígenas o incrementar la apoptosis de células cancerígenas.

La cantidad efectiva del compuesto puede, en un aspecto, ser una dosis de entre aproximadamente 0.01 y aproximadamente 100 mg/kg.

Cualquiera de los métodos proporcionados en la presente puede en un aspecto, comprender administrar a un individuo una composición farmacéutica que contiene una cantidad efectiva de un compuesto proporcionado en la presente o una sal del mismo y un excipiente farmacéuticamente aceptable.

Un compuesto o composición proporcionado en la presente puede ser administrado a un individuo de conformidad con un régimen de dosificación efectivo por un periodo de tiempo o duración deseada, tal como al menos aproximadamente un mes, al menos aproximadamente 2 meses, al menos aproximadamente 3 meses, al menos aproximadamente 6 meses, o al menos aproximadamente 12 meses o más, lo cual en algunas variaciones puede ser por la duración de la vida del individuo. En una variación, el compuesto es administrado en un esquema diario o intermitente. El compuesto puede ser administrado a un individuo continuamente (por ejemplo, al menos una vez diariamente) durante un periodo de tiempo. La frecuencia de

dosificación también puede ser menos de una diariamente, *por ejemplo*, aproximadamente una dosificación una vez semanalmente. La frecuencia de dosificación puede ser más de una vez diariamente, *por ejemplo*, dos veces o tres veces diariamente. La frecuencia de dosificación también puede ser intermitente (*por ejemplo*, una dosificación una vez diariamente por 7 días seguida por ninguna dosis por 7 días, repetida por cualquier periodo de tiempo de 14 días, tal como aproximadamente 2 meses, aproximadamente 4 meses, aproximadamente 6 meses o más). Cualquiera de las frecuencias de dosificación puede emplear cualquiera de los compuestos descritos en la presente junto con cualquiera de las dosificaciones descritas en la presente.

Los compuestos proporcionados en la presente o una sal del mismo pueden ser administrados a un individuo mediante varias rutas, que incluyen, por ejemplo, intravenosa, intramuscular, subcutánea, oral y transdérmica.

En un aspecto, se proporciona un método para tratar cáncer en un individuo administrando parenteralmente al individuo (por ejemplo, un humano) una cantidad efectiva de un compuesto o sal del mismo. En algunas modalidades, la ruta de administración es intravenosa, intra-arterial, intramuscular, o subcutánea. En algunas modalidades, la ruta de administración es oral. En todavía otras modalidades, la ruta de administración es transdérmica. En un aspecto se proporcionan

composiciones (que incluyen composiciones farmacéuticas) como se describe en la presente, para uso en el tratamiento de un trastorno metabólico o hiperproliferativo, tal como cáncer (por ejemplo, cáncer de próstata).

También se proporcionan composiciones (que incluyen composiciones farmacéuticas) como se describen en la presente para uso en el tratamiento, prevención, y/o retardo del comienzo y/o desarrollo de cáncer y otros métodos descritos en la presente. En ciertas modalidades, la composición comprende una formulación farmacéutica la cual está presente en una forma de dosificación unitaria.

También se proporcionan artículos de manufactura, que comprenden un compuesto proporcionado en la presente o una sal del mismo, composición, y dosificaciones unitarias descritas en la presente en envase adecuado para uso en los métodos descritos en la presente. El envasado adecuado se conoce en la técnica e incluye, por ejemplo, viales, recipientes, ampolletas, botellas, jarras, envasado flexible y similares. Un artículo de manufactura puede ser además, esterilizado y/o sellado.

Agentes Anti-Proliferativos

Un “agente anti-proliferativo” es una intervención que incrementa la apoptosis de células hiperproliferantes. En algunas modalidades, un compuesto de las Fórmulas (Ia), (Ib), (IIa) o (IIb), o cualquier variación aquí presentada, se usa

en conjunto con un agente anti-proliferativo el cual es un agente quimioterapéutico. Los agentes quimioterapéuticos incluyen cualquier agente farmacológico el cual es actualmente aprobado por la FDA en los Estados Unidos (o en otra parte por cualquier otro cuerpo regulador) para uso como tratamiento farmacológico para trastornos hiperproliferativos, que incluyen cáncer, o el cual está actualmente siendo usado experimentalmente como parte de un programa de ensayo clínico.

Métodos Sintéticos Generales

Los compuestos pueden ser preparados por un número de procesos como se describe en general abajo en los Esquemas de Reacción Sintéticos Generales y más específicamente en los Ejemplos posteriormente. En las descripciones de proceso siguientes, los símbolos cuando se usan en las Formulas representadas son para ser entendidos por representar aquellos grupos descritos anteriormente con relación a las fórmulas de la presente.

Los procedimientos de cromatografía, recristalización y otros de separación convencional, también pueden ser usados con intermediarios o productos finales en donde se desea obtener un isómero particular de un compuesto o de otro modo purificar un producto de una reacción.

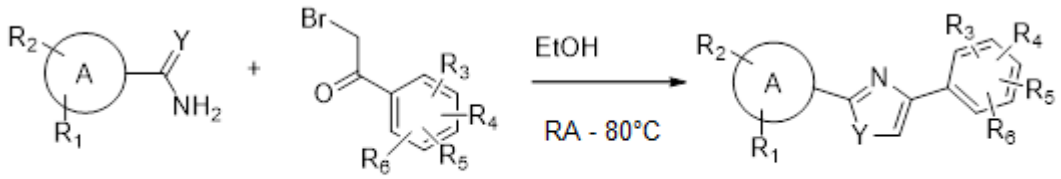
Las siguientes abreviaturas son usadas en la presente: cromatografía de capa delgada (TLC); hora (h); minuto (min); segundo (sec); etanol (EtOH); dimetilsulfóxido (DMSO);

N,N-dimetilformamida (DMF); ácido trifluoroacético (TFA); tetrahidrofurano (THF); Normal(N); acuoso (ac.); metanol (MeOH); diclorometano (DCM); acetato de etilo (EtOAc); factor de retención (Rf); temperatura ambiente (RT).

Los siguientes Esquemas de Reacción Sintéticos Generales y Ejemplos, se proporcionan para ilustrar, pero no limitar la invención. Aquellos expertos en la técnica serán familiares con muchas de las etapas de reacción descritas. Las publicaciones particulares son presentadas para asistir en ciertas etapas de la ruta sintética.

Esquema de Reacción Sintético General 1

El Esquema de Reacción Sintético General 1 proporciona métodos para preparar compuestos con un anillo B tiazol o imidazol como aquí se presenta. Los sustituyentes R_1-R_6 son como se ejemplifican en los Ejemplos abajo. Las síntesis de tiazoles, oxazoles e imidazoles, tricíclicos sustituidos, tal como aquellos aquí presentados, serán familiares para aquellos expertos en la técnica. Un ejemplo para ilustrar una síntesis de un tiazol sustituido se presenta abajo. Los detalles completos para las síntesis de los compuestos aquí presentados se proporcionan en los Ejemplos.



A = anillo aromático o heteroaromático
Y = O, S, NH

Procedimiento General: La isonicotinamida o piridin-4-carbotioamida sustituida correspondiente y el 2-bromoacetilbenceno sustituido correspondiente se disuelven en EtOH. La mezcla de reacción resultante se agita entre TA y 70 ºC por entre 30 min y 2 h. El progreso de la reacción se monitorea por TLC y LCMS. La mezcla de reacción se enfría a TA, se basifica con solución acuosa de bicarbonato de sodio y la mezcla se extrae con EtOAC. La capa orgánica se seca sobre sulfato de sodio y se concentra para obtener el producto crudo, el cual se purifica por cromatografía en columna de gel de sílice (malla 100-200) / por HPLC para obtener el producto deseado.

EJEMPLOS

Ejemplo 1. Preparación del compuesto No. 1

Piridina (0.02 mL, 0.248 mmol) se agregó a una solución de anhídrido tríflico (0.05 mL, 0.297 mmol) a 0 ºC bajo nitrógeno en DCM (2 mL). Después de 15 min, 4-(2-(2-propilpiridin-4-il)tiazol-4-il)anilina (70 mg, 0.236 mmol) se agregó por goteo a 0 ºC en DCM (3 mL). La reacción se dejó agitar a TA por 30 minutos adicionales, se monitoreó por TLC. Después del término, la mezcla de reacción se diluyó con agua (10 mL) y la mezcla se extrajo con EtOAc (2x20 mL). La capa orgánica combinada se secó sobre sulfato de sodio anhidro y se

concentró bajo presión reducida para proporcionar el producto crudo, el cual se purificó por HPLC preparativa de fase inversa para obtener 17 mg de 1,1,1-trifluor-N-(4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida (sólido amarillo). Esto se trató con HCl acuoso 2N para formación salina. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.77 (d, J = 6.2 Hz, 1H), 8.54 (s, 1H), 8.48 (d, J = 6.2 Hz, 1H), 8.36 (s, 1H), 8.13 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 3.18-2.98 (m, 2H), 1.91 (p, J = 7.7 Hz, 2H), 1.10 (t, J = 7.4 Hz, 3H).

Ejemplo 2. Preparación del compuesto No. 2

2-Propilpiridina-4-carbotioamida (50 mg,0.118 mmol) y N-(3-(2,2-dibromoacetil)fenil)-1,1,1-trifluormetansulfonamida (16.9 mg, 0.09 mmol) se cargaron en ácido acético (1 mL) y la mezcla de reacción se agitó a 80 ºC por 30 min. La reacción se monitoreó por LCMS y ácido acético se evaporó bajo vacío. La mezcla de reacción cruda se purificó usando cromatografía de fase inversa para conseguir 2.4 mg de 1,1,1-trifluor-N-(3-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida. ^{1}H NMR (CD_3OD) δ (ppm): 8.59 (d, J= 5.3 Hz, 1H), 8.08 (s, 1H), 8.00 (s, 1H), 7.94 (m, 2H), 7.49 (m, 1H), 7.33 (d, J=8.1 Hz, 1H), 2.99-2.77 (m, 3H), 1.83 (m, 2H), 1.03 (t, J=7.3 Hz, 3H).

Ejemplo 4. Preparación del compuesto No. 4

N-(4-(2-Bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida (50mg, 0.132 mmol) y 2-

propilpiridina-4-carbotioamida (23.8 mg, 0.132mmol) se cargaron en EtOH (10 mL) y la mezcla de reacción se calentó a 80 ºC por 1 h. La mezcla de reacción se concentró y se purificó a través de HPLC de fase inversa. Proporcionando: 17 mg sal TFA. ^{1}H NMR (sal TFA, CD_3OD) δ (ppm): 8.72 (d, J=6.0 Hz, 1H), 8.38 (d, J=7.6 Hz, 1H), 8.31 (d, J=6.0 Hz, 2H), 8.07 (d, J=8.5 Hz, 1H), 7.49 (s, 1H), 3.04 (t, J=7.8 Hz, 3H), 1.88 (m, 2H), 1.07 (s, J=7.3 Hz, 3H).

Ejemplo 5. Preparación del compuesto No. 5

2-terc-butilpiridina-4-carbotioamida (100 mg, 0.26 mmol) y N-(4-(2-bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida (51 mg, 0.26 mmol) se cargaron en EtOH (5 mL) y la mezcla de reacción se agitó a 80 ºC por 30 min. La reacción se monitoreó por LCMS, y entonces el EtOH se evaporó bajo vacío. La mezcla de reacción se purificó usando cromatografía de fase inversa para conseguir 43mg de N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluormetansulfonamida. ^{1}H NMR (sal de HCl, CD_3OD) δ (ppm): 8.76 (d, J =6.1 Hz, 1H), 8.50 (s, 1H), 8.43 (m, 2H), 8.06 (d, J=8.5 Hz, 1H), 7.50 (d, J=2.2Hz, 1H), 7.4 (m, 1H), 1.58 (s, 9H).

Ejemplo 6. Preparación del compuesto No. 57

síntesis de 1,1,1-trifluor-N-(2-metoxi-4-{2-[2-(2-metilpropil)piridin-4-il]-1,3-tiazol-4-il}fenil)metansulfonamida

Etapa-1: síntesis de cloruro de 3-metoxi-4-nitrobenzoilo

Ácido 3-Metoxi-4- nitrobenzoico (5) (3 g) y cloruro de tionilo (10 mL) se agregaron por goteo a 0 ºC. La mezcla de reacción se dejó llegar a TA y se calentó a reflujo durante la noche. Cloruro de tionilo se evaporó y se agregó hielo a la mezcla de reacción. La capa orgánica se extrajo en acetato de etilo (2x50 mL). La capa orgánica combinada se secó sobre sulfato de sodio anhidro y se concentró para conseguir 6 g de cloruro de 3-metoxi-4-nitrobenzoilo.

Etapa-2: síntesis de 1-(3-metoxi-4-nitrofenil)etanona

Una suspensión de cloruro de magnesio anhidro (932 mg, 9.8 mmol) en tolueno (13 mL) se trató con trietilamina (4.7 mL, 33.4 mmol) y dietilmalonato (2.7 mL, 16.74 mmol). La mezcla de reacción se agitó a TA por 1.5 h. Finalmente, se agregó cloruro de 3-metoxi-4-nitrobenzoilo (6) (3 g, 13.9 mmol) y la mezcla de reacción se agitó a TA por 18 h. se agregó ácido clorhídrico concentrado (10 mL) y la capa orgánica se separó. Se agregaron DMSO (11.5 mL) y agua (0.5 mL) y la mezcla se calentó a reflujo por 2 h. La mezcla de reacción se dejó llegar a TA y se dividió entre agua y EtOAc. La fase orgánica se lavó subsecuentemente con solución de bicarbonato de sodio saturado y salmuera y se concentró para conseguir 2.5 g de 1-(3-metoxi-4-nitrofenil)etanona.

Etapa-3: síntesis de 1-(4-amino-3-metoxifenil)etanona

1-(3-Metoxi-4-nitrofenil)etanona (2 g, 10.25 mmol) se cargó en MeOH (30 mL). Se agregó polvo de fierro (1.72 g, 30.76 mmol) y HCl concentrado (10 mL) se agregó por goteo con estiranilo constante. La mezcla de reacción se calentó a 60 ºC por 1 h. El polvo de fierro se filtró y se concentró MeOH. Se agregó agua (10 mL) y la capa orgánica se extrajo en EtOAc (3x50 mL). La capa orgánica combinada se secó sobre sulfato de sodio anhidro y se concentró para conseguir 1.2 g de 1-(4-amino-3-metoxifenil)etanona.

Etapa-4: síntesis de N-(4-acetil-2-metoxifenil)-1,1,1-trifluormetansulfonamida

Se cargó anhídrido tríflico (0.6ml 3.6 mmol) en DCM (20 mL). La mezcla de reacción se enfrió a 0 ºC y se agregó por goteo piridina con estiranilo constante. Después de 15 min, se disolvió 1-(4-amino-3-metoxifenil)etanona (500mg, 3.03 mmol) en DCM (10 mL) y se agregó lentamente a la mezcla de reacción. La mezcla de reacción se dejó llegar a TA y la mezcla de reacción se agitó a TA por 1 h. La reacción se monitoreó por TLC. Se agregó agua (15 mL) y la capa orgánica se extrajo en DCM (3x100 mL). La capa orgánica combinada se secó sobre sulfato de sodio anhidro y se concentró para conseguir 700 mg de N-(4-acetil-2-metoxifenil)-1,1,1-trifluormetansulfonamida.

Etapa-5: síntesis de N-(4-(2-bromoacetil)-2-

metoxifenil)-1,1,1-trifluormetansulfonamida

Se cargó N-(4-Acetil-2-metoxifenil)-1,1,1-trifluormetansulfonamida (700 mg, 2.35 mmol) en cloroformo (50 mL) y la mezcla de reacción se enfrió a 0 ºC. Se agregó por goteo Bromo líquido (0.125 mL, 2.35 mmol) y la mezcla de reacción se agitó a TA por 18 h. Se agregó una solución saturada tiosulfato de sodio (20 mL) y la capa de cloroformo se aisló y se concentró bajo presión reducida para conseguir 525 mg de N-(4-(2-bromoacetil)-2-metoxifenil)-1,1,1-trifluormetansulfonamida.

Etapa-6: síntesis de 1,1,1-trifluor-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-metoxifenil)metansulfonamida

Se cargaron N-(4-(2-Bromoacetil)-3-clorofenil)metansulfonamida (50 mg, 0.133 mmol) y compuesto de 2-isobutilpiridina-4-carbotioamida (20.6 mg, 0.10 mmol) en etanol (5 mL) y la mezcla de reacción se calentó a 80 ºC por 1 h. La mezcla de reacción se concentró bajo presión reducida y se purificó a través de HPLC de fase inversa para conseguir 16 mg de 1,1,1-trifluor-N-(2-metoxi-4-{2-[2-(2-metilpropil)piridin-4-il]-1,3-tiazol-4-il}fenil)metansulfonamida. ^{1}H NMR (400 MHz, Metanol-d4) : δ (ppm): 8.56 (d, J = 5.2 Hz, 1H), 7.96 – 7.70 (m, 3H), 7.58 (d, J = 1.9 Hz, 1H), 7.48 (dd, J = 8.3, 1.9 Hz, 1H), 7.33 (dd, J = 8.3, 2.1 Hz, 2H), 3.92 (s, 3H), 2.76 (d, J = 7.3 Hz, 2H), 2.12

(td, J = 14.0, 7.2 Hz, 1H), 0.98 (d, J = 6.6 Hz, 6H). LCMS: 473.2 (M+1).

Ejemplo 7. Preparación del compuesto No. 58

Etapas 1-5: síntesis de N-(4-(2-bromoacetil)-2-metoxifenil)-1,1,1-trifluormetansulfonamida

Véase Ejemplo 6.

Etapa-6: síntesis de N-(2-metoxi-4-(2-(2-propilpiridin-4-il)tiazol-4 il)fenil)metansulfonamida:

Se cargaron N-(4-(2-Bromoacetil)-3-clorofenil)metansulfonamida (50 mg, 0.133 mmol) y 2-propilpiridina-4-carbotioamida (18 mg, 0.1 mmol) en etanol (10 mL) y la mezcla de reacción se calentó a 80 ºC por 1 h. La mezcla de reacción se concentró bajo presión reducida y se purificó a través de HPLC de fase inversa para conseguir 17 mg de N-(2-metoxi-4-(2-(2-propilpiridin-4-il)tiazol-4 il)fenil)metansulfonamida. ^{1}H NMR (400 MHz, Metanol-d4) : δ (ppm): 8.68 (d, J = 5.8 Hz, 1H), 8.28 (d, J = 5.9 Hz, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.4, 1.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 4.02 (s, 3H), 3.01 (m, 2H), 1.87 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H). LCMS: (M+1) 458.3.

Ejemplo 8. Preparación del compuesto No. 59

Etapas 1-5: síntesis de N-(4-(2-bromoacetil)-2-metoxifenil)-1,1,1-trifluormetansulfonamida

Véase Ejemplo 6.

Etapa-6: síntesis de N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-2-metoxifenil)-1,1,1-trifluormetansulfonamida

N-(4-(2-Bromoacetil)-3-clorofenil)metansulfonamida (50 mg, 0.133 mmol) y se cargaron 2-terc-butilpiridina-4-carbotioamida (20.6 mg, 0.10 mmol) en etanol (5 mL) y la mezcla de reacción se calentó a 80 ºC por 1 h. La mezcla de reacción se concentró bajo presión reducida y se purificó a través de HPLC de fase inversa para conseguir 15 mg de N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-2-metoxifenil)-1,1,1-trifluormetansulfonamida. ^{1}H NMR (400 MHz, Metanol-d4): δ (ppm): 8.61 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 3.3 Hz, 2H), 7.82 (dd, J = 5.2, 1.6 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 8.3, 1.9 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 3.98 (s, 3H), 1.45 (s, 9H). LCMS: (M+1) 472.5.

Ejemplo 9. Preparación del compuesto No. 60

Se cargaron N-(4-(2-Bromoacetil)-3-clorofenil)-1,1,1,trifluorometan sulfonamida (100 mg, 0.263 mol) y 2-bencilpiridina-4-carbotioamida (54.1 mg, 0.237 mol) en etanol (5 mL) y la mezcla de reacción se calentó a 80 °C por 1 h. Se obtiene una mezcla de reacción sólida amarilla, la cual se filtró y el residuo se lavó con éter dietílico (15 mL) para conseguir N-{4-[2-(2-bencilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluormetansulfonamida (33 mg) como un sólido marrón. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.85-8.68 (d, J = 6.2 Hz, 1H), 8.55-8.39 (m, 2H), 8.03 (d, J=8.5 Hz, 1H),

7.49 (d, J=2.3 Hz, 1H), 7.48-7.31 (m, 7H), 4.51 (s, 2H). LCMS (M+1): 510.1.

Ejemplo 10. Preparación del compuesto No. 61

Etapa-1: síntesis de 2-aminopiridina-4-carbotioamida

A una solución de 2-aminoisonicotinamida (100 mg, 0.0729 mol, 1 eq.) en piridina (3 mL), se agregó pentasulfuro de fósforo (83 mg, 0.0365 mol, 0.5 eq.). La reacción se calentó a 100 ° C por 3 h. La reacción se monitoreó por LCMS. Después del término, se concentró piridina bajo presión reducida y residuo se disolvió en agua (5 mL) y la mezcla se extrajo con EtOAc (3x15 mL). Los extractos de EtOAc combinados, se secó sobre sulfato de sodio anhidro y se concentraron bajo presión reducida para conseguir 33 mg de 2-aminopiridina-4-carbotioamida como un sólido amarillo.

Etapa-2: síntesis de cloruro de 2-cloro-4-nitrobenzoilo

A un RBF de dos cuellos (1 litro) colocado en baño de hielo, se cargó ácido 2-cloro-4-nitrobenzoico (50 g, 0.248 mol, 1 eq.). Se agregó por goteo cloruro de tionilo (110 mL, 1.51 mol, 6.1 eq.) a 0 °C. La mezcla de reacción se dejó llegar a TA y después se calentó a reflujo. El reflujo se continuó durante la noche. Se evaporó cloruro de tionilo y se agregó hielo (aprox. 150 g) en la mezcla de reacción. La masa de reacción acuosa se extrajo con DCM (2x200 mL). Los extractos DCM combinados se secaron sobre sulfato de sodio anhidro y se

concentraron bajo vacío para conseguir 50 g (91.7 %) de cloruro de 2-cloro-4-nitrobenzoilo como un líquido amarillo ligero.

Etapa-3: síntesis de 1-(2-cloro-4-nitrofenil) etanona

Una suspensión de cloruro de magnesio anhidro (47 g, 0.214 mol, 0.7 eq.) en tolueno (300 mL) se trató con trietilamina (75.04 mL, 0.535 mol, 2.5 eq.) y dietilmalonato (41.09 g, 0.257 mol, 1.2 eq.). La mezcla de reacción se agitó a TA por 1.5 h. A esto se agregó cloruro de 2-cloro-4-nitrobenzoilo (4) (47 g, 0.214 mol, 1 eq.) agregado por goteo (se observó una reacción exotérmica hasta 50 ºC durante adición). Se usó tolueno (50 mL) para transferencia completa de cloruro de 2-cloro-4-nitrobenzoilo a la mezcla de reacción. La mezcla de reacción se agitó a TA por 18 h. La reacción se monitoreó por TLC y NMR. Después de que se completó el consumo del material de partida, se agregó ácido clorhídrico concentrado (35 % en solución) (300 mL) y se separó la capa de tolueno superior. Se evaporó tolueno bajo presión reducida por debajo de 50 °C. Al residuo después de la concentración, se agregaron DMSO (200 mL) y agua (10 mL) y la mezcla se calentó a 160 °C por 12 h. La reacción se monitoreó por TLC y NMR. La mezcla de reacción se dejó llegar a TA y se agregó agua (40 mL) a la mezcla de reacción. La mezcla de reacción se extrajo con EtOAc (3x200 mL). Los extractos de EtOAc combinados se lavaron con solución de salmuera (3x300 mL) y se secó sobre

sulfato de sodio anhidro. La capa de EtOAc se concentró para conseguir 43 g (100%) de 1-(2-cloro-4-nitrofenil)etanona como un líquido amarillo el cual solidificó después de refrigeración.

Etapa-4: síntesis de 1-(4-amino-2-clorofenil) etanona

1-(2-Cloro-4-nitrofenil) etanona (126 g, 0.63 mole 1 eq.) se disolvió en MeOH (600 mL). Polvo de fierro (105.8 g, 1.89 mol, 3 eq.) se agregó a la solución. Se agregó por goteo HCl concentrado (130 mL, 1.89 mol, 3 eq.) con estiranilo constante. La mezcla de reacción después se calentó a 70 °C por 12 h. La reacción se monitoreó por TLC y NMR. La mezcla de reacción mostró presencia del material de partida. La misma cantidad de polvo de fierro y HCl concentrado se agregaron nuevamente a 70 °C y el calentamiento se continuó a 70 °C por 4 h. La mezcla de reacción nuevamente se monitoreó por TLC y NMR. Después del término de la reacción, Polvo de fierro se filtró a través de una almohadilla de celite y el MeOH filtrado se concentró. Se agregó agua (100 mL) y la mezcla de reacción se extrajo en EtOAc (5x300 mL). Los extractos de EtOAc combinados, se secó sobre sulfato de sodio anhidro y se concentraron para conseguir 100 g del producto crudo. 71 g del producto crudo se purificó a través de columna de sílice (#100-200) usando 0-20% de EtOAc:hexano como eluyente para conseguir 38.6 g (52.5 %) de 1-(4-amino-3-metoxifenil)etanona (6) como

un sólido rosa. ^{1}H NMR (400 MHz, Cloroformo-d): δ (ppm): 7.62 (d, J = 8.5 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 6.54 (dd, J =8.5, 2.3 Hz, 1H), 4.07 (s, 2H), 2.61 (s, 3H).

Etapa-5: síntesis de N-(4-acetil-3-clorofenil)-1,1,1-trifluormetansulfonamida

Una solución de anhídrido tríflico (75.1 g, 0.266 mol, 1.5 eq.) en DCM (600 mL) se enfrió a 0 °C. Piridina (21.4 mL, 0.266 mol, 1.5 eq.) se agregó por goteo con estiranilo constante durante 30 min. La mezcla de reacción se agitó a misma temperatura por 1 h. Una solución de 1-(4-amino-2-clorofenil)etanona (30 g, 0.177 mol, 1 eq.) en DCM (400 mL) se agregó por goteo manteniendo la temperatura 0 °C con estiranilo constante durante un periodo de 45 min. La mezcla de reacción después se dejó llegar a TA y se agitó por 1 h a TA. La reacción se monitoreo por TLC y NMR. Después de la terminación, se agregó agua helada (500 mL) y la capa DCM se separó. La capa acuosa nuevamente se extrajo con DCM (2x100 mL). Los extractos DCM combinados se lavaron con agua helada (2x500 mL). La capa DCM se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida por debajo de 40 °C para obtener el producto crudo. Se agregaron éter dietílico (200 mL) y pentano (600 mL) en la mezcla de reacción y se agitó por 30 min. La mezcla de reacción se filtró y el licor madre se concentró y se trituró en pentano para conseguir 28 g (52.8%) de N-(4-acetil-3-clorofenil)-1,1,1-trifluormetansulfonamida como un sólido rosa

ligero.

Etapa-6: síntesis de N-(4-(2-bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida

Una solución de N-(4-acetil-3-clorofenil)-1,1,1-trifluormetansulfonamida (21 g, 0.07 mol, 1 eq.) en cloroformo (600 mL) se enfrió a 0 °C. Bromo líquido (2.9 mL, 0.004 mol, 0.8 eq.) disuelto en cloroformo (400 mL) se agregó por goteo durante un periodo de 40 min, manteniendo la temperatura entre 0-10 °C. La mezcla de reacción se dejó llegar a TA y se agitó a TA por 18 h. La reacción se monitoreó por TLC y NMR, lo cual indicó la presencia del material de partida y compuesto deseado junto con alguna cantidad de N-(3-cloro-4-(2,2-dibromoacetil)fenil)-1,1,1-trifluormetansulfonamida (impureza dibromo). Una solución saturada tiosulfato de sodio (200 mL) se agregó y la capa de cloroformo se separó. La capa acuosa se extrajo con cloroformo (2x100 mL). La capa de cloroformo principal y los extractos de cloroformo combinados, se secó sobre sulfato de sodio anhidro y se concentraron bajo presión reducida. Un líquido claro se obtiene como un residuo. A esto se agregaron dietiléter (50 mL) y pentano (250 mL) y la mezcla se agitó por 10 min. La mezcla de reacción se filtró y licor madre se concentró. El producto crudo obtenido se trituró con pentano (~50 mL) para obtener un sólido blanco. El sólido blanco obtenido se filtró y se secó bajo vacío para conseguir 20 g de N-(4-(2-bromoacetil)-3-clorofenil)-1,1,1-

trifluormetansulfonamida con contenido aproximadamente 35% del material de partida es decir N-(4-acetil-3-clorofenil)-1,1,1-trifluormetansulfonamida por NMR. La mezcla de ambos se usó directamente en la siguiente etapa.

Etapa-7: síntesis de N-(4-(2-(2-aminopiridin-4-il)tiazol-5-il)-3-clorofenil)-1,1,1-trifluormetansulfonamida:

N-(4-(2-Bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida (50 mg, 0. 132 mmol, 1 eq.) y 2-aminopiridina-4-carbotioamida (32.8 mg, 0.132 mmol, 1 eq.) se cargaron en etanol (5 mL) y la mezcla de reacción se calentó a 80 °C por 12 h. La mezcla de reacción se concentró y se purificó por cromatografía de fase inversa para conseguir 6.8 mg de N-(4-(2-(2-aminopiridin-4-il) tiazol-5-il)-3-clorofenil)-1,1,1-trifluormetansulfonamida. ^{1}H NMR (400 MHz, Metanol-d4): δ (ppm): 8.25 (s, 1H), 8.01 – 7.89 (m, 2H), 7.55 (d, J = 1.6 Hz, 1H), 7.46 – 7.40(m, 1H), 7.33 (dd, J = 8.5, 2.2 Hz, 1H). LCMS: (M+1) 435.1.

Ejemplo 11. Preparación del compuesto No. 62

Etapas 1-7: síntesis de N-{3-cloro-4-[2-(2-metansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida

Véase Ejemplo 10.

Etapa-8: síntesis de N-(3-cloro-4-(2-(2-(metilsulfonamido)piridin-4-il)tiazol-5-il)fenil)-1,1,1-trifluormetansulfonamida

N-(4-(2-(2-Aminopiridin-4-il)tiazol-5-il)-3-clorofenil)-1,1,1-trifluoro metan sulfonamida (50 mg, 0.115 mmol, 1 eq.) se cargó en piridina (3 mL). La mezcla de reacción se enfrió a 0 ºC y cloruro de metan sulfonilo (0.01 mL, 0.115 mol, 1 eq.) se agregó por goteo con estiranilo constante. La mezcla de reacción se dejó llegar a TA y la mezcla de reacción se agitó a TA por 1 h. Piridina se evaporó y se agregó agua y la mezcla se extrajo en EtOAc (3x100 mL). La capa orgánica combinada se concentró y se purificó usando cromatografía de fase inversa para conseguir 1.3 mg de N-(3-cloro-4-(2-(2-(metilsulfonamido)piridin-4-il)tiazol-5-il)fenil)-1,1,1-trifluormetansulfonamida. ^{1}H NMR (400 MHz, Metanol-d4): δ (ppm): 8.32 (d, J = 5.6 Hz, 1H), 8.17 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.59 (dd, J = 5.6, 1.6 Hz, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.6, 2.3 Hz, 1H), 3.2 (s, 1H). LCMS: 513 (M+1).

Ejemplo 12. Preparación del compuesto No. 63

Etapas 1-6: síntesis de N-(2-metoxi-4-(2-(2-propilpiridin-4-il)tiazol-4 il)fenil)metansulfonamida:

Véase Ejemplo 7.

Etapa-7: síntesis de 1,1,1-trifluor-N-(2-hidroxi-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida

1,1,1-Trifluor-N-(2-metoxi-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida (17 mg, 0.037 mmol, 1

eq.) cargado en DCM (5 mL) y la mezcla de reacción se enfrió a 0 ºC. Se agregó por goteo Una solución 1M de tribromuro de boro (0.12 mL, 0.11mmol). La mezcla de reacción se dejó llegar a TA y se agitó a TA por 12 h. La reacción se monitoreó por LCMS. Se agregó bicarbonato de sodio saturado y la mezcla se extrajo en EtOAc (3x25 mL). La capa orgánica combinada se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida y la mezcla de reacción cruda se purificó usando HPLC de fase inversa para conseguir (1.5 mg) de 1,1,1-trifluor-N-(2-hidroxi-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida como la sal TFA. ^{1}H NMR (400 MHz, Metanol-d4): δ (ppm): 8.63 (d, J = 5.6 Hz, 1H), 8.13 – 8.00 (m, 2H), 7.63 (d, J = 1.9 Hz, 1H), 7.53 – 7.38 (m, 2H), 2.94 (t, J = 7.7 Hz, 2H), 1.84 (p, J = 7.5 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H) LCMS (M+1): 444.4.

Ejemplo 13. Preparación del compuesto No. 64

N-(4-(2-Bromoacetil)-3-clorofenil)1,1,1-trifluoro metan sulfonamida (100 mg, 0.263 mol) y 2-(3,3,3-trifluoropropil) piridina-4-carbotioamida (55.5 mg, 0.237 mol) se cargaron en etanol (5 mL) y la mezcla de reacción se calentó a 80 °C por 1h. La mezcla de reacción resultante se concentró bajo presión reducida y se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[2-(3,3,3-trifluoropropil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (27 mg) como un sólido amarillo. ^{1}H

NMR (400 MHz, Metanol-d4) δ (ppm): 8.84 (d, J = 6.2 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.52 (d, J = 6.1 Hz, 1H), 8.42 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 2.3Hz, 1H), 7.40 (d, J = 8.5Hz, 1H), 3.42 (m 2H), 2.87 (m, 2H). LCMS (M+1): 516.1.

Ejemplo 14. Preparación del compuesto No. 65

Etapas 1-5: síntesis de N-(4-(2-bromoacetil)-2-metoxifenil)-1,1,1-trifluormetansulfonamida

Véase Ejemplo 6

Etapa-6: síntesis de 1,1,1-trifluor-N-(2-metoxi-4-(2-(2-neopentilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida

N-(4-(2-Bromoacetil)-3-clorofenil)metansulfonamida (50 mg, 0.133 mmol) y 2-neopentil piridina-4-carbotioamida (50 mg, 0.10 mmol) se cargó en etanol (5 mL) y la mezcla de reacción se calentó a 80 ºC por 1 h. La mezcla de reacción se concentró bajo presión reducida y se purificó a través de HPLC de fase inversa para conseguir 14 mg de piridin-4-il)tiazol-4-il)fenil)metansulfonamida de 1,1,1-trifluor-N-(2-metoxi-4-(2-(2-neopentilo. ^{1}H NMR (400 MHz, Metanol-d4): δ (ppm): 8.71 (d, J = 5.8 Hz, 1H), 8.33 – 8.14 (m, 2H), 7.76 (d, J = 1.9 Hz, 1H), 7.68 (dd, J = 8.4, 1.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 4.01 (s, 3H), 2.95 (s, 2H), 1.06 (s, 9H). LCMS: 486 (M+1).

Ejemplo 15. Preparación del compuesto No. 66

Una solución de anhídrido tríflico (0.03ml, 0.17

mmol, 1.5 eq.) en DCM (8 mL) se enfrió a 0 °C. Se agregó piridina (0.01 mL, 0.17 mmol, 1.5 eq.) por goteo con estiranilo constante durante 30 min. Una solución de N-(4-(2-(2-aminopiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluormetansulfonamida (50 mg, 0.115 mmol, 1 eq.) en DCM (2 mL) se agregó por goteo manteniendo la temperatura a 0 °C con estiranilo constante durante un periodo de 5 min. La mezcla de reacción después se dejó llegar a TA y se agitó por 1 h a TA. La reacción se monitoreo por LCMS y NMR. Después de la terminación, se agregó agua helada (10 mL) y la capa DCM se separó. La capa acuosa nuevamente se extrajo con DCM (2x20 mL). La capa DCM se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida y se purificó usando cromatografía de fase inversa para conseguir 9.26 mg de N-{3-cloro-4-[2-(2-trifluorometansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida. ^{1}H NMR (400 MHz, Metanol-d4): δ (ppm): 8.40 – 8.22 (m, 2H), 8.06 (dd, J = 7.6, 3.6 Hz, 2H), 7.72 (dd, J =6.6, 1.7 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.6, 2.3 Hz, 1H). LCMS (M+1): 566.8.

Ejemplo 16. Preparación del compuesto No. 67

N-[4-(2-Bromotiazol-4-il)-3-cloro-fenil]-1,1,1-trifluor-metansulfonamida (300 mg, 0.71 mmol, 1 eq.), ácido [4-(piperidin-1-carbonil)fenil]borónico (233 mg, 1.4 eq.) y carbonato de sodio (189 mg, 2.5 eq. en 1 mL agua) se cargaron en 5 mL de DMF en una botella de vidrio de 25 ml y aireado con

gas nitrógeno por 7 min. Después de la adición de $Pd(PPh_3)_4$ (82.5 mg, 0.1 mmol) la mezcla se purgó adicionalmente por 3 min y se calentó a 100 °C durante la noche. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA; se agregó agua (10 mL) y la mezcla se extrajo con EtOAc (3x50 mL). La capa orgánica combinada se lavó con agua (4x50 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[4-(piperidin-1-carbonil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (207 mg) como un sólido blanco como la base libre. ^{1}H NMR (400 MHz, Cloroformo -d) δ (ppm): 7.98 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.82 (s, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 2.2 Hz, 1H), 6.98 (dd, J = 8.5, 2.3 Hz, 1H), 3.78 (s, 2H), 3.37 (s, 2H), 1.72 (s, 4H), 1.55 (s, 2H). LCMS (M+1): 530.1.

Ejemplo 17. Preparación del compuesto No. 68

Se cargaron sulfonamida de N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (200 mg, 0.4761 mmol) y 1-isopentilo-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirazol (150.9 mg, 0.5714 mmol), carbonato de sodio (100 mg, 0.952 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (55 mg, 0.0476

mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA; se agregó agua (10 mL) y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[1-(3-metilbutil)-1H-pirazol-5-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (135 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.05 (s, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 4.75 (m, 2H), 1.77 (m, J = 9.4 Hz, 2H), 1.60 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H). LCMS (M+1): 479.1.

Ejemplo 18. Preparación del compuesto No. 69

Etapa-1: síntesis de N-[3-cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil] metansulfonamida

3-Cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (506 mg, 1 mmol, 1 eq.) se suspendió en DCM (18 mL) se agregó después TEA (808 mg, 4 eq.) y se agitó por 5 min a TA. La mezcla se mantuvo a condiciones de baño de hielo y se agregó por goteo cloruro de mesilo (458 mg, 2 eq.) y se agitó por 2 h a la misma temperatura. La reacción se monitoreó por 1H-NMR. Después del término de la reacción, el solvente se evaporó para conseguir el producto deseado como un sólido el

cual se usó por la siguiente etapa sin alguna purificación adicional.

Etapa-2: síntesis de 4-(4-bromo-2-tienil)-2-terc-butil-piridina

Se cargaron 2,4-Dibromotiofeno (150 mg, 0.62 mmol), 2-terc-butil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (242 mg, 1.5 equiv) y carbonato de sodio (164 mg, 1.54 mmol, 2.5 eq. en 1.0 mL agua) en dimetil formamida (5 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 8 min. Después de la adición de $Pd(PPh_3)_4$ (35 mg, 0.05 mmol) y Xantphos (35.8 mg, 0.1 eq.), la mezcla se purgó adicionalmente por 3 min, y se calentó a 100 °C durante la noche. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA; se agregó agua (10 mL) y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener 4-(4-bromo-2-tienil)-2-terc-butil-piridina crudo, el cual se usó como tal por la siguiente etapa de síntesis sin alguna purificación adicional.

Etapa-3: síntesis de N-[4-[5-(2-terc-butil-4-piridil)-3-tienilo]-3-cloro-fenil]metansulfonamida

4-(4-Bromo-2-tienil)-2-terc-butil-piridina (170 mg, 0.576 mmol, 1 eq.), N-[3-cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil] metansulfonamida (286 mg, 1.5 eq.) y

carbonato de sodio (152 mg, 2.5 equiv) se cargaron en DMF (5 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 7 min. Después de la adición de $Pd(PPh_3)_4$ (66 mg, 0.1 mmol) la mezcla se purgó adicionalmente por 3 min y se calentó a 100 °C durante la noche. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó llegar a TA, se agregó agua (10 mL) y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{4-[5-(2-terc-butilpiridin-4-il)tiofen-3-il]-3-clorofenil}metansulfonamida (64 mg) como un sólido amarillo ligero como la sal de formiato. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.53 (d, J = 5.2 Hz, 1H), 7.99 (s, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.57 (d, J= 8.4 Hz, 1H), 7.47 (d, J = 5.2 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 8.2, 2.1 Hz, 1H), 3.07 (s, 3H), 1.36 (s, 9H). LCMS (M+1): 421.1.

Ejemplo 19. Preparación del compuesto No. 70

N-(4-(2-Bromoacetil)-3-clorofenil) 1,1,1-trifluoro metano sulfonamida (200 mg, 0.527 mol) y 2-(ciclohexilometil) piridina-4-carbotioamida (111 .2 mg, 0.475 mol) se cargaron en etanol (10 mL) y la mezcla de reacción se calentó a 80 °C por 1h. La mezcla de reacción resultante se concentró bajo presión reducida y se purificó por HPLC de fase inversa para

proporcionar N-(3-cloro-4-{2-[2-(ciclohexilometil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (45 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.75 (d, J = 6.2 Hz, 1H), 8.46-8.36 (m, 3H), 8.07 (d, j=8.5 Hz, 1H), 7.49 (d, J=2.3Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 2.98 (d, J = 7.3Hz, 2H), 1.88 (m, J = 10.9Hz, 1H), 1.76 (m 5H), 1.35 (m, 5H). LCMS (M+1): 516.1.

Ejemplo 20. Preparación del compuesto No. 71

Se cargaron sulfonamida de N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido naftalen-1-il-borónico (61.3 mg, 0.3571 mmol), carbonato de cesio (155 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(naftalen-1-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (40 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.69-8.60 (d, J = 6.2 Hz, 1H), 8.18 (s, 1H), 8.10 (d, J = 8.1 Hz,

1H), 8.04-7.96 (m, 2H), 7.92 (d, J = 7.2 Hz, 1H), 7.6 (m, 3H), 7.53 (d, J = 2.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H). LCMS (M+1): 469.0.

Ejemplo 21. Preparación del compuesto No. 72

Se cargaron sulfonamida de N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido 1H-indole-6-il-borónico (57.4 mg, 0.357mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla de reacción se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(1H-indol-6-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (43 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.10 (d, J = 6.2 Hz, 1H), 8.04 (d, J = 1.9 Hz, 1H), 7.88 (s, 1H), 7.65 (m, 2H), 7.48 (d, J = 2.2 Hz, 1H), 7.39 (m, 2H), 6.52 (d, J = 7.2 Hz, 1H). LCMS (M+1): 457.9.

Ejemplo 22. Preparación del compuesto No. 73

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-

clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido 3-(benciloxi)-4-(trifluorometil)feniloborónico (105.7 mg, 0.357 mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(4-{2-[3-(benciloxi)-4-(trifluorometil)fenil]-1,3-tiazol-4-il}-3-clorofenil)-1,1,1-trifluormetansulfonamida (10 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.06-7.94 (m, 2H), 7.91-7.80 (d, J = 1.9 Hz, 1H), 7.71-7.67 (d, J = 1.9 Hz, 1H), 7.65-7.60 (m, 1H), 7.48-7.40 (m, 3H), 7.38-7.27 (m, 4H), 3.33 (d, J = 15.4 Hz, 2H). LCMS (M+1): 593.2.

Ejemplo 23. Preparación del compuesto No. 74

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido bifenil-2-ilborónico (70 mg, 0.357 mmol), carbonato de potasio (65 mg, 0.476mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con

gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.238 mol), la mezcla se calentó a 100 °C por 18h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, se agregó agua (10 mL) y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(2-fenilofenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (18 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 7.92 (d, J =7.8 Hz, 2H), 7.72-7.59 (m, 2H), 7.57-7.47 (m, 2H), 7.43 (d, J =2.2 Hz 1H), 7.43-7.35 (m, 3H), 7.28 (m, 3H). LCMS (M+1): 495.

Ejemplo 24. Preparación del compuesto No. 75

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido isoquinolin-4-ilborónico (61.7mg, 0.357 mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio y se concentró bajo

presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(isoquinolin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (18 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 9.41 (s, 1H), 9.08 (d, J = 8.5 Hz, 1H) 8.95 (s, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.28 (s, 1H), 7.98-8.12 (m, 2H), 7.88 (m, 1H)), 7.58 (s, 1H), 7.39 (d, J = 5.5 Hz, 1H). LCMS (M+1): 469.9.

Ejemplo 25. Preparación del compuesto No. 76

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y 1-metil-4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina-2-il)piperazin (108 mg, 0.357 mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[2-(4-metilpiperazin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (54.2 mg) como un

sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.28 (d, J = 5.6 Hz, 1H), 8.19 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.67 (s, 1H), 7.52-7.43 (m, 2H), 7.38 (d, J =8.4, Hz, 1H), 4.60 (d, J =14.5 Hz, 2H), 3.67 (d, J =12.5 Hz, 2H), 3.42 (s, 2H), 3.22 (d, J =10.5 Hz, 2H), 2.99 (s, 3H). LCMS (M+1): 518.06.

Ejemplo 26. Preparación del compuesto No. 77

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y 3,5-dimetil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)isoxazol (79.6 mg, 0.357 mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(dimetil-1,2-oxazol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (3.2 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.20 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.41 (d, J =2.2 Hz, 1H), 7.32 (d, J =8.5 Hz, 1H), 2.73 (s, 3H), 2.52 (s, 3H). LCMS (M+1): 437.9.

Ejemplo 27. Preparación del compuesto No. 78

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y 4-metil-N-(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)bencensulfonamida (133 mg, 0.357 mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-[4-(2-cloro-4-trifluorometansulfonamidofenil)-1,3-tiazol-2-il]fenil}-4-metilbenzene-1-sulfonamida (35.2 mg) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.48 (s, 1H), 8.11 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.78-7.66 (m, 3H), 7.62 (d, J =7.8 Hz, 1H), 7.43-7.34 (m, 2H), 7.37-7.27 (m, 2H), 7.23 (d, J =8.0 Hz, 1H), 2.32 (s, 3H). LCMS (M+1): 588.

Ejemplo 28. Preparación del compuesto No. 79

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido (3,4-dimetoxifenil)borónico (64.9 mg, 0.3571 mmol),

carbonato de cesio (155 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(3,4-dimetoxifenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (11 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 7.70 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.90(s, 3H). LCMS (M+1): 479.0.

Ejemplo 29. Preparación del compuesto No. 80

N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380 mmol) y 1H-indole-4-il-borónico ácido (57.5 mg, 0.3571 mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) se cargaron en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100

°C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(1H-indol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (30 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.10 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.72 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.43 (t, J =2. 8 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 5.4 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H). LCMS (M+1): 457.7.

Ejemplo 30. Preparación del compuesto No. 81

Etapa-1: síntesis de 4-fluoro-2-(trifluorometil)benzamida

Una solución de 4-fluoro-2-(trifluorometil)benzonitrilo (100 mg, 0.528 mmol) en ácido sulfúrico concentrado (1.2 mL) y ácido acético glacial (0.8 mL) se calentó a 120 °C por 0.5h, se monitoreó por TLC. La reacción se diluyó con agua y la mezcla se extrajo con EtOAc (2x30 mL). La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para proporcionar 80 mg of 4-fluoro-2-(trifluorometil)benzamida como un sólido blancuzco.

Etapa-2: síntesis de 4-fluoro-2-(trifluorometil)bencencarbotioamida

Una solución de 4-fluoro-2-(trifluorometil)benzamida (500 mg, 2.414 mmol) y Reactivo de Lawesson (1.95 g, 4.821 mmol) en tolueno (30 mL) se calentó a 80 °C por 1h. El progreso de la reacción se monitoreó por TLC. La reacción se diluyó con agua (30 mL) y la mezcla se extrajo con EtOAc (2x50 mL). La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para proporcionar un producto crudo, el cual se purificó por cromatografía en columna (gel de sílice, 230-400 malla) usando 10 % de EtOAc en hexano como eluyente para obtener 100 mg de 4-fluoro-2-(trifluorometil)bencencarbotioamida como un compuesto pegajoso amarillo.

Etapa-3: síntesis de N-[3-cloro-4-[2-[4-fluoro-2-(trifluorometil)fenil]tiazol-4-il]fenil]-1,1,1-trifluor-metansulfonamida

Una solución de 4-fluoro-2-(trifluorometil)bencencarbotioamida (50 mg, 0224 mmol) y N-[4-(2-bromoacetil)-3-cloro-fenil]-1,1,1-trifluor-metansulfonamida (170 mg, 0.446 mmol) en etanol (10 mL) se calentó a 70 °C por 40 min, se monitoreó por TLC. La reacción se diluyó con solución $NaHCO_3$ saturado acuoso (25 mL) y la mezcla se extrajo con EtOAc (2x50 mL). La capa orgánica combinada se secó sobre sulfato de sodio anhidro y se concentró

bajo presión reducida para proporcionar un producto crudo, el cual se purificó por HPLC preparativa de fase inversa para obtener N-[3-cloro-4-[2-[4-fluoro-2-(trifluorometil)fenil]tiazol-4-il]fenil]-1,1,1-trifluor-metansulfonamida (22 mg) como un sólido blancuzco. ^{1}H NMR (400 MHz, Metanol-d4): δ (ppm): 7.98 (s, 1H), 7.81 (dd, J = 8.6, 5.4 Hz, 1H), 7.68 (dd, J = 8.9, 3.0 Hz, 2H), 7.53 (td, J = 8.4, 2.6 Hz 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H).

Ejemplo 31. Preparación del compuesto No. 82

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido 2,3-dihidrobenzofuran-5-borónico (58.5 mg, 0.3571 mmol), carbonato de potasio (65 mg, 0.476 mmol), dimetil formamida (5 mL), agua (0.5 mL) en un matraz de fondo redondo de 2 cuellos y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA; agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(2,3-dihidro-1-benzofuran-5-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida

(15 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 7.97 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.63 (t, J = 8.7 Hz, 2H), 2.17 (t, J = 9.3 Hz, 2H). LCMS (M+1): 460.6.

Ejemplo 32. Preparación del compuesto No. 83

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido [3-(bromometil)fenil]borónico (61.3 mg, 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se dejó enfriar a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[3-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (9 mg) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.13 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.97 – 7.79 (m, 1H), 7.51 – 7.43 (m, 2H), 7.41 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.6, 2.2 Hz, 1H), 4.59 (s, 2H). LCMS

(M+1): 448.9.

Ejemplo 33. Preparación del compuesto No. 84

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido [2-(bromometil)fenil]borónico (56 mg, 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[2-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (25 mg) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.20 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.79 – 7.71 (m, 1H), 7.54 (dd, J = 7.5, 1.3 Hz, 1H), 7.43 (dt, J = 3.7, 1.9 Hz, 2H), 7.35 (dd, J = 8.5, 2.3 Hz, 1H), 4.87 (s, 2H). LCMS (M+1): 449.1.

Ejemplo 34. Preparación del compuesto No. 85

se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y

ácido [2-(1-piperidil)-4-piridil]borónico (53 mg, 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[2-(piperidin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (56 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.23 – 8.07 (m, 2H), 7. 38 (s, 1H) 7.83 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.19 –7.09 (m, 2H), 3.62 (t, J = 5.1 Hz, 4H), 3.17 (s, 2H), 1.60 (dt, J = 9.7, 5.7 Hz, 4H). LCMS (M+1): 504.0.

Ejemplo 35. Preparación del compuesto No. 86

Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y ácido (3-metil-4-piridil)borónico (35 mg, 0. 0.261 mmol), carbonato de sodio (63 mg, 0. 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de

$Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(3-metilpiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (13 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.80 (s, 1H), 8.70 (s, 1H), 8.41 (s, 2H), 8.04 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 2.86 (s, 3H). LCMS (M+1): 434.4.

Ejemplo 36. Preparación del compuesto No. 87

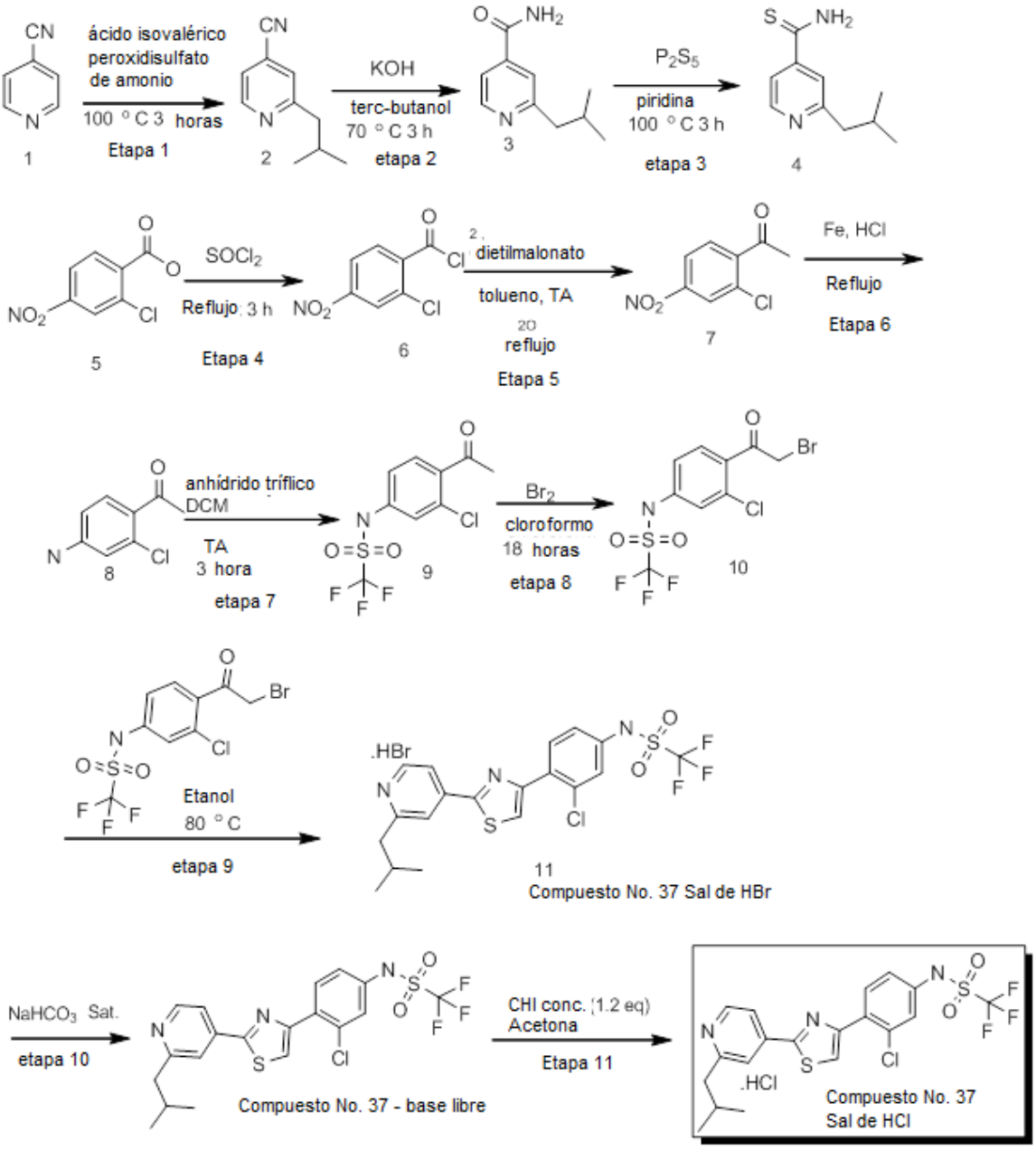
Se cargaron sulfonamida N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano (100 mg, 0.2380 mmol) y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol[2,3-b]piridina (63 mg, 0. 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, se agregó agua (10 mL) y la mezcla se

extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-[3-cloro-4-(2-{1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluormetansulfonamida (37 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.39 (d, J = 5.6 Hz, 1H), 8.29 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 3.5 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.43 – 7.33 (m, 2H). LCMS (M+1): 459.5.

Ejemplo 37. Preparación del compuesto No. 37

Se cargaron N-(4-(2-Bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida (50mg, 0.132 mmol) y 2-isobutilpiridina-4-carbotioamida (25.34 mg, 0.132mmol) en EtOH (10 mL) y la mezcla de reacción se calentó a 80 ºC por 1 h. La mezcla de reacción se concentró y se purificó a través de HPLC de fase inversa. (Proporcionando: 17 mg Sal TFA). ^{1}H NMR (Sal TFA, CD_3OD) δ (ppm): 8.73 (d, J=5.9 Hz, 1H), 8.38 (d, J=2.9 Hz, 1H), 8.31 (d, J = 6.2 Hz, 1H), 8.07 (d, J= 8.5 Hz, 1H), 7.49 (s, 1H), 7.39 (d, J=8.2 Hz, 1H), 2.94 (d, J=7.3 Hz, 2H), 2.19 (m, 2H), 1.07 (d, J=6.6 Hz, 6H).

Síntesis completa del compuesto No. 37



Etapa 1: síntesis de 2-isobutilpiridina-4-carbonitrilo (2)

A una suspensión de 4-ciano piridina **(1)** (30 g, 0.288 mol, 1 equiv.) en agua (210 mL), se concentró ácido sulfúrico (15.3 mL, 0.288 mol, 1 equiv.) se agregó por goteo manteniendo

la temperatura a 20-25 °C. Después de la formación de una solución clara, se agregaron $AgNO_3$ (4.9 g, 0.028 mmol, 0.0001 equiv.) seguido por ácido isovalérico (160 mL, 1.47 mol, 5 equiv.) en la mezcla de reacción. Se formó una solución turbia blanca. Después se agregó peroxidisulfato de amonio (66 g, 0.288 mol, 1 equiv.) disuelto en agua (90 mL). Se formó una solución clara negra. La mezcla de reacción después se calentó a reflujo a 100 °C por 3 h. La reacción se monitoreó por TLC. Después del término, la mezcla de reacción se basificó (pH = 7-8) usando una solución saturada de bicarbonato de sodio, y se extrajo con EtOAc (3x750 mL). Los extractos se combinaron y se lavaron con salmuera (3x300 mL) y se secaron sobre sulfato de sodio anhidro. La solución se concentró bajo presión reducida y el producto crudo se purificó por cromatografía en columna (gel de sílice: #100-200) usando 0-6 % de EtOAc en hexano como eluyente para proporcionar 2-isobutilpiridina-4-carbonitrilo **(2)** (15 g (32.5 % de rendimiento)) como un líquido amarillo pálido. ^{1}H NMR (400 MHz, Cloroformo -*d*): δ (ppm): 8.78 – 8.63 (m, 1H), 7.41 – 7.27 (m, 2H), 2.72 (d, *J* = 7.2 Hz, 2H), 1.35 – 1.23 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 6H).

Etapa 2: síntesis de 2-isobutilpiridina-4-carboxamida (3)

Se disolvió 2-Isobutilpiridina-4-carbonitrilo **(2)** (15 g, 0.093 mol, 1 equiv.) y KOH (15.7 g, 0.281 mol, 3 equiv.) en *terc*-butanol (160 mL). La mezcla de reacción se agitó a 70

°C por 90 min. La reacción se monitoreó por TLC. Después del término, el *terc*-butanol se removió bajo presión reducida; el residuo se disolvió en agua y se extrajo con EtOAc (3x275 mL). Los extractos se combinaron, se secaron sobre sulfato de sodio anhidro y se concentraron bajo presión reducida. El producto crudo se trituró con *n*-hexano (3x200 mL). Al residuo se agregó éter dietílico (50 mL) y después se concentró bajo presión reducida para proporcionar 2-isobutilpiridina-4-carboxamida (**3)** (13.5 g (81.3 % rendimiento)) como un sólido blanco. ^{1}H NMR (400 MHz, Cloroformo -*d*): δ (ppm): 8.68 (d, *J* = 5.1 Hz, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 5.1 Hz, 1H), 6.14(s, 1H), 5.81 (s, 1H), 2.73 (d, *J* = 7.3 Hz, 2H), 2.13 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 6H).

Etapa 3: síntesis de 2-isobutilpiridina-4-carbotioamida (4)

A una solución de 2-isobutilpiridina-4-carboxamida **(3)** (13.5 g, 0.075mol, 1 equiv.) en piridina (135 ml), se agregó P_2S_5 (8.45 g, 0.037 mol, 0.5 equiv.). La reacción se calentó a 100 °C por 3 h. El progreso de la reacción se monitoreó por TLC. Después del término, la piridina se evaporó bajo presión reducida; el residuo se disolvió en agua (100 mL) y se extrajo con EtOAc (3x250 mL). Los extractos de EtOAc combinados, se secaron sobre sulfato de sodio anhidro y se concentraron bajo presión reducida. El producto crudo obtenido se trituró con *n*-hexano (3x200 mL) para proporcionar 2-

isobutilpiridina-4-carbotioamida **(4)** (8 g (54.4 % rendimiento)) como un sólido amarillo. ^{1}H NMR (400 MHz, Cloroformo -*d*): δ (ppm): 8.62 (d, *J* = 5.1 Hz, 1H), 7.73 – 7.64 (amplio, 1H), 7.52 – 7.40 (m, 2H), 7.32 – 7.25 (m, 1H), 2.72 (d, *J* = 7.2 Hz, 2H), 2.13 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H).

Etapa 4: síntesis de cloruro de 2-cloro-4-nitrobenzoilo (6)

A un matraz de dos cuellos (1L) colocado en baño de hielo se colocó ácido 2-cloro-4-nitrobenzoico **(5)** (50 g, 0.248 mol, 1 equiv.). Se agregó por goteo cloruro de tionilo (110 ml, 1.51 mol, 6.1 equiv.) a 0 °C. La mezcla de reacción se dejó llegar a TA y después se calentó a reflujo. El calentamiento se continuó durante la noche. El cloruro de tionilo se evaporó y se agregó hielo (aprox. 150 g) a la mezcla de reacción. La mezcla de reacción acuosa se extrajo con DCM (2x200 mL). Los extractos DCM combinados se secaron sobre sulfato de sodio anhidro y se concentraron bajo vacío para conseguir cloruro de 2-cloro-4-nitrobenzoilo **(6)** (50 g (91.7 % rendimiento)) como un líquido amarillo ligero. ^{1}H NMR (400 MHz, Cloroformo -*d*): δ (ppm): 8.37 (d, *J* = 2.2 Hz, 1H), 8.25 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H).

Etapa 5: síntesis de 1-(2-cloro-4-nitrofenil)etanona (7)

Una suspensión de cloruro de magnesio anhidro (47 g, 0.214 mol, 0.7 equiv.) en tolueno (300 mL) se trató con

trietilamina (75.04 mL, 0.535 mol, 2.5 equiv.) y dietilmalonato (41.09 g, 0.257 mol, 1.2 equiv.). La mezcla de reacción se agitó a TA por 1.5 h. A esto se agregó cloruro de 2-cloro-4-nitrobenzoilo **(6)** (47 g, 0.214 mol, 1 equiv.) por goteo (una reacción exotérmica hasta 50 °C se observó durante adición). Se usó tolueno (50 mL) para transferencia completa de cloruro de 2-cloro-4-nitrobenzoilo a la mezcla de reacción. La mezcla de reacción se agitó a TA por 18 h. La reacción se monitoreó por TLC y NMR. Después de que se completó el consumo del material de partida, se agregó ácido clorhídrico concentrado (35 % solución) (300 mL) y la capa de tolueno superior se separó. El tolueno se evaporó bajo presión reducida por debajo de 50 °C. Al residuo se agregaron DMSO (200 mL) y agua (10 mL), y la mezcla se calentó a 160 °C por 12 h. La reacción se monitoreó por TLC y NMR. La mezcla de reacción se dejó llegar a TA y se agregó agua (40 mL). La mezcla de reacción se extrajo con EtOAc (3x200 mL). Los extractos de EtOAc se combinaron y se lavaron con solución de salmuera (3x300 mL) y se secaron sobre sulfato de sodio anhidro. La capa de EtOAc se concentró para conseguir 1-(2-cloro-4-nitrofenil)etanona **(7)** (43 g (84 % rendimiento)) como un líquido amarillo el cual solidificó después de refrigeración. ^{1}H NMR (400 MHz, Cloroformo -*d*): δ (ppm): 8.29 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.65 (d, *J* =8.4 Hz, 1H), 2.66 (s, 3H).

Etapa 6: síntesis de 1-(4-amino-2-clorofenil)

etanona (8)

1-(2-Cloro-4-nitrofenil)etanona (87.8 g, 0.43 mol, 1 equiv.) se cargó en metanol (600 mL). La mezcla de reacción se calentó a 70 °C y se agregó por goteo HCl concentrado (131 mL, 1.29 mol, 3 equiv.) con estiranilo constante. Después del término de la adición, se agregó polvo de fierro (98.2 g, 1.75 mol, 4 equiv.) en cuatro partes a intervalos de 5 minutos. La mezcla de reacción se calentó a 70 °C por 7 h y la reacción se monitoreó por TLC y NMR. Después del término de la reacción, la mezcla se dejó llegar a TA y después se filtró a través de una almohadilla de celite. Lo filtrado se concentró bajo presión reducida y la almohadilla de celite se lavó con EtOAc para obtener producto crudo adicional. Ambas porciones se combinaron y se agregó agua (200 mL). La capa de EtOAc se separó y la capa acuosa se extrajo con EtOAc (2x500 mL). La capa orgánica combinada se secó sobre sulfato de sodio anhidro y se concentró para conseguir el producto crudo (57 g). Este producto crudo se hizo precipitar en pentano para conseguir 1-(4-amino-3-metoxifenil)etanona (**8**) (50g (67 % rendimiento)) como un sólido rosa. ^{1}H NMR (400 MHz, Cloroformo -*d*): δ (ppm): 7.62 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.54 (dd, *J* =8.5, 2.3 Hz, 1H), 4.07 (s, 2H), 2.61 (s, 3H).

Etapa 7: síntesis de N-(4-acetil-3-clorofenil)-1,1,1-trifluormetansulfonamida (9)

Una solución de anhídrido tríflico (75.1 g, 0.266

mol, 1.5 equiv.) en DCM (600 mL) se enfrió a 0 °C. Se agregó piridina (23.4 mL, 0.266 mol, 1.5 equiv.) por goteo con estiranilo constante durante 30 min. La mezcla de reacción se agitó a la misma temperatura por 1 h. Una solución de 1-(4-amino-2-clorofenil)etanona **(8)** (30 g, 0.177 mol, 1 equiv.) en DCM (400 mL) se agregó por goteo manteniendo la temperatura a 0 °C con estiranilo constante durante un periodo de 45 min. La mezcla de reacción después se dejó llegar a TA y se agitó por 1 h a TA. La reacción se monitoreó por TLC y NMR. Después de la terminación, se agregó agua enfriada con hielo (500 mL) y la capa DCM se separó. La capa acuosa nuevamente se extrajo con DCM (2x100 mL). Los extractos DCM combinados se lavaron con agua enfriada con hielo (2x500 mL). La capa DCM se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida por debajo de 40 °C para obtener el producto crudo. Se agregaron éter dietílico (200 mL) y pentano (600 mL) a la mezcla la cual después se agitó por 30 min. La mezcla se filtró y lo filtrado se concentró y se trituró en pentano para conseguir N-(4-acetil-3-clorofenil)-1,1,1-trifluormetansulfonamida **(9)** (28 g (52.8% rendimiento)) como un sólido rosa ligero. ^{1}H NMR (400 MHz, Cloroformo -*d*): δ (ppm): 7.63 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.28 – 7.21(m, 1H), 2.66 (s, 3H).

Etapa 8: síntesis de N-(4-(2-bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida (10)

Una solución de N-(4-acetil-3-clorofenil)-1,1,1-trifluormetansulfonamida **(9)** (21 g, 0.07 mol, 1 equiv.) en cloroformo (600 mL) se enfrió a 0 °C. Se agregó por goteo bromo líquido (2.9 mL, 0.004 mol, 0.8 equiv.) disuelto en cloroformo (400 mL) durante un periodo de 40 min, manteniendo la temperatura de reacción entre 0-10 °C. La mezcla se dejó llegar a TA y después se agitó a TA por 18 h. La reacción se monitoreó por TLC y NMR. Existe una indicación de la presencia del material de partida y compuesto deseado junto con alguna cantidad de N-(3-cloro-4-(2,2-dibromoacetil)fenil)-1,1,1-trifluormetansulfonamida (impureza de dibromo). Una solución saturada de tiosulfato de sodio (200 mL) se agregó y la capa de cloroformo se separó. La capa acuosa se extrajo con cloroformo (2x100 mL). La capa de cloroformo principal y los extractos de cloroformo se combinaron, se secaron sobre sulfato de sodio anhidro y se concentraron bajo presión reducida. Un líquido claro se obtiene como el residuo. A esto se agregaron dietiléter (50 mL) y pentano (250 mL) y la mezcla se agitó por 10 min. La mezcla de reacción se filtró y lo filtrado se concentró. El producto crudo obtenido se trituró con pentano (~50 mL) para obtener un sólido blanco. Este sólido blanco se filtró y se secó bajo vacío para conseguir N-(4-(2-bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida **(10)** (20 g) tal contenido aproximadamente 35% del material de partida es decir N-(4-acetil-3-clorofenil)-1,1,1-

trifluormetansulfonamida **(9)** por NMR. La mezcla de los productos se usó directamente por la siguiente etapa sin alguna purificación adicional. ^{1}H NMR (400 MHz, Cloroformo-*d*): δ (ppm): 7.64 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.30 –7.27 (m, 1H), 4.51 (s, 2H).

Etapa 9: síntesis de N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluormetansulfonamida (11)

Se cargaron N-(4-(2-Bromoacetil)-3-clorofenil)-1,1,1-trifluormetansulfonamida **(10)** (15.5 g, 0.041 mol, 1 equiv.) y 2-isobutilpiridina-4-carbotioamida (5.2 g, 0.027 mol, 0.65 equiv.) en etanol (40 mL) y la mezcla de reacción se calentó a 80 °C por 30 min. La mezcla de reacción se enfrió en un baño de hielo y se agitó a 0 °C por 30 min. Lo sólido obtenido se aisló por filtración y se lavó con etanol frío (2x5 mL). Lo sólido obtenido se secó bajo vacío para conseguir N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluormetansulfonamida **(11)** (10.2 g (53.6% rendimiento)) como la sal de bromhidrato. ^{1}H NMR (400 MHz, Metanol-*d*4): δ (ppm): 8.80 (d, *J* = 6.3 Hz, 1H), 8.57 – 8.45 (m, 3H), 8.08 (d, *J* = 8.5 Hz, 1H),7.50 (d, *J* = 2.2 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.01 (d, *J* = 7.4 Hz, 2H), 2.21 (m,1H), 1.06 (d, *J* = 6.6 Hz, 6H). UPLC: En el método, Columna Tipo: ACQUITY BEH SHIELD C18, Columna ID:2.1*50 mm, 1.7µ; Velocidad de flujo - 0.35 mL/min, Fase móvil A: 0.05% de TFA;

Fase móvil B: acetonitrilo. Gradiente: 10% B a 50% B en 1min., mantenido por 0.5 min, 50% B a 90% B en 0.1 min, mantenido por 1 min, 90% B a 10% B in 0.4 min compuesto eluido al momento de la retención de 2.66 min.

Etapa 10: síntesis de N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluormetansulfonamida - base libre (12)

sal bromhidrato de N-(3-Cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluormetansulfonamida (**11**) (88.5. g) se cargó en un matraz y una solución saturada de bicarbonato de sodio (300 mL) se agregó de manera que el pH llegó a ser ligeramente básico (pH=7-8). Se agregó EtOAc (3x500 mL) y la mezcla de reacción se agitó a TA hasta que la mezcla llegó a ser clara. La capa orgánica se separó y se lavó con agua (50 mL). La capa de EtOAc se secó sobre sulfato de sodio anhidro y se concentró para conseguir N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluormetansulfonamida (**12**) (46.3g (61% rendimiento)) como la base libre. ^{1}H NMR (400 MHz, Metanol-d): δ (ppm): 8.56 (d, J = 5.3 Hz, 1H), 8.10 (s , 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.92 – 7.80 (m, 2H), 7.44 (d, J= 2.2 Hz, 1H), 7.31 (dd, J = 8.5, 2.3 Hz, 1H), 3.06 (s , 3H), 2.86 (dd, J = 8.6, 6.7 Hz, 2H), 1.88 – 1.74 (m, 2H), 1.01 (t, J = 7.4 Hz,3H).

Etapa 11: síntesis de Clorhidrato de N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-

trifluormetansulfonamida (13)

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il) fenil)-1,1,1-trifluormetansulfonamida - base libre (**12**) (46.4 g, 0.097 mol, 1 equiv.) se cargó en acetona (1.5 L) y se agitó a TA por 5-10 min hasta que se obtiene una solución clara. Se agregó por goteo una solución de ácido clorhídrico concentrado [~35% v/v] (13.3 mL, 0.126 mol, 1.3 equiv.) en acetona (85 mL) con estiranilo constante. Después de la adición, el pH de la mezcla de reacción fue 1-2. La mezcla de reacción se agitó por 30 min a TA. Lo sólido obtenido se filtró bajo vacío y se lavaron con acetona (3x100 mL) (el lavado se realizó sin vacío y una vez que la acetona se absorbió por lo sólido, el solvente se removió por filtración a vacío). El lavado se repitió hasta que lo filtrado fue incoloro. Lo sólido amarillo ligero obtenido se secó a 50 °C bajo presión reducida por 2 h para conseguir N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluormetansulfonamida - sal clorhidrato de (13) (44 g (88 % rendimiento)). ^{1}H NMR (400 MHz, Metanol-*d*4): δ (ppm): 8.81 (d, *J* = 6.3 Hz, 1H), 8.58 – 8.45 (m, 3H), 8.08 (d, *J* = 8.5 Hz,1H), 7.49 (t, *J* = 2.8 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.4 Hz, 1H), 3.02 (d, *J* = 7.3 Hz, 2H), 2.22 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 6H). Punto de fusión: 165 °C – 173 °C (FB). LCMS – (M+1):475.9 (99.5%). En el método, Tipo de Columna: HIPERSILGOLD, C18, Columna_ID: 4.6*50 mm, 5µ; Fase móvil A: 0.05% ácido fórmico en H_2O; Fase móvil B: 0.01% ácido

fórmico en acetonitrilo. Gradiente: 10% B a 90% B desde 0.2 a 2 min, mantenido por 2.5 min, 10%B en 0.1 min. Flujo: 0.7 mL/min. El compuesto deseado tiene TA de 4.514 min. UPLC – En el método, Tipo de Columna: ACQUITY BEH C18; Columna ID: 2.1*50 mm, 1.7µ; Velocidad de flujo: 0.35 mL/min. Fase móvil A: 0.05% TFA de Fase móvil B: Acetonitrilo, Gradiente: 10% B a 90% B en 2.5 min, mantenido por 1 min, 90% B a 10% B en 0.3 min. El compuesto deseado tiene TA de 2.793 min. Punto de fusión: 220 °C - 227 °C (Sal de clorhidrato).

Ejemplo 38. Preparación del compuesto No. 88

Se cargaron N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380 mmol) y ácido [3-(1-piperidil)fenil]borónico (53 mg, 0. 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de Pd-acetato (8 mg, 0.035 mmol) y xantphos (27.5 mg, .0476 mmol), la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[3-(piperidin-1-il)fenil]-1,3-tiazol-4-

il}fenil)-1,1,1-trifluormetansulfonamida (25 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.23 (s, 1H), 8.11 – 7.94 (m, 3H), 7.71 – 7.59 (m, 2H), 7.47 (d, J = 2.2 Hz, 1H), 7.37 (dd, J = 8.6, 2.2 Hz, 1H), 3.63 (t, J = 5.5 Hz, 4H), 2.01 (q, J = 6.2 Hz, 4H), 1.80 (q, J = 6.0 Hz, 2H). LCMS (M+1): 502.5.

Ejemplo 39. Preparación del compuesto No. 89

Se cargaron N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380 mmol) y [5-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirrol[2,3-b]piridin-1-il]-triisopropil-silano (109 mg, 0. 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-[3-cloro-4-(2-{5-fluoro-1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluormetansulfonamida (35 mg) como un sólido de color blanco. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 12.10 (s, 1H), 8.43

(d, J = 2.2 Hz, 2H), 8.08 (d, J = 8.5 Hz, 1H), 7.74 (t, J = 3.0 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.45 – 7.36 (m, 2H). LCMS (M+1): 477.1.

Ejemplo 40. Preparación del compuesto No. 90

Se cargaron N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380mmol) y ácido benzotiofen-3-ilborónico (47 mg, 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{4-[2-(1-benzotiofen-3-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluormetansulfonamida (59 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.80 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.99 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.51 – 7.43 (m, 2H), 7.38 (dd, J = 8.6, 2.3 Hz, 1H). LCMS (M+1): 475.

Ejemplo 41. Preparación del compuesto No. 91

Se cargaron N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380 mmol) y 1-[[5-fluoro-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]metil]pirrolidina (80 mg, 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[4-fluoro-2-(pirrolidin-1-ilmetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (80 mg) como un sólido rojo pálido. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.11 (dd, J = 8.7, 5.4 Hz, 1H), 7.98 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.56 (dd, J = 9.0, 2.7 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.33 (dd, J = 8.4, 2.2 Hz, 1H), 4.61 (s, 2H), 3.43 (t, 2H), 3.25 (t, 2H), 2.17 (m, 2H), 1.97 (m, 2H). LCMS (M+1): 521.4.

Ejemplo 42. Preparación del compuesto No. 92

Se cargaron N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380 mmol) y N-

ciclopentil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-3-amina (76 mg, 0. 0.261 mmol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA; se agregó agua (10 mL) y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-(3-cloro-4-{2-[2-(ciclopentilamino)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluormetansulfonamida (96 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.25 (s, 1H), 7.94 (dd, J = 14.6, 7.6 Hz, 2H), 7.57 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.38 – 7.29 (m, 1H), 4.11 (q, J = 6.1 Hz, 1H), 2.14 (dt, J = 13.2, 6.4 Hz, 2H), 1.84 (dt, J = 6.6 Hz, 2H), 1.71 (tt, J = 24.6, 11.7, 6.0 Hz, 4H). LCMS (M+1): 503.8.

Ejemplo 43. Preparación del compuesto No. 93

Se cargaron N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380 mmol) y 3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-indole (64 mg, 0.261 mmol), carbonato de sodio (63 mg, 0.595), dimetil

formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó adicionalmente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla de reacción se enfrió a TA, agua (10 mL) se agregó y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio y se concentró bajo presión reducida para obtener el producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-{3-cloro-4-[2-(1H-indol-3-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluormetansulfonamida (42 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 8.24 – 8.19 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.50 – 7.45 (m, 2H), 7.36 (dd, J = 8.5, 2.3 Hz, 1H), 7.26 – 7.20 (m, 2H). LCMS (M+1): 458.3.

Ejemplo 44. Preparación del compuesto No. 94

Se cargaron N-(4-(2-Bromotiazol-4-il)-3-clorofenil)-1,1,1-trifluorometano sulfonamida (100 mg, 0.2380 mmol) y ácido 4-quinolil borónico (61.7 mg, 0.3571 mol), carbonato de sodio (63 mg, 0.595 mmol), dimetil formamida (4 mL), agua (1.0 mL) en una botella de vidrio de 25 ml y aireado con gas nitrógeno por 5 min. Después de la adición de $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) la mezcla se purgó nuevamente por 2 min y se calentó a 100 °C por 18 h. La reacción se monitoreó por LCMS. La mezcla

de reacción se dejó enfriar a TA, se agregó agua (10 mL) y la mezcla se extrajo con EtOAc (3x25 mL). La capa orgánica combinada se lavó con agua (4x30 mL), se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para obtener un producto crudo, el cual se purificó por HPLC de fase inversa para proporcionar N-[3-cloro-4-[2-(4-quinolil)tiazol-4-il]fenil]-1,1,1-trifluor-metansulfonamida (37 mg) como un sólido blanco. ^{1}H NMR (400 MHz, Metanol-d4) δ (ppm): 7.94 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.46 – 7.38 (m, 4H), 7.31 (dd, J = 8.5, 2.3 Hz, 2H), 6.16 (s, 1H), 5.64 (s, 1H). LCMS (M+1): 445.3

Ejemplo 45. Preparación de los Compuestos Nos. 6-36, 38-56, y 95-152

Los Compuestos nos. 6-36, 38-56, y 95-152 se pueden preparar usando la condición análoga a aquellos en tanto los Métodos Generales como Ejemplos proporcionados anteriormente.

Ejemplo B1. Efecto de los Compuestos en el Desdoblamiento y Viabilidad Celular de SREBP2 en Células HepG2.

Se midió el desdoblamiento de SREBP2 en células HepG2 en la presencia de los compuestos descritos en la Tabla 1. Las células HepG2 se sembraron a 500,000 células por cavidad en placas de 6 pocillos en DMEM suplementado con 10% de FBS. Después de 2 días, las células se trataron con los compuestos (20 µM) por 1 día en DMEM sin FBS. Los manchados Western se normalizaron con respecto a la actina.

Para mediciones de viabilidad, las células HepG2 se sembraron a 5,000 células por pocillo en placas de 96 pocillos en DMEM suplementado con 10% de FBS. Después de 1 día de cultivo, las células se trataron con los compuestos (20 µM y 5 µM) por 3 días en DMEM sin FBS. La viabilidad se midió por MTS. El tratamiento con los compuestos (20µM y 5 µM) se llevó a cabo en medio sin FBV, y la viabilidad se midió por MTS.

Los resultados se muestran en la Tabla 3 como porcentaje de inhibición @ 20 µM, y en la Tabla 4 como porcentaje de inhibición @ 5 µM.

Tabla 3 (20 µM)

Compuesto No.	**Desdoblamiento de SREBP2 promedio (% de Inhibición, n=3)**	**Viabilidad Promedio (% de Inhibición, n=3)**
1	73.7	92.07
2	73	80.5
4	96.07	94.38
5	81.7	99.2
37	94.59	95.03
57	46.9	56.4
58	29.4	67.9
59	60.6	99.8
60	99.0	100.0
61	2.0	43.0

Tabla 3 (20 µM)		
Compuesto No.	**Desdoblamiento de SREBP2 promedio (% de Inhibición, n=3)**	**Viabilidad Promedio (% de Inhibición, n=3)**
62	0.0	0.0
63	39.0	47.0
64	97.0	100.0
66	0.0	11.0
67	3.0	20.0

Tabla 4 (5 µM)		
Compuesto No.	**Desdoblamiento de SREBP2 promedio (% de Inhibición, n=3)**	**Viabilidad Promedio (% de Inhibición, n=3)**
37	75	94
70	73	100
71	77	97
72	61	94
73	64	99
74	76	97
75	55	88
76	7	3
77	56	41
78	38	87
79	65	74
80	90	86
81	44	88
82	77	82

Tabla 4 (5 µM)		
Compuesto No.	**Desdoblamiento de SREBP2 promedio (% de Inhibición, n=3)**	**Viabilidad Promedio (% de Inhibición, n=3)**
83	2	0
84	20	18
85	82	93
86	54	27
87	50	9
88	90	19
89	53	5100
90	64	99
91	16	4
92	59	94
93	28	82
94	35	84
95	39	86

El Compuesto #37 fue probado además a varias concentraciones para obtener una IC_{50} para el desdoblamiento de SREBP2 de 4.6 µM y Viabilidad de 2.15 µM, como se muestra en la **Figura 1**.

Ejemplo B2. Efecto de los compuestos en un injerto heterólogo LnCap humano.

Se inocularon células LnCap en ratones desnudos macho. Los animales se aleatorizaron en grupos de 3 tratamientos (n=10 por grupo) cuando el tamaño del tumor alcanzó 100mm^3. Un grupo se trató por alimentación forzada oral con la solución del vehículo dos veces al día; y otro grupo se

trató a 40 mg/kg/po/dos veces al día del compuesto #37. El volumen de tumor se midió por mediciones de calibre dos veces a la semana durante el curso del experimento (4 semanas). Los resultados se muestran en la **Figura 2**.

Ejemplo B3. Efecto de los compuestos en varias líneas de células

Citotoxicidad y determinación de IC_{50}

Plaqueo celular: se cultivaron células en medio con 10% de FBS regular, las células se recolectaron respectivamente durante el periodo de crecimiento logarítmico y se contaron usando Countstar. Las células se dividieron en dos series: una serie se cultivó en medio + 5% de FBS regular y la otra serie se cultivó en medio + 5% de LDFBS (FBS reducida en lípido). Las concentraciones celulares se ajustaron a 2.22×104 células/mL con medio de cultivo respectivo por 3 días de ensayo CGT. (La densidad celular se optimizó antes del estudio actual; la densidad celular usada en la prueba puede variar para diferentes líneas de células). Para cada condición de suero, 90 µl de suspensiones celulares se agregaron a dos placas de 96 pocillos (placa A y B), con la densidad celular final de 2×103 células/pocillo por 3 días de ensayo CTG (La densidad celular se optimizó antes del estudio actual; la densidad celular usada en la prueba puede variar por diferentes líneas de células). 10 µl de medio de cultivo se agregaron a cada cavidad del grupo de placa A para 10 lecturas. Todas las placas

se incubaron (grupos A y B) durante la noche en incubadora humidificada a 37°C con 5% de CO2.

Día 0: lectura T0: Para el grupo de placa A, se agregó reactivo CellTiter-Glo® a un volumen igual de medio de cultivo celular presente en cada pocillo (por ejemplo, se agregaron 100µl de reactivo a 100µl de medio que contiene células para una placa de 96 pocillos). Los contenidos se mezclaron por 2 min en un sacudidor orbital para facilitar la lisis celular. La placa se dejó incubar a TA por 10 min para estabilizar la señal luminiscente. Nota: la señal luminiscente desigual dentro de placas estándares puede ser causada por gradientes de temperatura, sembrado desigual de células o efectos de borde en placas de paredes múltiples. Una etiqueta negra de sello posterior se fijó al fondo de cada placa. La luminiscencia se registró (T0) usando el Lector de Etiqueta Múltiple EnVision.

Día 0: tratamiento del compuesto: Los compuestos de prueba y controles positivos se disolvieron con PBS como solución de base a la concentración indicada en el mapa de Dilución de Artículo de Prueba. Se preparó una solución 500× en DMSO, después se diluyó con medio de cultivo apropiado (1:50) en soluciones de trabajo 10×. 10µl (10×) de soluciones de fármaco se dispensaron en cada pocillo (triplicado para cada concentración de fármaco) del grupo de placa B de conformidad con el mapa de inoculación de placa. Las placas de prueba se

incubaron por 3 días en la incubadora humidificada a 37°C con 5% de CO2.

Día 3: Lectura del grupo de Placa B. Se agregó reactivo CellTiter-Glo® a un volumen igual de medio de cultivo celular presente en cada pocillo (por ejemplo, se agregaron 100µl de reactivo a 100µl de medio que contiene células para una placa de 96 pocillos). Los contenidos se mezclaron por 2 min en un sacudidor orbital para inducir la lisis celular. La placa se dejó incubar a TA por 10 min para estabilizar la señal luminiscente. Nota: la señal luminiscente desigual dentro de placas estándares puede ser causada por gradientes de temperatura, sembrado desigual de células o efectos de borde en placas de paredes múltiples. Una etiqueta negra de sello posterior se fijó al fondo de cada placa. Se registró la luminiscencia usando el Lector de Etiqueta Múltiple EnVision. Se calcularon los valores IC_{50} para cada compuesto para cada línea celular. Los resultados se muestran en la **Figura 3** para el compuesto #37.

Ejemplo B4. Datos de PK para compuestos representativo.

Se recolectaron parámetros de PK estándares en Ratón y Perro para el compuesto #37 en ratón (**Figura 4A**) y perro (**Figura 4B**). Se recolectaron los datos para los compuestos adicionales y se presentan en la Tabla B4:

Tabla B4: Parámetros de PK para compuestos

representativos

Comp. No.	i.v. @ 2 mg/kg					p.o. @ 10 mg/kg				Biodisponibilidad
	Cmáx (µM)	$AUC_{mínima}$ (µM*h)	Terminal $t_{1/2}$ (h)	CL (L/h/kg)	V_d (L/kg)	$C_{máx}$ (µM)	$T_{máx}$ (h)	$AUC_{mínimo}$ (µM*h)	Terminal $t_{1/2}$ (h)	
5	10.2	41	2.51	0.095	0.345	20.3	1	302	6.96	149.0%
60	3.38	12.6	3.08	0.288	1.28	6.58	4	57.1	>8hrs	90.20%
64	7.13	38.5		0.055	1.95	32.1	24	526	>8hrs	273%
70	4	2.2	1.1	3.28	5.22	2.2	0.5	5.19	1.04	46.4%
71	3.57	13.6	3.5	0.251	1.27	7.57	4	51.5	>8hrs	75.9%
80	3.63	8.94	2.8	4.25	1.72	20.6	4	130	>8hrs	291.0%
82	12.6	25.4	3.64	0.137	0.719	25.8	4	175	>8hrs	138.0%
85	0.241	0.655	4.08	4.63	27.3	0.45	2	2.27	>8hrs	69.3%
88	3.44	10.6	3.35	0.3	1.45	8.41	2	51.5	>8hrs	96.8%

Ejemplo B5. Efecto de los compuestos en un injerto heterólogo MDA-MB-453 *in vivo* humano

Línea celular: La línea de células de cáncer de mama humano MD-MB-453 se adquirió de ATCC (Manassas, VA). Las células se hicieron crecer a $C0_2$ atmosférico en medio L-14 que contiene 10% de suero bovino fetal, penicilina estreptomicina, L-glutamina, y piruvato de sodio. Las células se centrifugaron y se resuspendieron a una concentración de 6.0E07 células/mL en medio libre de suero sin aditivos, después se combinaron 1:1 con Matrigel™ (Trevigen, Gaithersburg, MD).

Implante quirúrgico de pelotillas DHT: Una semana después de la castración, los animales se anesteziaron con una mezcla de isoflurano y oxígeno y el área quirúrgica se esterilizó usando yodo y alcohol. Cada animal se implantó con

12.5 mg de pelotillas de 5α-DHT de 60-de liberación lenta (Innovative Research of America, Sarasota, FL) en el lado lateral del cuello entre el oído y el hombro. La piel se cerrón con una sutura de seda de 6-0.

Inyección de células ortotópicas: Dos días después del implante de la pelotilla, los ratones se inocularon por inyección por debajo del pezón de la almohadilla de grasa mamaria número 4 con 200µL (células 6.0E06) por ratón de la mezcla MD-MB-453:Matrigel recientemente preparada. Todos los procedimientos se llevaron a cabo en campanas de flujo laminar filtradas con HEPA.

Diseño de estudio: Cuando los tumores alcanzaron un volumen medio de aproximadamente 100 mm^3, sesenta animales con tumores establecidos y pesos corporales moderados se aleatorizaron en 6 grupos de tratamiento (Grupo 1-6, n=10 ratones cada uno). El Grupo 1 se trató una vez diariamente con vehículo (20% de HPBCD). Los Grupos 2 a 5 se trataron una vez diariamente con el Compuesto #37 con (respectivamente) 1, 3, 10, o 30 mg/kg. El Grupo 6 se trató dos veces diariamente (a intervalos de ~8-10 h) con el Compuesto #37 a 10 mg/kg. Todos los tratamientos se administraron como alimentación forzada oral (PO) a un volumen de dosis de 5 mL/kg. Las dosis se administraron partiendo al día de estadificación y se continuó por 42 días (Días 0-41).

El volumen del tumor se midió por mediciones de

calibre dos veces a la semana durante el curso del experimento (4 semanas). Los resultados se muestran en la **Figura 5**.

Ejemplo B6. Efecto de los compuestos en un injerto heterólogo de adenocarcinoma de próstata humano LnCAP *in vivo*.

Se realizó un estudio de eficacia del compuesto #37 en Injerto Heterólogo de Cáncer LnCap en ratones SCID por MuriGenics, Inc.

Animales experimentales: Noventa y cinco ratones macho Beige con deficiencia severa inmune combinada (SCID) se adquirieron de Charles River (Hollister, CA) como ratones de 6- a 7- semanas de edad. Después de la llegada, los animales se pesaron usando una báscula electrónica (Ohaus SCOUT® PRO, Parsippany, NJ), dando una examinación clínica para asegurarse que los animales estuvieran en buenas condiciones, y se alojaron 5 por jaula. Los animales se mantuvieron en un ambiente filtrado con HEPA en un sistema de alojamiento de roedor de ventilación completa del Sistema de Jaulas Modulares para Animales (MACS) (Alternative Design, Arkansas). Los controles de las sales de animales se ajustaron para mantener la temperatura y humedad relativa a 22 °C ± 4 °C y 50% ± 20%, respectivamente. Las sales de alojamiento fueron en un ciclo de 12:12 luz/oscuridad. Las jaulas fueron sometidas a autoclave. El agua se sometió a autoclave y se suministró a albedrío a cada jaula mediante botellas de agua. SE IRRADIÓ 16% de dieta de proteína de roedor de 2016 Teklad Global y los

lechos irradiados con SaniChip 7090A se obtuvieron de Harlan Teklad (Hayward, CA).

Formulación del Compuesto: Las suspensiones de dosis del compuesto #37 se formularon en 20% de HPCD a 5.0, 15.0, 50.0, y 150 mg/mL (para administración a 1, 3, 10, y 30 mg/kg (mg/kg), respectivamente). Específicamente, el vehículo se dispensó en un vial que contiene una cantidad medida de polvo de artículo de prueba y el vial se sometió a vórtices y se sonicó hasta que el artículo de prueba se suspendió completamente, aproximadamente 5-15 minutos. Los contenidos del vial entonces se llevaron al volumen requerido con vehículo adicional, y la solución se sometió a vórtices y se sonicó por unos 2-5 minutos adicionales. Las suspensiones de dosificación (artículo de prueba en 20% de HPCD) se prepararon recientemente y se usaron dentro de una hora de la formulación.

Línea celular: La línea de células de cáncer de adenoma de próstata humano LnCaP se adquirió de ATCC (Manassas, VA). Las células se hicieron crecer en 1640 RPMI que contiene 10% de suero bovino fetal. Las células se centrifugaron y se resuspendieron a una concentración de 5.0E07 células/mL en medio libre de suero sin aditivos, después se combinaron 1:1 con Matrigel™ (Trevigen, Gaithersburg, MD).

Inyección de células: A aproximadamente 5 semanas antes del inicio proyectado de la dosificación, cada ratón se implantó, bajo anestesia de isoflurano, por inyección en el

flanco izquierdo con 200 µL (5.0E06 células) por ratón de la mezcla LnCaP:Matrigel recientemente preparada (50:50). Todos los procedimientos se llevaron a cabo en campanas de flujo laminar filtradas con HEPA.

Diseño de Estudio: El diseño de estudio y tratamientos de todos los grupos se muestran en B6.

Tabla B6. Diseño de Estudio

Grupo	Fase de Tratamiento (Días 0-39)			
	Agente	Dosis (mg/kg, PO)	Frecuencia	n
1	Vehículo	0	QD	10
2	Compuesto #37	1	QD	10
3	Compuesto #37	3	QD	10
4	Compuesto #37	10	QD	10
5	Compuesto #37	30	QD	10
6	Compuesto #37	10	BID	10

Cuando los tumores alcanzaron un volumen medio de aproximadamente 100 mm^3, setenta animales con tumores establecidos y pesos corporales moderados se aleatorizaron en 6 grupos de tratamiento (Grupo 1-6, n=10 ratones cada uno). El Grupo 1 se trató una vez diariamente con vehículo. Los Grupos 2 a 5 se trataron una vez diariamente con el Compuesto #37 con (respectivamente) 1, 3, 10 o 30 mg/kg. El Grupo 6 se trató dos veces diariamente (a intervalos de ~8-10 hr) con el Compuesto #37 a 10 mg/kg. Todos los tratamientos se administraron como alimentación forzada oral (PO) a un volumen de dosis de 5 mL/kg. Las dosis se administraron partiendo en el día de la

estadificación y se continuó por 40 días (Días 0-39).

Los pesos corporales se midieron dos veces por semana usando una báscula electrónica (Ohaus SCOUT® PRO). Los tamaños del tumor se midieron dos veces por semana usando microcalibradores (Mitutoyo, Aurora, Illinois) para medir la dimensión menor perpendicular (W) y dimensión mayor (L). El volumen del tumor (mm^3) se calculó usando la fórmula L x W x H/2.

En 1 hr después de la administración de la dosis final en el Día 39, los animales se sometieron a cardiocentesis terminal y se eutanizaron. Para cada animal, se recolectó la sangre como plasma K_2EDTA, se dividió en 2 alícuotas (mínimo 50 µL cada una), y se congeló a -80 ºC. Una alícuota de cada animal se proporcionó a Integrated Analytical Soluciones, Inc. (Berkeley, CA), para evaluación de la exposición del artículo de prueba; las alícuotas restantes se retuvieron a -80 °C en MuriGenics pendiente de instrucciones adicionales del cliente. En la necropsia, los pesos corporales terminales se registraron, y los tumores se escindieron, pesaron y dividieron en dos. Las mitades separadas de cada espécimen se congelaron instantáneamente en hielo seco y se almacenaron a -80 °C o se gotearon fijas en 10% de formalina amortiguada neutral (NBF) pendiente para análisis adicionales.

Análisis Estadísticos: Se realizaron análisis descriptivos e inferenciales usando las funciones

correspondientes de Excel 2010 (Microsoft, Redmond, WA). El análisis inferencial consiste de comparaciones de la prueba-t (heteroscedasticidad asumida de dos colas) a la fecha, a partir de los animales dosificados con vehículo (Grupo 1). Los valores de $p \leq 0.05$ fueron considerados estadísticamente significantes. Los resultados en el efecto del compuesto #37 en el volumen de los tumores son presentados en las **Figuras 6A y 6B**.

Ejemplo B7. Efecto de los compuestos en un modelo de esteatosis hepática de ratón

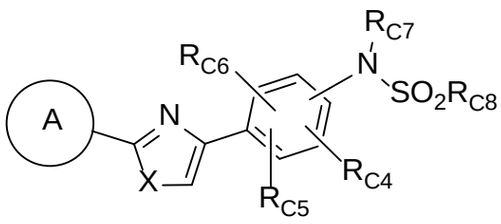
Los efectos de los compuestos de la invención en un modelo de selección de ratón con esteatohepatitis no alcohólica (NASH) se determinarán, proporcionado por Physiogenex. Ratones macho C57BL/6J (n=40), de 8 semanas de edad, son alimentado en una dieta alta en grasa/colesterol/acídica cólica (dieta "Paigen") por hasta 21 días, y los compuestos de la dosificaicón son dosificados una vez diariamente a tanto 5 mg/kg como 20 mg/kg. Los parámetros que serán determinados incluyen bioquímica de plasma (ALT, AST, triglicéridos, colesterol total, ácidos grasos, IL-6), bioquímica hepática (triglicéridos, colesterol total, ácidos grasos, expresión del gen 15 por RT-qPCR para evaluar el metabolismo líquido, metabolismo de colesterol, proteólisis de SREBP, estrés ER, estrés oxidativo, inflamación, y fibrosis), e histología hepática (H/E, Aceite Rojo con cuantificación). Los cambios en el peso del hígado, colesterol, triglicéridos, ácidos grasos,

y enzimas, serán evaluados.

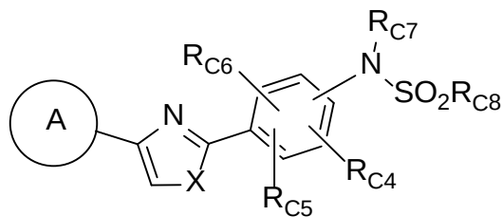
REIVINDICACIONES

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes.

1. Un compuesto de las Fórmulas (Ia) o (Ib):



(Ia)



(Ib)

o una sal del mismo farmacéuticamente aceptable, caracterizado porque:

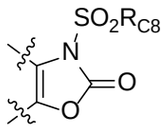
A es cualquiera de:

i. un arilo o heteroarilo, cada uno tiene solamente un anillo, sustituido con 1, 2, o 3 sustituyentes seleccionados del grupo que consiste de halógeno, CN, CF_3, OH, alquilo lineal o ramificado C1-C6, cicloalquilo C3-C6, cicloalquenilo C3-C6, hidroxialquilo lineal o ramificado C1-C6, alcoxi lineal o ramificado C1-C3, cicloalquilometilo C3-C6, -$(CH_2)_m CF_3$, =O, -CH_2OCH_3, -OBn, -CO_2H, -CO_2-alquilo, -NR10R11, y -CONR10R11; o

ii. un arilo o heteroarilo, cada uno tiene más de un anillo, opcionalmente sustituido con 1, 2, o 3 sustituyentes seleccionados del grupo que consiste de halógeno, CN, CF_3, OH, alquilo lineal o ramificado C1-C6, cicloalquilo C3-C6, cicloalquenilo C3-C6, hidroxialquilo lineal o ramificado C1-C6, alcoxi lineal o ramificado C1-C3, cicloalquilometilo C3-C6, -$(CH_2)_m CF_3$, =O, -CH_2OCH_3, -CH_2OH, -OBn, -CO_2H, -CO_2-alquilo,

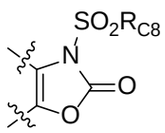
-NR10R11, y -CONR10R11;

Cada R_{C4}, R_{C5}, y R_{C6}, es independientemente hidrógeno, halógeno, CN, CF_3, OH, alquilo lineal o ramificado C1-C3, alquenilo C2-C3, alquinilo C2-C3, cicloalquilo C3-C6, cicloalquenilo C3-C6, alcoxi lineal o ramificado C1-C3, $-CO_2H$, -CONR10R11, o $-NHCONH_2$; o se toman con R_{C7} para formar la porción



;

R_{C7} es hidrógeno, alquilo lineal o ramificado C1-C6, hidroxialquilo lineal o ramificado C1-C6, $-(CR_{9a}R_{9b})_mNR10R11$, $-CO_2$-alquilo, $-(CR_{9a}R_{9b})_mO$-alquilo, $-(CR_{9a}R_{9b})_mOPO_3Na_2$, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$-alquilo, $-(CR_{9a}R_{9b})_mO(C=O)$-alquilo, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$-alquilo, $-(C=O)CH=CH_2$, $-SO_2R_{C8'}$; o se toman con uno de R_{C4}, R_{C5} o R_{C6} para formar la porción



;

R_{C8} es un perhalquilo C1-C6 lineal o ramificado, un perhaloalquilo C2-C6 lineal o ramificado, un perhaloalquinilo C2-C6 lineal o ramificado, un alquilo C1-C6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C2-C6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C2-C6 lineal o ramificado que tiene al menos un átomo de halógeno;

$R_{C8'}$ es un alquilo C1-C6 lineal o ramificado, un perhaloalquilo C1-C6 lineal o ramificado, un perhaloalquilo C2-C6 lineal o ramificado, un perhaloalquinilo C2-C6 lineal o

ramificado, un alquilo C1-C6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C2-C6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C2-C6 lineal o ramificado que tiene al menos un átomo de halógeno;

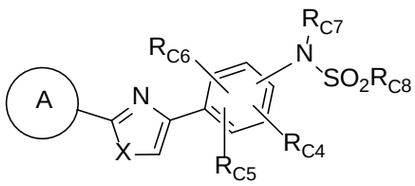
Cada $\mathbf{R_{9a}}$ y $\mathbf{R_{9b}}$, en donde está presente, es independientemente hidrógeno o alquilo lineal o ramificado C1-C6;

R10 y **R11** son independientemente hidrógeno, $-SO_2\mathbf{R_{C8'}}$, alquilo lineal o ramificado C1-C6, alquenilo lineal o ramificado C2-C6, cicloalquilo C3-C6, o cicloalquenilo C3-C6; o son tomados junto con el N al cual están unidos para formar un heterociclo C3-C6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, una $1\lambda^6$,2-tiazolidin-1,1-diona, una $1,2\lambda^6$,3-oxatiazolidin-2,2-diona, o una $1\lambda^6$,2,5-tiadiazolidin-1,1-diona;

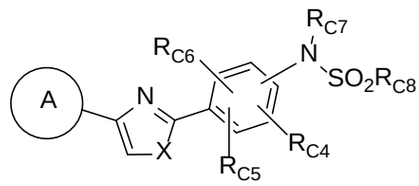
X es un heteroátomo seleccionado de S, O; o $N\mathbf{R_B}$ en donde $\mathbf{R_B}$ es hidrógeno, un alquilo lineal o ramificado C1-C6, o un cicloalquilo C3-C6; y

cada ***m*** y ***n*** es 1, 2 o 3.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque el compuesto es de las Fórmulas (IIa) o (IIb):



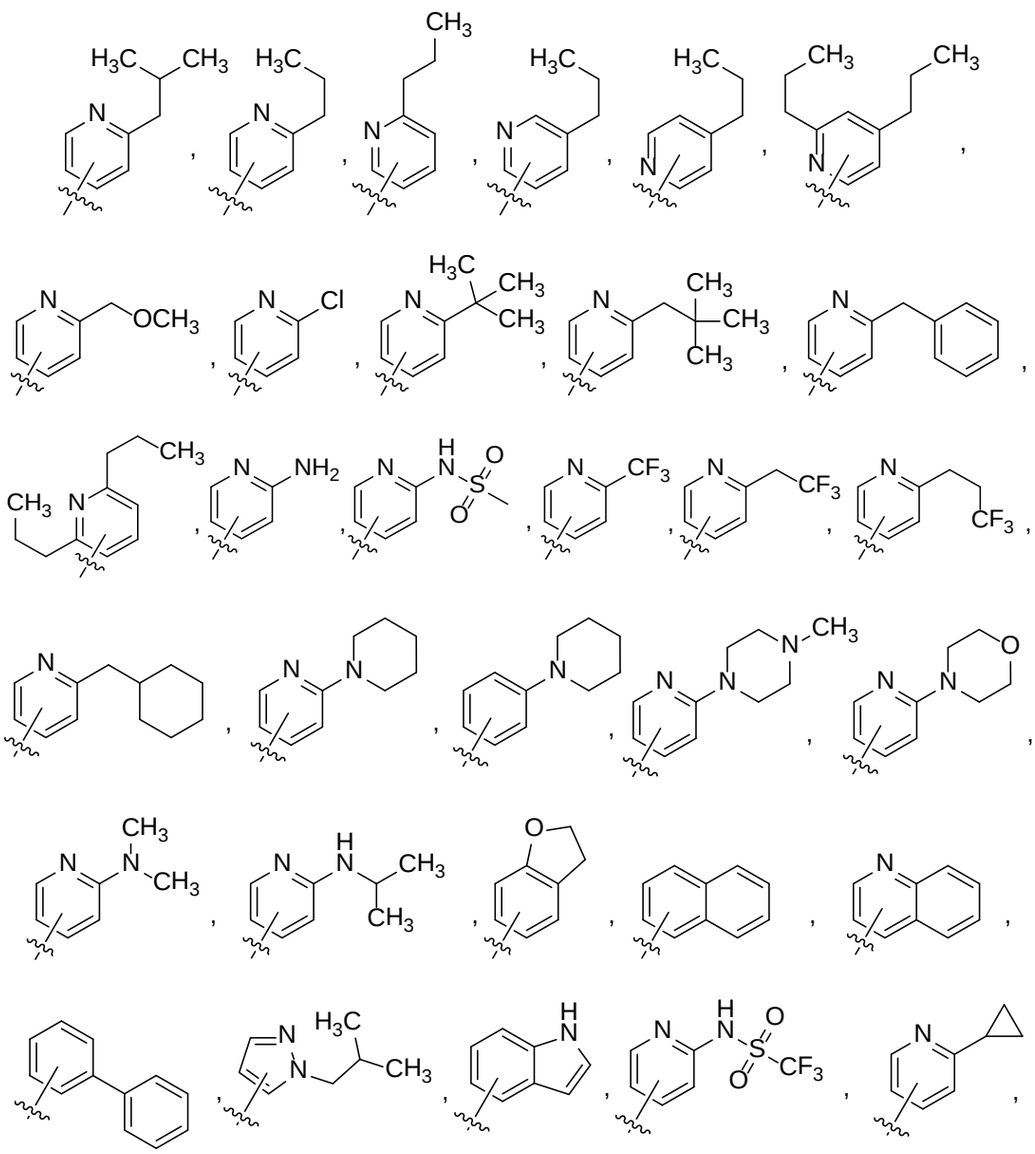
(IIa)

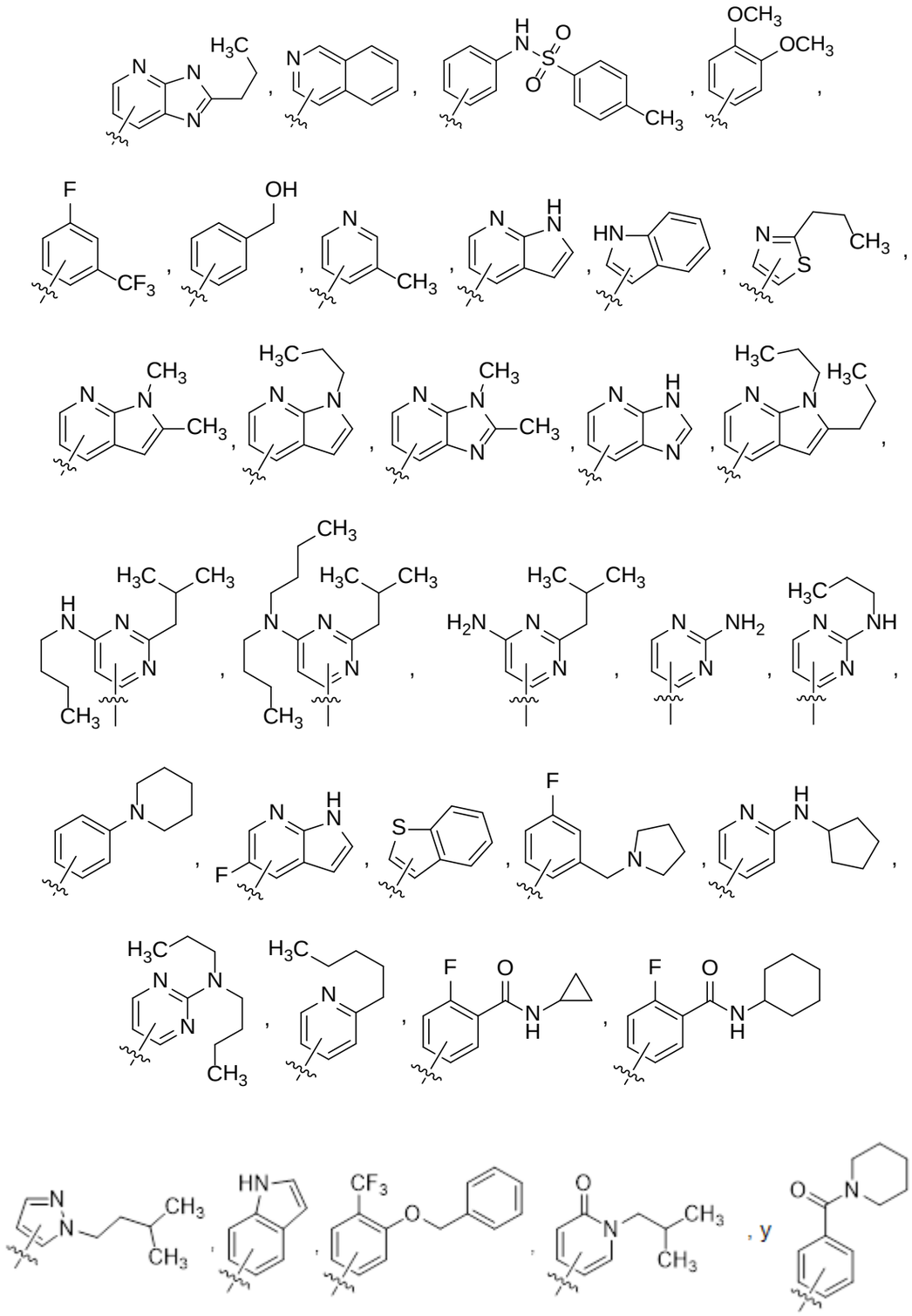


(IIb)

o una sal del mismo farmacéuticamente aceptable, en donde:

A es una porción seleccionada del grupo que consiste de:

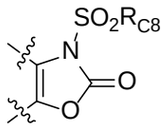




en donde el anillo que contiene X está unido al anillo A en cualquier posición disponible en el anillo A;

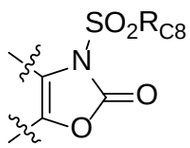
Cada **R_{C4}, R_{C5}, y R_{C6},** es independientemente hidrógeno,

halógeno, CN, CF_3, OH, alquilo lineal o ramificado C1-C3, alquenilo C2-C3, alquinilo C2-C3, cicloalquilo C3-C6, cicloalquenilo C3-C6, alcoxi lineal o ramificado C1-C3, $-CO_2H$, -CON**R10R11**, o $-NHCONH_2$; o se toman con $\mathbf{R_{C7}}$ para formar la porción



;

$\mathbf{R_{C7}}$ es hidrógeno, alquilo lineal o ramificado C1-C6, hidroxialquilo lineal o ramificado C1-C6, $-(C\mathbf{R_{9a}R_{9b}})_m N\mathbf{R10R11}$, $-CO_2$-alquilo, $-(C\mathbf{R_{9a}R_{9b}})_m O$-alquilo, $-(C\mathbf{R_{9a}R_{9b}})_m OPO_3Na_2$, $-(C\mathbf{R_{9a}R_{9b}})_m O(C\mathbf{R_{9a}R_{9b}})_n O$-alquilo, $-(C\mathbf{R_{9a}R_{9b}})_m O(C{=}O)$-alquilo, $-(C\mathbf{R_{9a}R_{9b}})_m O(C\mathbf{R_{9a}R_{9b}})_n O(C{=}O)$-alquilo, $-(C{=}O)CH{=}CH_2$, $-SO_2\mathbf{R_{C8'}}$; o se toman con uno de $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ o $\mathbf{R_{C6}}$ para formar la porción



;

$\mathbf{R_{C8}}$ es un perhalquilo C1-C6 lineal o ramificado, un perhaloalquilo C2-C6 lineal o ramificado, un perhaloalquinilo C2-C6 lineal o ramificado, un alquilo C1-C6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C2-C6 lineal o ramificado que tiene al menos un átomo de halógeno, o un alquinilo C2-C6 lineal o ramificado que tiene al menos un átomo de halógeno;

$\mathbf{R_{C8'}}$ es un alquilo C1-C6 lineal o ramificado, un perhaloalquilo C1-C6 lineal o ramificado, un perhaloalquilo C2-C6 lineal o ramificado, un perhaloalquinilo C2-C6 lineal o ramificado, un alquilo C1-C6 lineal o ramificado que tiene al menos un átomo de halógeno, un alquenilo C2-C6 lineal o

ramificado que tiene al menos un átomo de halógeno, o un alquinilo C2-C6 lineal o ramificado que tiene al menos un átomo de halógeno;

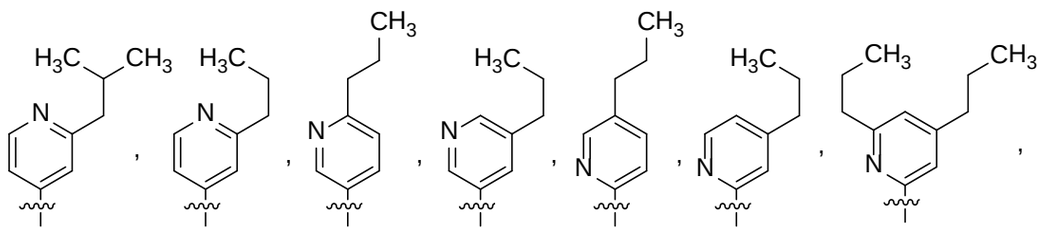
Cada **R_{9a}** **y** **R_{9b}**, en donde está presente, es independientemente hidrógeno o alquilo lineal o ramificado C1-C6;

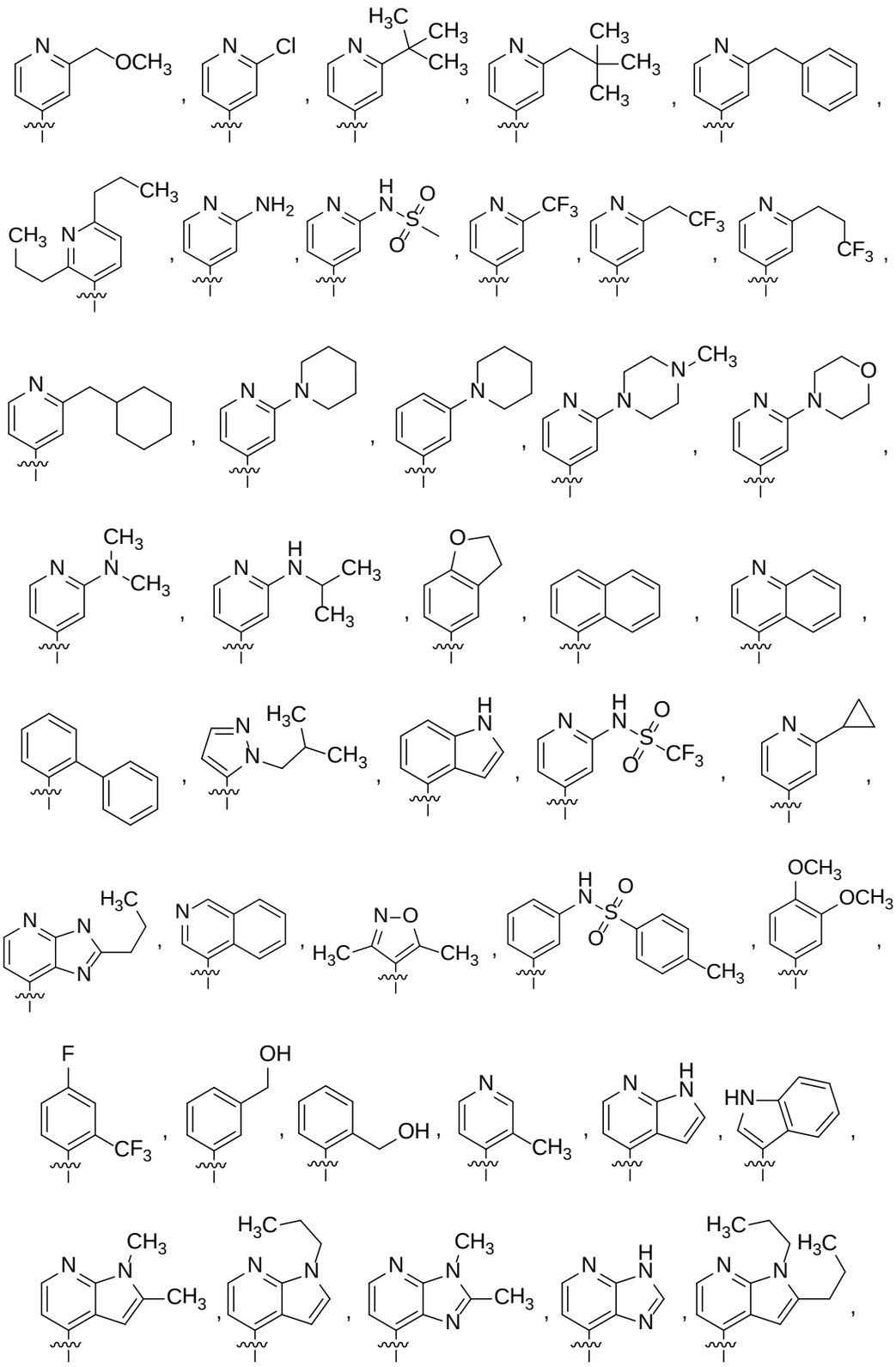
R10 y **R11** son independientemente hidrógeno, -SO_2**$R_{C8'}$**, alquilo lineal o ramificado C1-C6, alquenilo lineal o ramificado C2-C6, cicloalquilo C3-C6, o cicloalquenilo C3-C6; o son tomados junto con el N al cual están unidos para formar un heterociclo C3-C6, pirrolidinona, piperidinona, oxazolidinona, oxazinanona, imidazolidinona, tetrahidropirimidin-2(1H)-ona, a 1λ^6,2-tiazolidin-1,1-diona, a 1,2λ^6,3-oxatiazolidin-2,2-diona, o una 1λ^6,2,5-tiadiazolidin-1,1-diona;

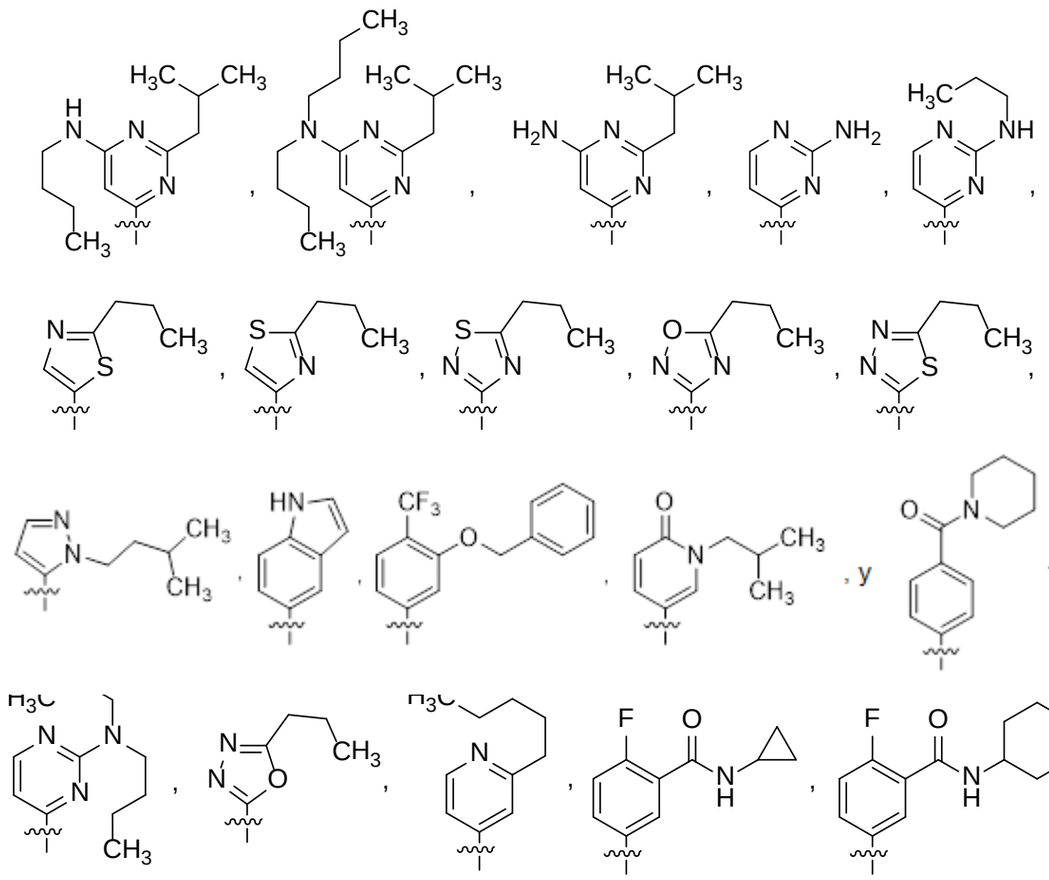
X es un heteroátomo seleccionado de S, O; o N**R_B** en donde **R_B** es hidrógeno, un alquilo lineal o ramificado C1-C6, o un cicloalquilo C3-C6; y

Cada ***m*** y ***n*** es 1, 2 o 3.

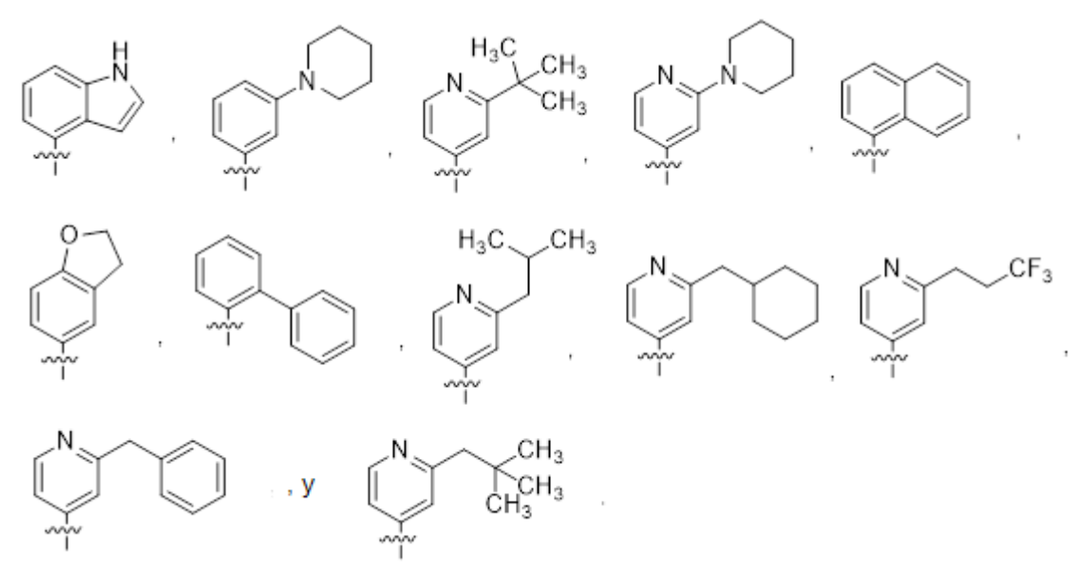
3. El compuesto de conformidad con la reivindicación 2, caracterizado porque A es una porción seleccionada del grupo que consiste de:



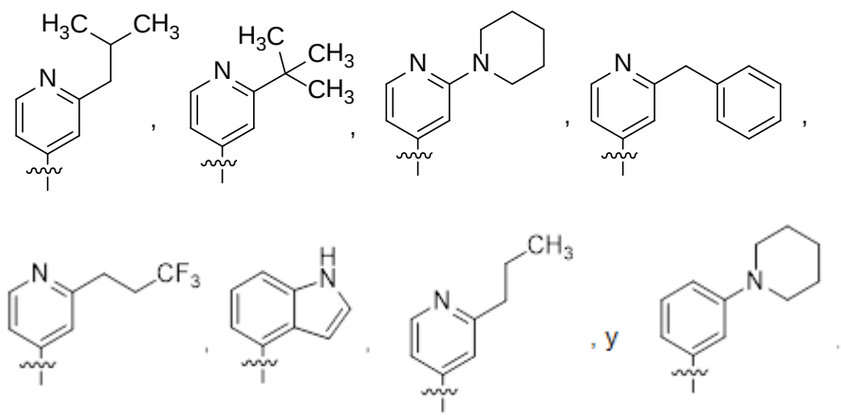




4. El compuesto de conformidad con la reivindicación 3, caracterizado porque A es una porción seleccionada del grupo que consiste de:



5. El compuesto de conformidad con la reivindicación 4, caracterizado porque A es una porción seleccionada del grupo que consiste de:



6. El compuesto de conformidad con cualquiera de las reivindicaciones 1-4, caracterizado porque X es S.

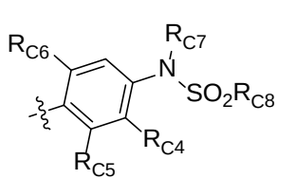
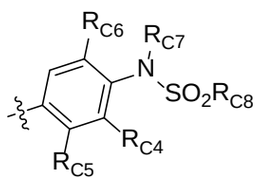
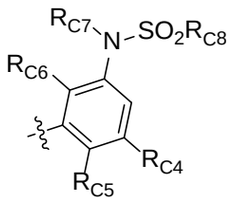
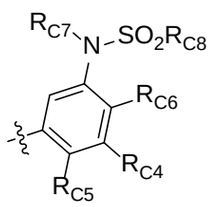
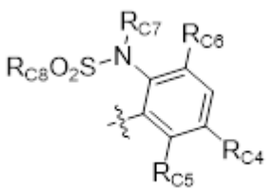
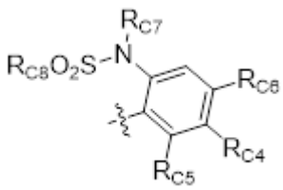
7. El compuesto de conformidad con cualquiera de las reivindicaciones 1-4, caracterizado porque X es NR_B, en donde R_B es un alquilo C1-C6 lineal o ramificado.

8. El compuesto de conformidad con la reivindicación 7, caracterizado porque R_B es un alquilo lineal C1-C6 seleccionado de metilo, etilo, n-propilo, n-butilo, n-pentilo o n-hexilo.

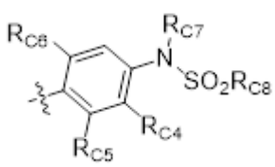
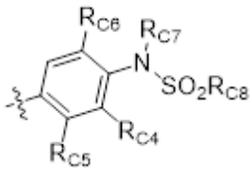
9. El compuesto de conformidad con la reivindicación 7, caracterizado porque R_B es un alquilo ramificado C1-C6 seleccionado de iso-propilo, iso-pentilo, y terc-butilo.

10. El compuesto de conformidad con cualquiera de las reivindicaciones 1-9, caracterizado porque el anillo fenilo

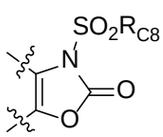
que contiene los grupos **R_{C4}**, **R_{C5}**, **R_{C6}**, y **$-NR_{C7}SO_2R_{C8}$**, es una porción seleccionada de:


,

,

,

,

, y

.

11. El compuesto de conformidad con la reivindicación 10, caracterizado porque el anillo fenilo que contiene los grupos **R_{C4}**, **R_{C5}**, **R_{C6}**, y **$-NR_{C7}SO_2R_{C8}$**, es una porción seleccionada de:


, y

.

12. El compuesto de conformidad con cualquiera de las reivindicaciones 1-11, caracterizado porque cada **R_{C4}**, **R_{C5}** y **R_{C6}**, es independientemente hidrógeno, halógeno, CN, CF_3, OH, alquilo lineal o ramificado C1-C3, alquenilo C2-C3, alquinilo C2-C3, cicloalquilo C3-C6, cicloalquenilo C3-C6, alcoxi lineal o ramificado C1-C3, $-CO_2H$, -CON**R10R11**, o $-NHCONH_2$; o se toman con **R_{C7}** para formar la porción


.

13. El compuesto de conformidad con cualquiera de

las reivindicaciones 1-12, caracterizado porque al menos uno de R_{C4}, R_{C5} y R_{C6} es hidrógeno.

14. El compuesto de conformidad con la reivindicación 13, caracterizado porque dos de R_{C4}, R_{C5} y R_{C6} son hidrógeno.

15. El compuesto de conformidad con la reivindicación 13, caracterizado porque cada R_{C4}, R_{C5} y R_{C6} es hidrógeno.

16. El compuesto de conformidad con cualquiera de las reivindicaciones 1-12, caracterizado porque al menos uno de R_{C4}, R_{C5} y R_{C6} es halógeno.

17. El compuesto de conformidad con la reivindicación 16, caracterizado porque dos de R_{C4}, R_{C5} y R_{C6} son halógeno.

18. El compuesto de conformidad con la reivindicación 16, caracterizado porque cada R_{C4}, R_{C5} y R_{C6} es halógeno.

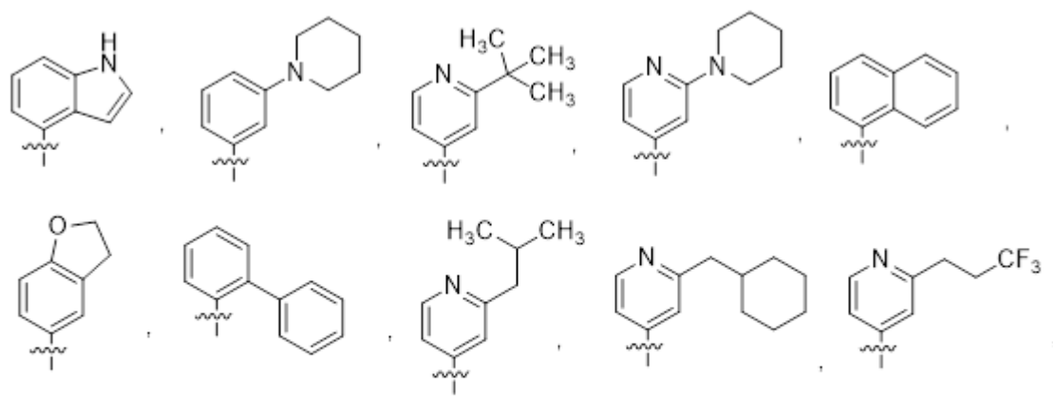
19. El compuesto de conformidad con cualquiera de las reivindicaciones 1-12, caracterizado porque uno de R_{C4}, R_{C5} y R_{C6} es hidrógeno, y los restantes dos de R_{C4}, R_{C5} y R_{C6} son halógeno.

20. El compuesto de conformidad con cualquiera de las reivindicaciones 1-12, caracterizado porque dos de R_{C4}, R_{C5} y R_{C6} son hidrógeno, y los restantes uno de R_{C4}, R_{C5} y R_{C6} es halógeno.

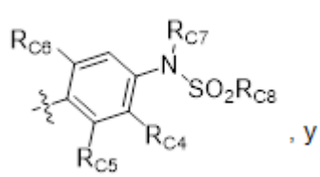
21. El compuesto de conformidad con cualquiera de las reivindicaciones 1-12, caracterizado porque R_{C4}, R_{C5} y R_{C6} son cada uno halógeno.

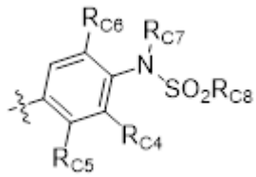
22. El compuesto de conformidad con cualquiera de las reivindicaciones 1 o 6-21, caracterizado porque:

A es una porción seleccionada de



X es S, y el anillo fenilo que contiene los grupos **R_{C4}**, **R_{C5}**, **R_{C6}**, y **$-NR_{C7}SO_2R_{C8}$**, es una porción seleccionada de:

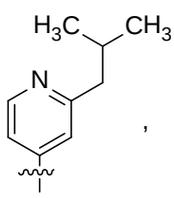


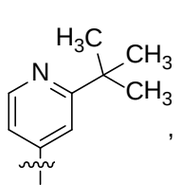
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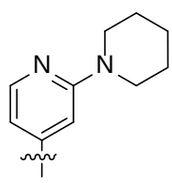
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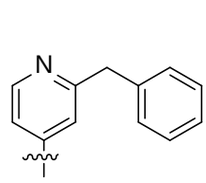
23. El compuesto de conformidad con cualquiera de las reivindicaciones 1 o 6-21, caracterizado porque:

A es una porción seleccionada de

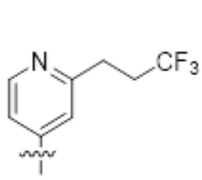


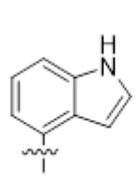
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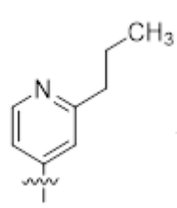
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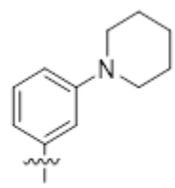
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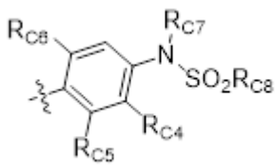
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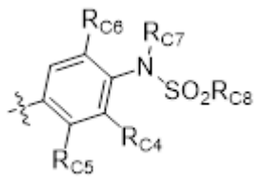
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X es S, y el anillo fenilo que contiene los grupos

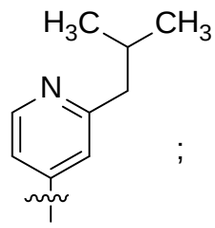
R_{C4}, R_{C5}, R_{C6} y **$-NR_{C7}SO_2R_{C8}$,** es una porción seleccionada de



, y


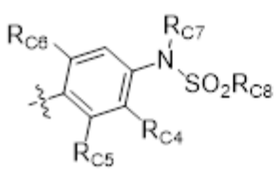
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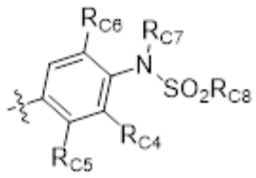
24. El compuesto de conformidad con cualquiera de las reivindicaciones 1-23, caracterizado porque:

A es 

;

X es S, y el anillo fenilo que contiene los grupos **R_{C4}, R_{C5}, R_{C6},** y **$-NR_{C7}SO_2R_{C8}$,** es seleccionado de



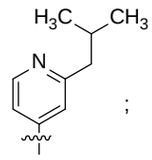
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25. El compuesto de conformidad con cualquiera de las reivindicaciones 1-24, caracterizado porque el compuesto es de Fórmula (IIa).

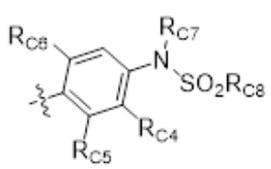
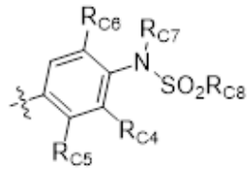
26. El compuesto de conformidad con cualquiera de las reivindicaciones 1-24, caracterizado porque el compuesto es de Fórmula (IIb).

27. El compuesto de conformidad con cualquiera de las reivindicaciones 1-25, caracterizado porque el compuesto es de Fórmula (IIa), en donde:

A es  ;

X es S;

el anillo fenilo que contiene los grupos R_{C4}, R_{C5}, R_{C6}, y $-NR_{C7}SO_2R_{C8}$, es seleccionado de

 , y  .

28. Un compuesto caracterizado porque se selecciona a partir del grupo que consiste de:

1,1,1-trifluoro-N-(4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(3-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(3-cloro-4-(2-(1-isobutil-1H-pirazol-5-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1,2-dimetil-1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1-propil-1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2,3-dimetil-3H-imidazo[4,5-

b]piridin-7-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(3-propil-3H-imidazo[4,5-b]piridin-7-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(3H-imidazo[4,5-b]piridin-7-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1,2-dipropil-1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(6-(butilamino)-2-isobutilpirimidin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(6-(dibutilamino)-2-isobutilpirimidin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(6-amino-2-isobutilpirimidin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-aminopirimidin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(propilamino)pirimidin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(dibutilamino)pirimidin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2'-propil-2,4'-bitiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,2,4-tiadiazol-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,2,4-oxadiazol-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2'-propil-2,5'-bitiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,3,4-tiadiazol-2-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(5-propil-1,3,4-oxadiazol-2-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(1-isobutil-6-oxo-1,6-dihidropiridin-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(4-fluoro-3-isobutilfenil)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3,5-dicloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-(trifluorometil)fenil)metansulfonamida;

N-(2-ciclopropil-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-metilfenil)metansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-isopropilfenil)metansulfonamida;

N-(2-etinilo-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-3-etinilo-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-6-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-6-metilfenil)-1,1,1-trifluorometansulfonamida;

N-(4-(4-(2-terc-butilpiridin-4-il)-1-metil-1H-imidazol-2-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(1-metil-2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-3-cloro-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-5-cloro-4-(1-metil-2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(4-(2-terc-butilpiridin-4-il)oxazol-2-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)oxazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(dimetilamino)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-N-(trifluorometilsulfonil)acrilamida;

N-(3-cloro-4-(2-(2-(metilsulfonamido)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(3,3,3-trifluoropropil)piridin-

4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(2-hidroxi-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(2-hidroxi-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-2-hidroxifenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(2-metoxi-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-2-metoxifenil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-2-metoxifenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-3-(trifluorometil)fenil)metansulfonamida;

N-(3-cloro-4-(2-(2-neopentilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

6-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-3-(trifluorometilsulfonil)benzo[d]oxazol-2(3H)-ona;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,2,2,2-pentafluoroetansulfonamida;

1,1,1-trifluoro-N-(2-metoxi-4-{2-[2-(2-metilpropil)piridin-4-il]-1,3-tiazol-4-il}fenil)metansulfonamida;

1,1,1-trifluoro-N-{2-metoxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-{4-[2-(2-terc-butilpiridin-4-il)-1,3-tiazol-4-

il]-2-metoxifenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-bencilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-aminopiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-metansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-{2-hidroxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(3,3,3-trifluoropropil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(4-{2-[2-(2,2-dimetilpropil)piridin-4-il]-1,3-tiazol-4-il}-2-metoxifenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-trifluorometansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(4-(piperidin-1-carbonil)fenil)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[1-(3-metilbutil)-1H-pirazol-5-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{4-[5-(2-terc-butilpiridin-4-il)tiofen-3-il]-3-clorofenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(ciclohexilometil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(naftalen-1-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-6-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(4-{2-[3-(benciloxi)-4-(trifluorometil)fenil]-1,3-tiazol-4-il}-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-fenilofenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(isoquinolin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(4-metilpiperazin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(dimetil-1,2-oxazol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-[4-(2-cloro-4-trifluorometansulfonamidofenil)-1,3-tiazol-2-il]fenil}-4-metilbencen-1-sulfonamida;

N-{3-cloro-4-[2-(3,4-dimetoxifenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(trifluorometil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2,3-dihidro-1-benzofuran-5-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(piperidin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(3-metilpiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(piperidin-1-il)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{5-fluoro-1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-{4-[2-(1-benzotiofen-3-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(pirrolidin-1-ilmetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(ciclopentilamino)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-3-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(quinolin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-cloropiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-hidroxietil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-(2-oxopirrolidin-1-il)etil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-il)etil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-(2-oxoimidazolidin-1-il)etil)metansulfonamida;

N-(2-bromo-4-(2-(2-(piperidin-1-il)piridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

2-(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)etil acetato;

(2-(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)etoxi)metilacetato;

N-{4-[2-(2-tert-butilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-N-(2-{[4-(3-clorofenil)-2-oxo-1,3,2λ^5-dioxafosfinan-2-il]oxi}etil)-1,1,1-trifluorometansulfonamida;

(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)metilacetato;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(metoximetil)metansulfonamida;

N-{4-[2-(2-tert-butilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-N-({[4-(3-clorofenil)-2-oxo-1,3,2λ^5-dioxafosfinan-2-il]oxi}metil)-1,1,1-trifluorometansulfonamida;

4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenilo(trifluorometilsulfonil)carbamato de metilo;

(N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometilsulfonamido)metil fosfato de sodio;

1-(N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometilsulfonamido)etil isobutirato;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-il)etil)metansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluoro-N-(2-hidroxietil)metansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-(2-(pirrolidin-1-il)etil)metansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-N-(2-(dietilamino)etil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-N-(2-(dimetilamino)etil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(3-fluoro-4-(2-(2-propilpiridin-

4-il)tiazol-4-il)fenil)metansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-(2-hidroxietil)metansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluoro-N-metilmetansulfonamida;

1,1,1-trifluoro-N-(3-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(2-bromo-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-metil-N-(4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(2-butilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida

1,1,1-trifluoro-N-(4-(2-(2-(metoximetil)piridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(4,6-dipropilpiridin-2-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(4-propilpiridin-2-il)tiazol-4-il)fenil)metansulfonamida;

N-(4-(2-(2,6-dipropilpiridin-3-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-(ciclohexilometil)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)-3-metoxifenil)metansulfonamida;

N-(3-cloro-4-(2-(2-((trifluorometilsulfonil)metil)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(1H-pirrol[2,3-b]piridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propil-3H-imidazo[4,5-b]piridin-7-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

5-(4-(2-cloro-4-(trifluorometilsulfonamido)fenil)tiazol-2-il)-N-ciclopropil-2-fluorobenzamida;

5-(4-(2-cloro-4-(trifluorometilsulfonamido)fenil)tiazol-2-il)-N-ciclohexilo-2-fluorobenzamida;

N-(4-(2-(1H-indol-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(3-(piperidin-1-il)fenil)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-(piperidin-1-il)piridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-4-(2-(2-terc-butilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-cloro-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(2-bromo-5-cloro-4-(2-(2-propilpiridin-4-il)-1H-imidazol-4-il)fenil)-1,1,1-trifluorometansulfonamida; and

N-(2-bromo-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida.

29. El compuesto de conformidad con la reivindicación 28, caracterizado porque el compuesto se selecciona del grupo que consiste de:

1,1,1-trifluoro-N-(4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

1,1,1-trifluoro-N-(3-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)metansulfonamida;

N-(3-cloro-4-(2-(1-isobutil-1H-pirazol-5-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-(2-metoxi-4-{2-[2-(2-metilpropil)piridin-4-il]-1,3-tiazol-4-il}fenil)metansulfonamida;

1,1,1-trifluoro-N-{2-metoxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-{4-[2-(2-terc-butilpiridin-4-il)-1,3-tiazol-4-il]-2-metoxifenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-bencilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-aminopiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-metansulfonamidopiridin-4-il)-

1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

1,1,1-trifluoro-N-{2-hidroxi-4-[2-(2-propilpiridin-4-il)-1,3-tiazol-4-il]fenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(3,3,3-trifluoropropil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(4-{2-[2-(2,2-dimetilpropil)piridin-4-il]-1,3-tiazol-4-il}-2-metoxifenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-trifluorometansulfonamidopiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(4-(piperidin-1-carbonil)fenil)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[1-(3-metilbutil)-1H-pirazol-5-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{4-[5-(2-terc-butilpiridin-4-il)tiofen-3-il]-3-clorofenil}metansulfonamida;

N-(3-cloro-4-{2-[2-(ciclohexilometil)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(naftalen-1-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-6-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(4-{2-[3-(benciloxi)-4-(trifluorometil)fenil]-1,3-tiazol-4-il}-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2-fenilofenil)-1,3-tiazol-4-

il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(isoquinolin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(4-metilpiperazin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(dimetil-1,2-oxazol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-[4-(2-cloro-4-trifluorometansulfonamidofenil)-1,3-tiazol-2-il]fenil}-4-metilbencen-1-sulfonamida;

N-{3-cloro-4-[2-(3,4-dimetoxifenil)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(trifluorometil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(2,3-dihidro-1-benzofuran-5-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(hidroximetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(piperidin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(3-metilpiridin-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[3-(piperidin-1-il)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-[3-cloro-4-(2-{5-fl-uoro-1H-pirrol[2,3-b]piridin-4-il}-1,3-tiazol-4-il)fenil]-1,1,1-trifluorometansulfonamida;

N-{4-[2-(1-benzotiofen-3-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[4-fluoro-2-(pirrolidin-1-ilmetil)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(ciclopentilamino)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-3-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida; y

N-(3-cloro-4-(2-(quinolin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida.

30. El compuesto de conformidad con la reivindicación 29, caracterizado porque el compuesto se selecciona del grupo que consiste de:

N-(3-cloro-4-(2-(2-propilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-(4-(2-(2-terc-butilpiridin-4-il)tiazol-4-il)-3-clorofenil)-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida;

N-{4-[2-(2-bencilpiridin-4-il)-1,3-tiazol-4-il]-3-clorofenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(3,3,3-trifluoropropil)piridin-

4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida;

N-{3-cloro-4-[2-(1H-indol-4-il)-1,3-tiazol-4-il]fenil}-1,1,1-trifluorometansulfonamida;

N-(3-cloro-4-{2-[2-(piperidin-1-il)piridin-4-il]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida; and

N-(3-cloro-4-{2-[3-(piperidin-1-il)fenil]-1,3-tiazol-4-il}fenil)-1,1,1-trifluorometansulfonamida.

31. Un compuesto caracterizado porque es N-(3-cloro-4-(2-(2-isobutilpiridin-4-il)tiazol-4-il)fenil)-1,1,1-trifluorometansulfonamida.

32. Una composición farmacéutica, caracterizada porque comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1-31, y un vehículo farmacéuticamente aceptable.

33. Un método para tratar un trastorno metabólico, caracterizado porque comprende administrar a un individuo en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de conformidad con cualquiera de las reivindicaciones 1-31.

34. Un método para tratar un trastorno hiperproliferativo, caracterizado porque comprende administrar a un individuo en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de conformidad con cualquiera de las reivindicaciones 1-31.

35. El método de conformidad con la reivindicación 34, caracterizado porque el trastorno hiperproliferativo es cáncer.

36. El método de conformidad con la reivindicación 35, caracterizado porque el cáncer es cáncer de mama, cáncer de próstata, o cáncer de ovario.

37. Uso de un compuesto de conformidad con cualquiera de las reivindicaciones 1-31, en la manufactura de un medicamento para tratar un trastorno metabólico o un trastorno hiperproliferativo.

38. Uso de un compuesto de conformidad con cualquiera de las reivindicaciones 1-31, para tratar un trastorno metabólico o un trastorno hiperproliferativo.

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(54) Title: HETEROCYCLIC COMPOUNDS AND METHODS OF USE

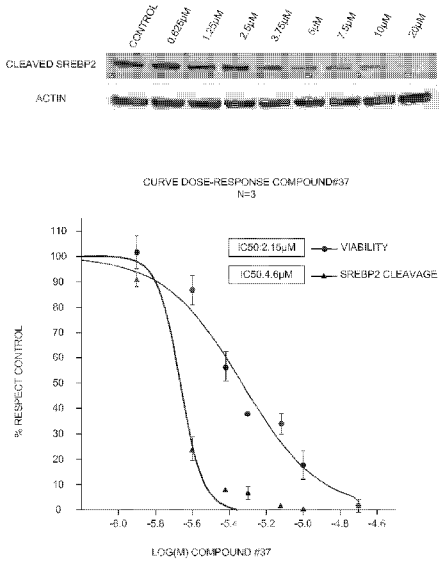


FIG. 1

(57) Abstract: This disclosure provides compounds and methods of using those compounds to treat metabolic disorders and hyperproliferative disorders, including administration of the compounds in conjunction with hormone receptor antagonists. Compounds of the invention may also find use in treating cancer. Presented herein are novel compounds bearing a perhaloalkylsulfonamide moiety. Such compounds, in addition to being highly effective SREBP inhibitors, are also unexpectedly highly bioavailable in vivo. Heteroaromatic compounds bearing sulfonamide groups are prone to several ionic states, based on the inherent pKa values.

WO 2015/031650 A1

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HETEROCYCLIC COMPOUNDS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to Indian Patent Application No. 2816/MUM/2013 filed August 28, 2013, and Indian Patent Application No. 3497/MUM/2013 filed November 4, 2013.

TECHNICAL FIELD

[002] This disclosure relates generally to therapeutics for treatment of hyperproliferative disorders, metabolic disorders, and pancreatitis.

BACKGROUND OF THE INVENTION

[003] Sterol regulatory element-binding proteins (SREBPs) are major transcription factors regulating the biosynthesis of cholesterol, fatty acid, and triglyceride. They control the expression of crucial genes involved in lipogenesis and uptake. Inhibition of the SREBP pathway can reduce lipid biosynthesis and thus can be a strategy to treat metabolic diseases, such as type II diabetes, insulin resistance, fatty liver and atherosclerosis [Xiao, et al. *Acta Biochim. Biophys. Sin* (2013) 45:1, pp 2-10]. In mammals, three SREBP isoforms are known, designated SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1a controls a broad range of SREBP targets including production of fatty acids, triglycerides, phospholipids and cholesterol. SREBP-1c preferentially activates genes of fatty acid and triglyceride metabolism, whereas SREBP-2 preferentially activates genes of cholesterol metabolism, both of which have been studied in human and mice models [Horton, et al. *J. Clin. Invest.* (2002) 109:9, pp 1125-1131], as well as *Drosophila* [Rawson. *Nature Rev. Mol. Cell Biol.* (2003) 4:8, pp 631-640].

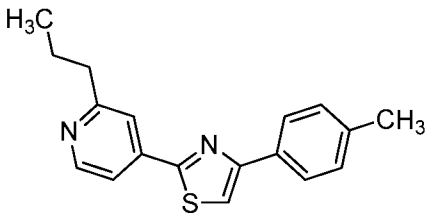
[004] Recent studies have also presented a link between upregulation of lipid synthesis and prostate cancer [Suburu, et al. *Prostaglandins Other Lipid Mediat.* (2012) 98:0, pp 1-10]. The metabolic shift from catabolic to anabolic metabolism is a hallmark of cancer cells. Many cancers require synthesis of fatty acids, and other lipids such as cholesterol and androgens are implicated in prostate cancer. SREBP-1c is the major transcriptional regulator of enzymes in the fatty acid synthesis pathway, and its expression can be stimulated by androgens and epidermal growth factor (EGF) in prostate cancer cells. Overexpression of SREBP-1c is sufficient to cause tumorigenicity and invasion of prostate cancer cells. SREBP-1 can also increase expression of NOX5, a prominent producer of reactive oxygen species (ROS) and regulator of prostate cancer cell growth [Brar, et al. *Am. J. Physiol. Cell Physiol.* (2003) 285:2, pp C353-369; Huang, et al.

Mol. Cancer Res. (2012) 10:1, pp 133-142; Huang, et al. *Cancer Research* (2012) 72:8, SUPPL. 1; Huang, et al. *Mol. Cancer Res.* (2014) 13:4, pp 855-866].

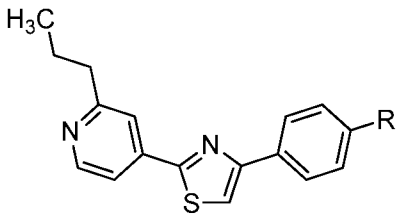
[005] SREBP-2, a regulator of androgen synthesis, is also itself regulated by androgens, demonstrating a direct feedback circuit for regulation of androgen production. SREBP-2 expression increases during disease progression and is significantly higher after castration. This transcription factor also lacks its feedback inhibition in prostate cancer cells, implicating a role for cholesterol and androgen synthesis in prostate cancer [Eberle, et al. *Biochimie* (2004) 86:11, pp 839-848; Ettinger, et al. *Cancer Res.* (2004), 64:6, pp2212-2221; Chen, et al. *Int. J. Cancer* (2001), 91:1, pp 41-45].

[006] Blocking SREBP functions linked to disease states therefore represents an important therapeutic approach for limiting lipid/cholesterol synthesis in membrane production which occurs in metabolic diseases and in cancer progression, as well as in viral pathogenesis [Naar, et al. *Clin. Lipidol.* (2012) 7:1, pp 27-36]. Small molecule therapeutics affecting metabolic regulators such as mTOR, AMPK or SIRT1, including Rapamycin, Metformin, or Resveratrol, respectively, may impinge on the transcriptional activity of SREBPs. Recently, two non-sterol small molecules, fatostatin and betulin have been found to inhibit SREBP processing [Kamisuki, et al. *Chem. Biol.* (2009) 16:8, pp 882-892; Tang, et al. *Cell. Metab.* (2011) 13:1, pp 44-56]. Methods for the treatment of cancers having a p53 mutation, such as breast cancer cells, using SREBP inhibitors have been presented [Freed-Pastor, et al. *PCT. Publication* WO2013-110007A1].

[007] Fatostatin analogs have recently been described as potential therapeutics for the treatment of metabolic disorders [Uesugi, et al. *U.S. Patent No.* 8,207,196]. Key compounds presented therein are based around Formula X:



Fatostatin



Formula X

wherein R is H, F, Cl, Br, OBz, OH, OCH_3, OCH_2CO_2Me, OCH_2CO_2H, NH_2, NHiPr, $NHCOCH_3$, $NHSO_2Me$, NH[benzyl], NH[cyclopropyl], NH[tertbutyloxycarbonyl], NH[cyclohexyl], NH[tosyl], NH[quinolin-8-yl], and NH[thiophen-2-yl]. In particular, one compound (FGH10019), the methanesulfonamide derivative of fatostatin above wherein R is

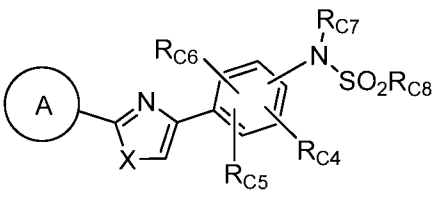
$NHSO_2Me$, has been described as a lead candidate [Kamisuki, et al. *J. Med. Chem.* (2011) 54:13, pp 4923-4927].

BRIEF SUMMARY OF THE INVENTION

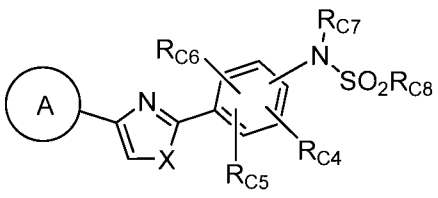
[008] This disclosure relates generally to therapeutics for treatment of hyperproliferative disorders, metabolic disorders, and pancreatitis. This disclosure provides compounds and methods of using those compounds to treat benign and malignant hyperproliferative disorders, as well as metabolic disorders and pancreatitis, as described below. Compounds of the invention may also find use in treating cancer.

[009] Presented herein are novel compounds bearing a perhaloalkylsulfonamide moiety. Such compounds, in addition to being highly effective SREBP inhibitors, are also unexpectedly highly bioavailable *in vivo*. Heteroaromatic compounds bearing sulfonamide groups are prone to several ionic states, based on the inherent pKa values. When placed in aqueous solution, they could exist in neutral, zwitterionic or anionic forms dependent upon the pH of that solution. Each of these forms can have dramatically different solubility, and require complex pharmaceutical formulation studies to maximize *in-vivo* exposure. Such studies could necessitate solid dispersions, micronization, coprecipitation, salt selection, lipid emulsifiers, cosolvents, complexation carriers, solubility enhancer excipients, and the like, each of which presents its own challenges, resource requirements and unpredictability [see, for example, Julémont, et al. *J. Med. Chem.* (2004) 47:27, pp6749-6759; Anand, et al. *US Patent Publication* US2014-128431A1; Patel, et al. *PCT Publication* WO2000-072884]. Perhaloalkylsulfonamides have, in general, a lower pKa and higher acidity relative to non-fluorinated alkylsulfonamides, with a potential to form the anion at physiological pH, depending on the remaining functionality in the molecule. This unpredictability of how perhaloalkylsulfonamide-containing compounds can be formulated as pharmaceuticals typically renders them unappealing to the skilled medicinal chemist. As presented herein, the high bioavailability of compounds of the invention is attributed to unexpectedly low pKa values found for the compounds, affording them optimal characteristics for therapeutic applications.

[010] In some embodiments, compounds disclosed herein fall within formulae (Ia) or (Ib):



(Ia)



(Ib)

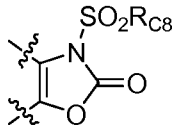
or a pharmaceutically acceptable salt thereof, wherein:

A is either:

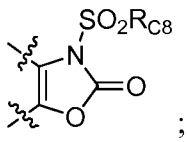
i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -OBn, -CO_2H, -CO_2-Alkyl, -N**R10R11**, and -CON**R10R11**; or

ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -CH_2OH, -OBn, -CO_2H, -CO_2-Alkyl, -N**R10R11**, and -CON**R10R11**;

Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO_2H, -CON**R10R11**, or -$NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety 

;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -$(CR_{9a}R_{9b})_mNR10R11$, -CO_2-Alkyl, -$(CR_{9a}R_{9b})_mO$-Alkyl, -$(CR_{9a}R_{9b})_mOPO_3Na_2$, -$(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$-Alkyl, -$(CR_{9a}R_{9b})_mO(C{=}O)$-Alkyl, -$(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C{=}O)$-Alkyl, –$(C{=}O)CH{=}CH_2$, -$SO_2R_{C8}$; or is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety 

;

$\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

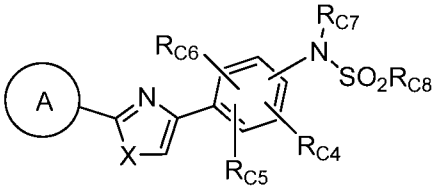
Each $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, $-SO_2\mathbf{R_{C8'}}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

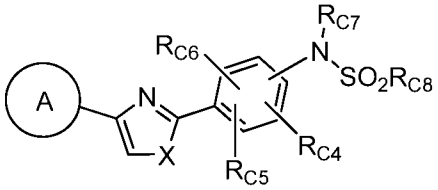
X is a heteroatom selected from S, O; or $N\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

[011] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):



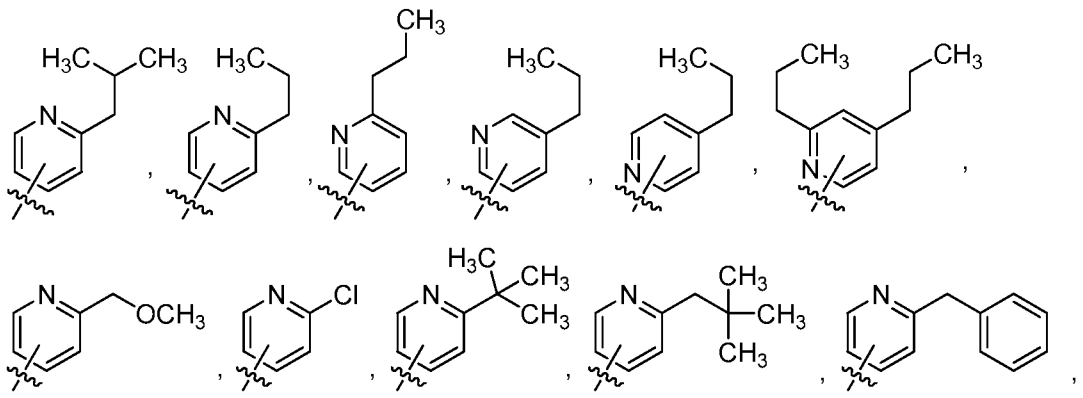
(IIa)

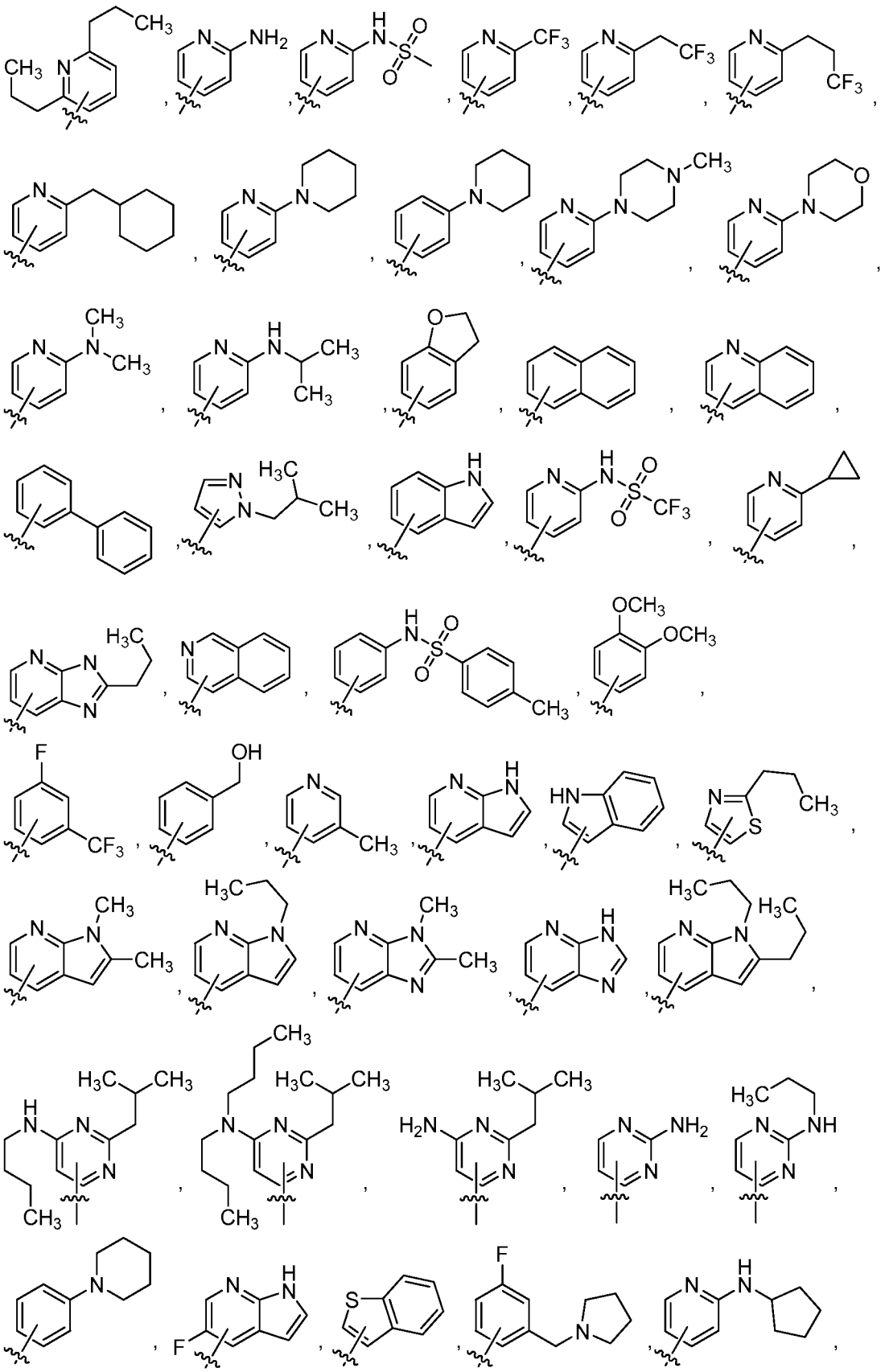


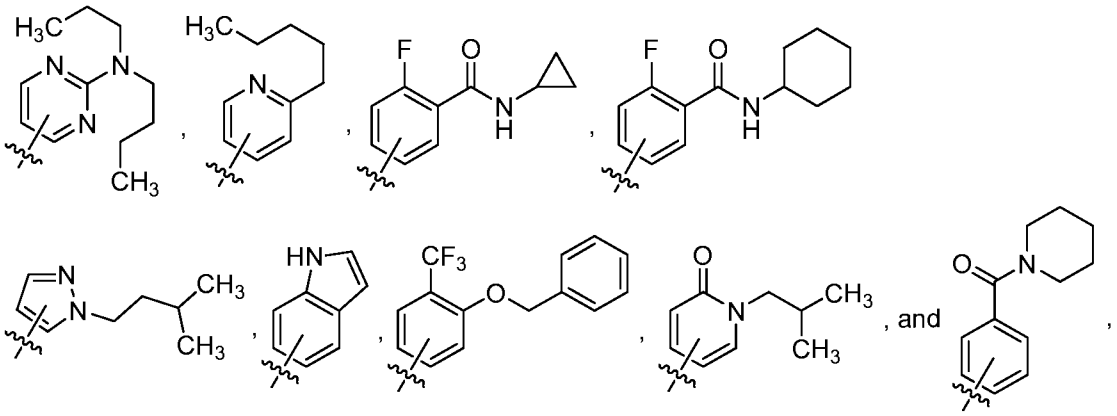
(IIb)

or a pharmaceutically acceptable salt thereof, wherein:

A is a moiety selected from the group consisting of:

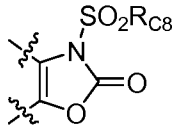


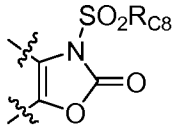




wherein the ring containing X is linked to ring A at any available position on ring A;

Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-CO_2H$, -CON**R10R11**, or $-NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety  ;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, $-(CR_{9a}R_{9b})_mNR10R11$, $-CO_2$-Alkyl, $-(CR_{9a}R_{9b})_mO$-Alkyl, $-(CR_{9a}R_{9b})_mOPO_3Na_2$, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$-Alkyl, $-(CR_{9a}R_{9b})_mO(C=O)$-Alkyl, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$-Alkyl, $-(C=O)CH=CH_2$, $-SO_2R_{C8'}$; or is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety  ;

$\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

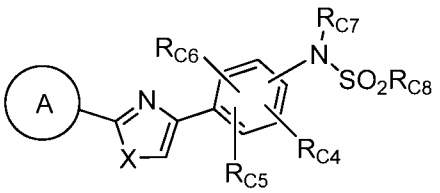
Each $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, $-SO_2\mathbf{R_{C8}}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

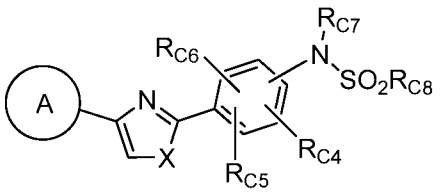
X is a heteroatom selected from S, O; or $N\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

[012] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):



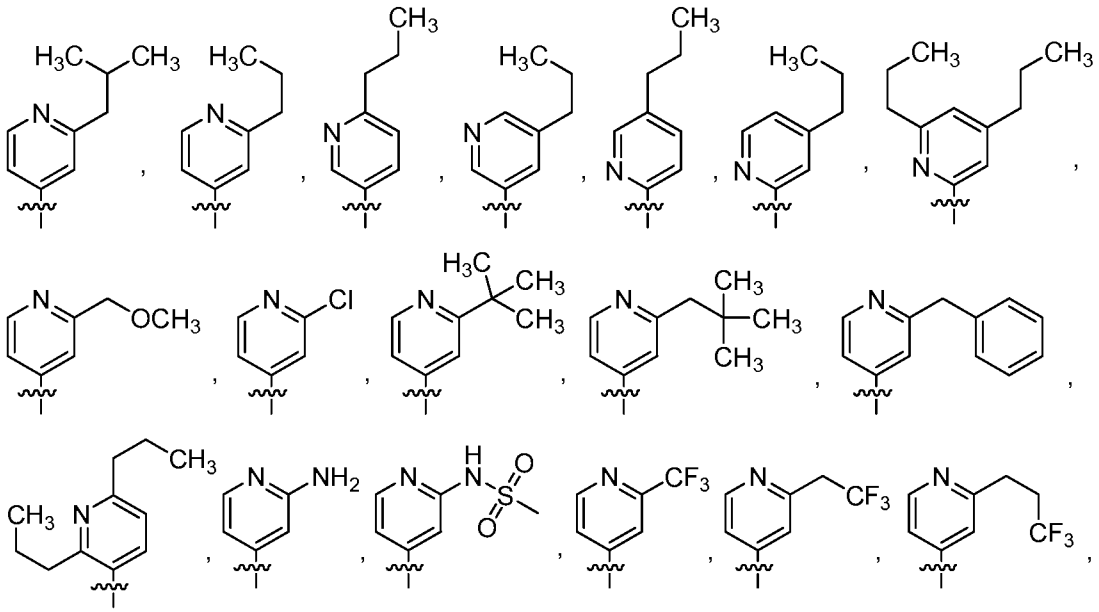
(IIa)

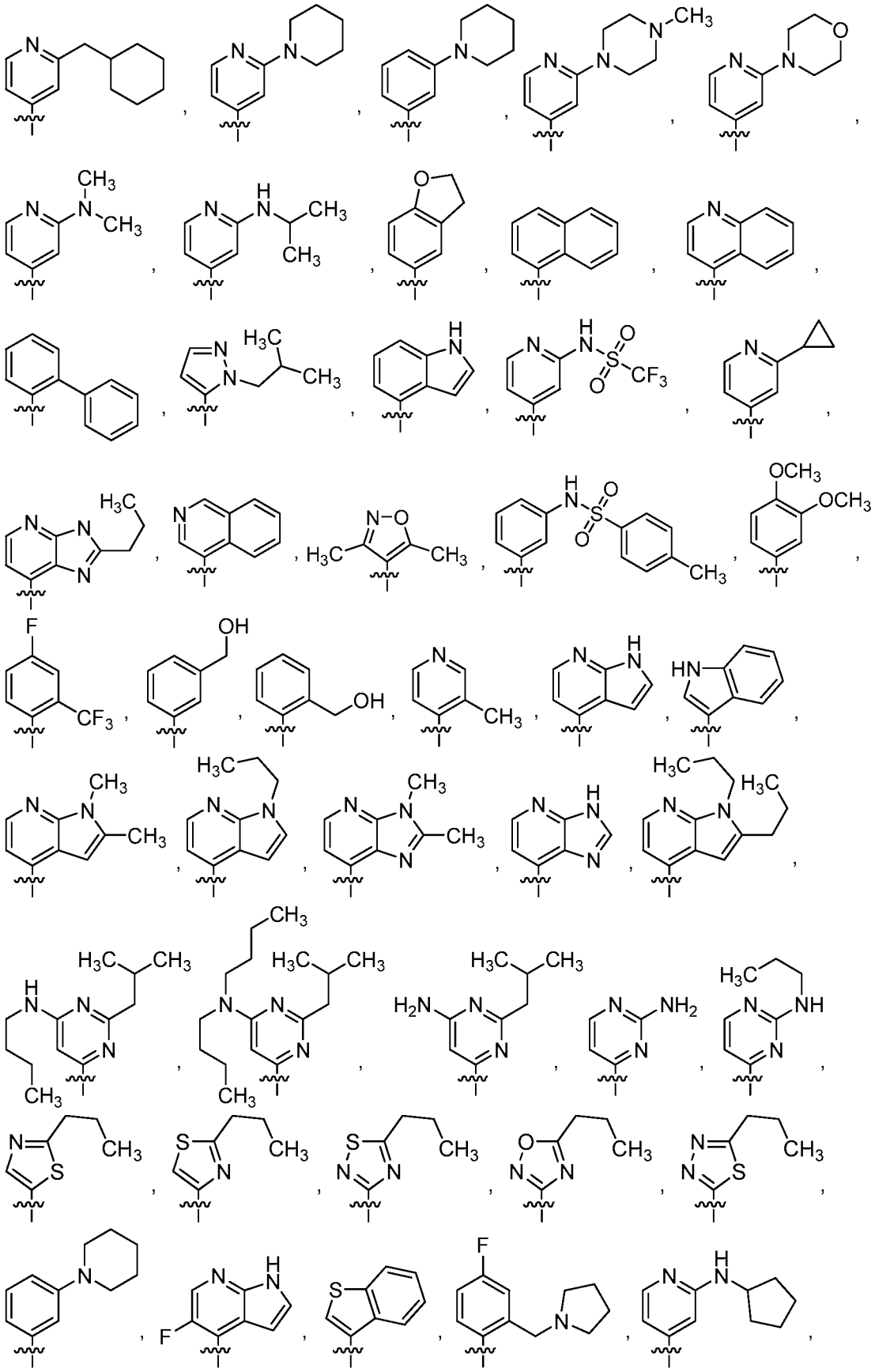


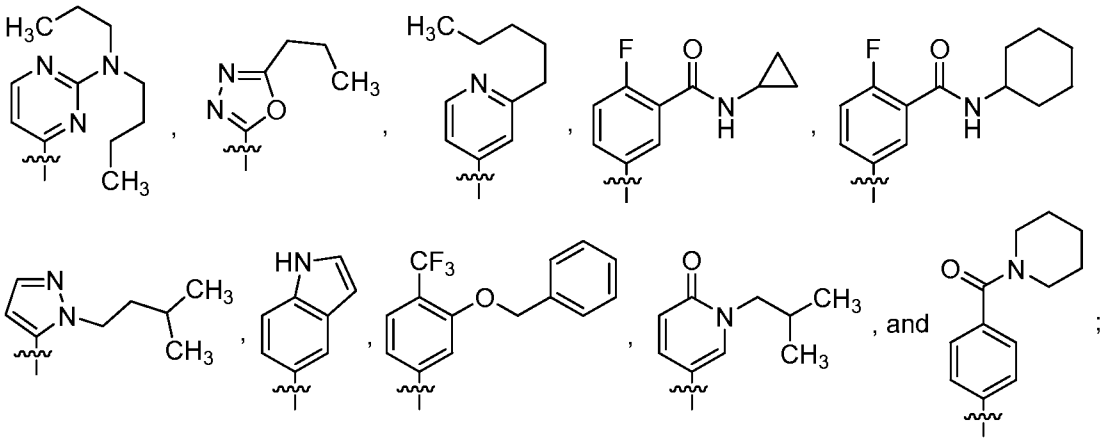
(IIb)

or a pharmaceutically acceptable salt thereof, wherein:

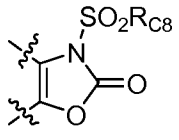
A is a moiety selected from the group consisting of:

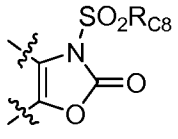






Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-CO_2H$, -CON**R10R11**, or $-NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety  ;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, $-(CR_{9a}R_{9b})_mNR10R11$, $-CO_2$-Alkyl, $-(CR_{9a}R_{9b})_mO$-Alkyl, $-(CR_{9a}R_{9b})_mOPO_3Na_2$, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$-Alkyl, $-(CR_{9a}R_{9b})_mO(C=O)$-Alkyl, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$-Alkyl, $-(C=O)CH=CH_2$, $-SO_2R_{C8'}$; or is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety  ;

$\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

Each $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, -SO_2R_{C8}, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or NR_B wherein R_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

[013] In one aspect, compounds of invention are described in Table 1, such as a compound selected from the group consisting of Compound Nos. 1 to 152; or a pharmaceutically acceptable salt, solvate, prodrug, or N-oxide thereof.

[014] Further provided is a pharmaceutical composition, comprising a compound of Formulae (Ia), (Ib), (IIa), or (IIb), or any variations described herein, or a salt thereof, and a pharmaceutically acceptable carrier or excipient.

[015] Further provided is a kit, comprising a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variations described herein, or a salt thereof, and instructions for use.

[016] Further provided are methods of treating one or more of the following: hyperproliferative disorders, metabolic disorders and/or pancreatitis in individuals in need thereof, such as humans, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of Formulae (Ia), (Ib), (IIa), or (IIb), or any variations described herein, or a pharmaceutically acceptable salt thereof.

[017] Further provided are methods of treating any diseases or conditions for which the modulation of SREBP is believed to be or is beneficial, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of Formulae (Ia), (Ib), (IIa), or (IIb), or any variations described herein, or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[018] **FIG. 1**. Western-blots and dose response curves, with IC_{50} values, of compound #37 in HepG2 cells: cell viability and SREBP-2 cleavage.

[019] **FIG. 2**. Graph showing effect of compound #37 on a human LnCap xenograft.

[020] **FIG. 3.** Cell line panel IC_{50} data for Compound #37.

[021] **FIG. 4A.** Pharmacokinetic parameters for Compound #37 (mouse).

[022] **FIG. 4B.** Pharmacokinetic parameters for Compound #37 (dog).

[023] **FIG. 5.** Graph showing the effect of Compound #37 on a human *in vivo* MDA-MB-453 xenograft.

[024] **FIGS. 6A-B.** Graph showing the effect of Compound #37 on a human in vivo LNCaP xenograft: **FIG. 6A**, tumor volume at three concentrations. **FIG. 6B**, tumor volume fold change at several doses.

DETAILED DESCRIPTION

Definitions

[025] For use herein, unless clearly indicated otherwise, use of the terms "a", "an" and the like refers to one or more.

[026] As used herein, reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[027] "Alkyl" refers to and includes saturated linear or branched univalent hydrocarbon structures and combinations thereof. Particular alkyl groups are those having 1 to 6 carbon atoms (a "C1-C6 alkyl"). When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "butyl" is meant to include *n*-butyl, *sec*-butyl, *iso*-butyl, and *tert*-butyl; "propyl" includes *n*-propyl and *iso*-propyl. This term is exemplified by groups such as methyl, *t*-butyl, *n*-heptyl, octyl, and the like.

[028] "Alkenyl" refers to an unsaturated hydrocarbon group having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C) and preferably having from 2 to 10 carbon atoms and more preferably 2 to 8 carbon atoms. Examples of alkenyl include but are not limited to ethenyl "$–CH=CH_2$", $–CH_2-CH=CH-CH_3$ and $–CH=CH-CH=CH_2$.

[029] "Alkynyl" refers to an unsaturated hydrocarbon group having at least one site of acetylenic unsaturation (*i.e.*, having at least one moiety of the formula C≡C) and preferably having from 2 to 10 carbon atoms and more preferably 2 to 8 carbon atoms and the like. Examples of alkynyl include but are not limited to ethynyl "-C≡CH", $-CH_2-C≡C-CH_3$ and -C≡C-C≡CH.

[030] "Cycloalkyl" refers to and includes cyclic univalent hydrocarbon structures. Cycloalkyl can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantyl. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. A preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 13 annular carbon atoms. A more preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 6 annular carbon atoms (a "C3-C6 cycloalkyl"). Examples of cycloalkyl groups include adamantyl, decahydronaphthalenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[031] "Cycloalkenyl" refers to an unsaturated hydrocarbon group within a cycloalkyl having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C). Cycloalkenyl can consist of one ring, such as cyclohexyl, or multiple rings, such as norbornenyl. A more preferred cycloalkenyl is an unsaturated cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_3-C_8 cycloalkenyl"). Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and the like.

[032] "Heterocycle", "heterocyclic", or "heterocyclyl" refers to a saturated or an unsaturated non-aromatic group having a single ring or multiple condensed rings, and having from 1 to 10 annular carbon atoms and from 1 to 4 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like. A heterocycle comprising more than one ring may be fused, spiro or bridged, or any combination thereof. In fused ring systems, one or more of the rings can be aryl or heteroaryl. A heterocycle having more than one ring where at least one ring is aromatic may be connected to the parent structure at either a non-aromatic ring position or at an aromatic ring position. In one variation, a heterocycle having more than one ring where at least one ring is aromatic is connected to the parent structure at a non-aromatic ring position.

[033] "Aryl" as used herein refers to an unsaturated aromatic carbocyclic group having a single ring *(e.g.,* phenyl) or multiple condensed rings *(e.g.,* naphthyl or anthryl) which condensed rings mayor may not be aromatic. The aryl group may be optionally substituted independently with one or more substituents described herein. Particular aryl groups are those having from 6 to 14 annular (i.e., ring) carbon atoms (a "C6-C14 aryl"). An aryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, an aryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[034] "Heteroaryl" as used herein refers to an unsaturated aromatic cyclic group having from 1 to 14 annular (i.e., ring) carbon atoms and at least one annular heteroatom, including but not

limited to heteroatoms such as nitrogen, oxygen and sulfur. A heteroaryl group may have a single ring (e.g., pyridyl, furyl) or multiple condensed rings (e.g., indolizinyl, benzothienyl) which condensed rings mayor may not be aromatic. The heteroaryl group may be optionally substituted independently with one or more substituents described herein. Particular heteroaryl groups are 5- to 14-membered rings having 1 to 12 annular (i.e., ring) carbon atoms and 1 to 6 annular (i.e., ring) heteroatoms independently selected from nitrogen, oxygen and sulfur; 5- to 10-membered rings having 1 to 8 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur; and 5-,6- or 7-membered rings having 1 to 5 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In one variation, heteroaryl includes monocyclic aromatic 5-, 6- or 7-membered rings having from 1 to 6 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In another variation, heteroaryl includes polycyclic aromatic rings having from 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. A heteroaryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, a heteroaryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[035] "Alkoxy" refers to the group alkyl-O-, which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

[036] "Hydroxyalkyl" refers to the group alkyl-OH, which includes, by way of example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxyprop-1-yl, 2-hydroxyprop-2-yl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl, 6-hydroxyhexyl, and the like.

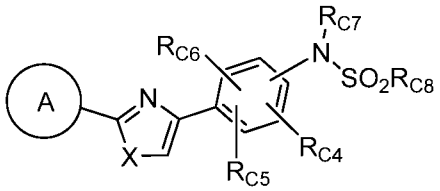
[037] "Halogen" refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include the radicals of fluorine, chlorine, bromine and iodine. Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, e.g., dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two ("di") or three ("tri") halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each H is replaced with a halo group is referred to as a "perhaloalkyl." An alkenyl group in which each H is replaced with a halo group is referred to as a "perhaloalkenyl." An alkynyl group in which each H is replaced with a halo

group is referred to as a "perhaloalkynyl." A preferred perhaloalkyl group is trifluoroalkyl (-CF_3). Similarly, "perhaloalkoxy" refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (–OCF_3).

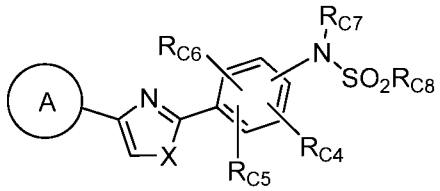
[038] Any and all stereoisomers, including geometric isomers (*cis*/*trans* or *E*/*Z* isomers), tautomers, salts, N-oxides, and solvates of the compounds described herein can be used in the disclosed methods. This disclosure also provides methods of making such compounds.

Compounds

[039] In some embodiments, compounds disclosed herein fall within formulae (Ia) or (Ib):



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof, wherein:

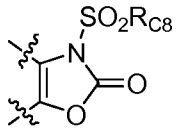
A is either:

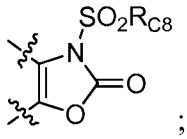
i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -OBn, -CO_2H, -CO_2-Alkyl, -N**R10R11**, and -CON**R10R11**; or

ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -CH_2OH, -OBn, -CO_2H, -CO_2-Alkyl, -N**R10R11**, and -CON**R10R11**;

Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6

cycloalkenyl, C1-C3 linear or branched alkoxy, -CO_2H, -CON**R10R11**, or -$NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety  ;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -($C\mathbf{R_{9a}R_{9b}})_mN\mathbf{R10R11}$, -$CO_2$-Alkyl, -($C\mathbf{R_{9a}R_{9b}})_m$O-Alkyl, -($C\mathbf{R_{9a}R_{9b}})_m OPO_3Na_2$, -($C\mathbf{R_{9a}R_{9b}})_m$O($C\mathbf{R_{9a}R_{9b}})_n$O-Alkyl, -($C\mathbf{R_{9a}R_{9b}})_m$O(C=O)-Alkyl, -($C\mathbf{R_{9a}R_{9b}})_m$O($C\mathbf{R_{9a}R_{9b}})_n$O(C=O)-Alkyl, –(C=O)CH=$CH_2$, -$SO_2\mathbf{R_{C8'}}$; or is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety  ;

$\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

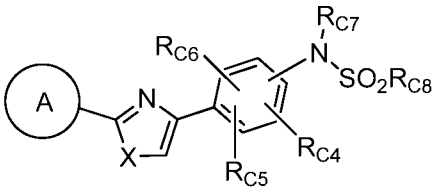
Each $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, -$SO_2\mathbf{R_{C8'}}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

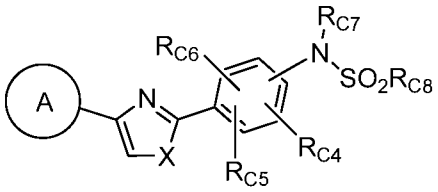
X is a heteroatom selected from S, O; or $N\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

[040] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):



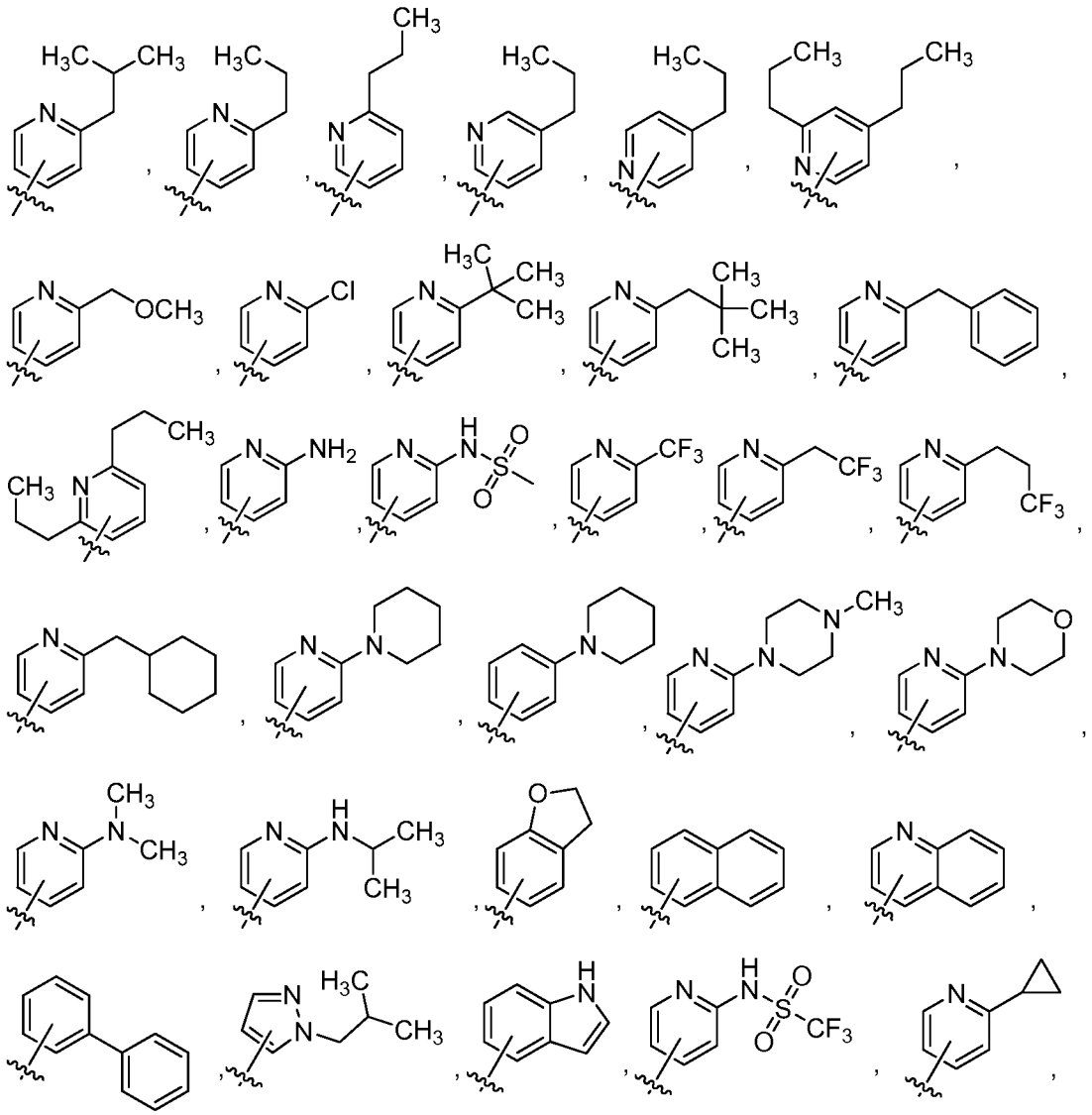
(IIa)

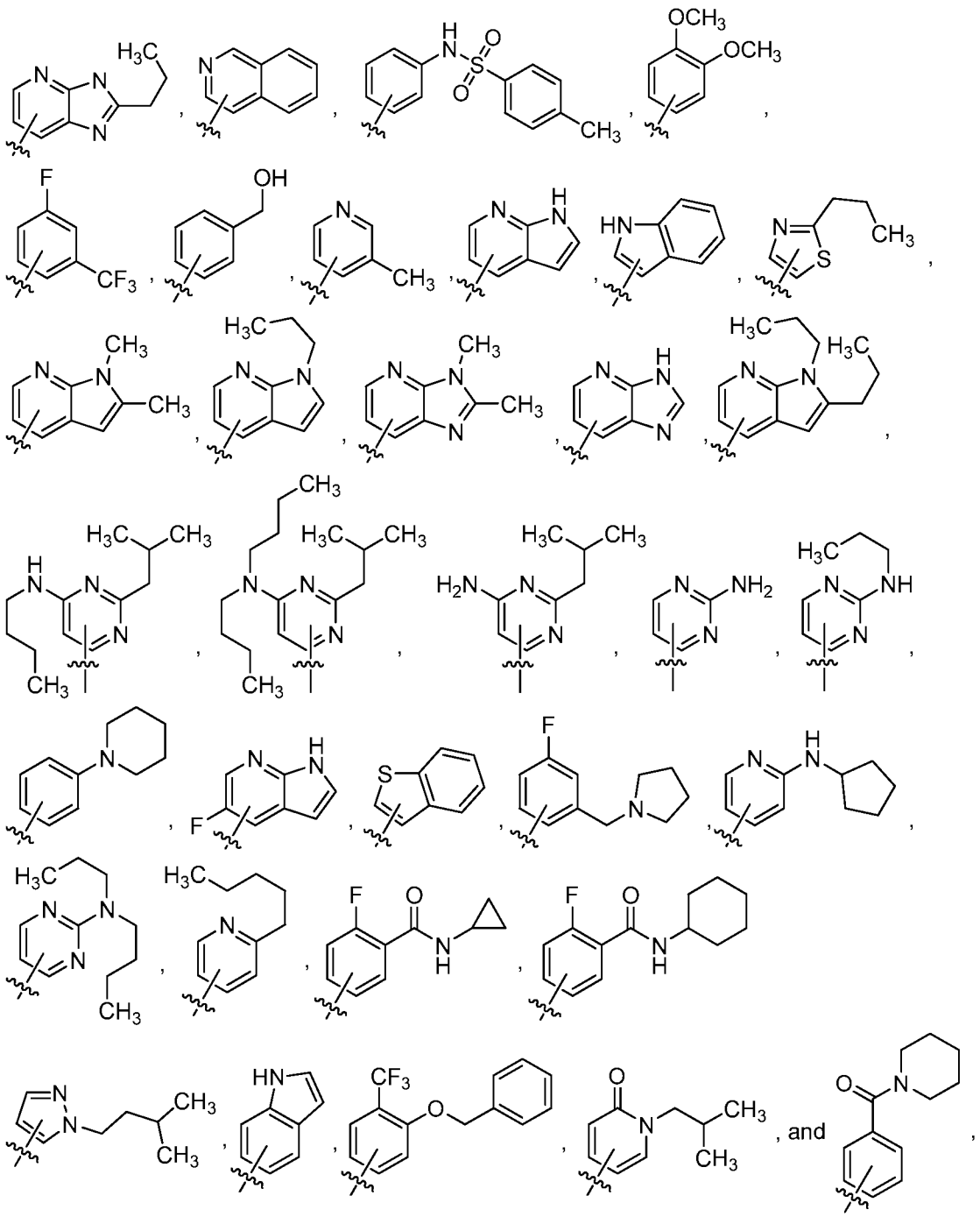


(IIb)

or a pharmaceutically acceptable salt thereof, wherein:

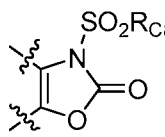
A is a moiety selected from the group consisting of:

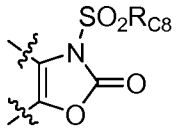




wherein the ring containing X is linked to ring A at any available position on ring A;

Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-CO_2H$, -CON**R10R11**, or $-NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety  ;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$N**R10R11**, -CO_2-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$$OPO_3Na_2$, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O($C\mathbf{R_{9a}R_{9b}}$)$_n$O-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O(C=O)-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O($C\mathbf{R_{9a}R_{9b}}$)$_n$O(C=O)-Alkyl, –(C=O)CH=$CH_2$, -$SO_2\mathbf{R_{C8'}}$; or is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety 

;

$\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

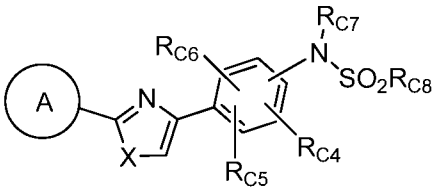
Each $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, -$SO_2\mathbf{R_{C8'}}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

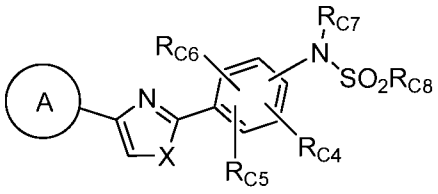
X is a heteroatom selected from S, O; or N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

[041] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):



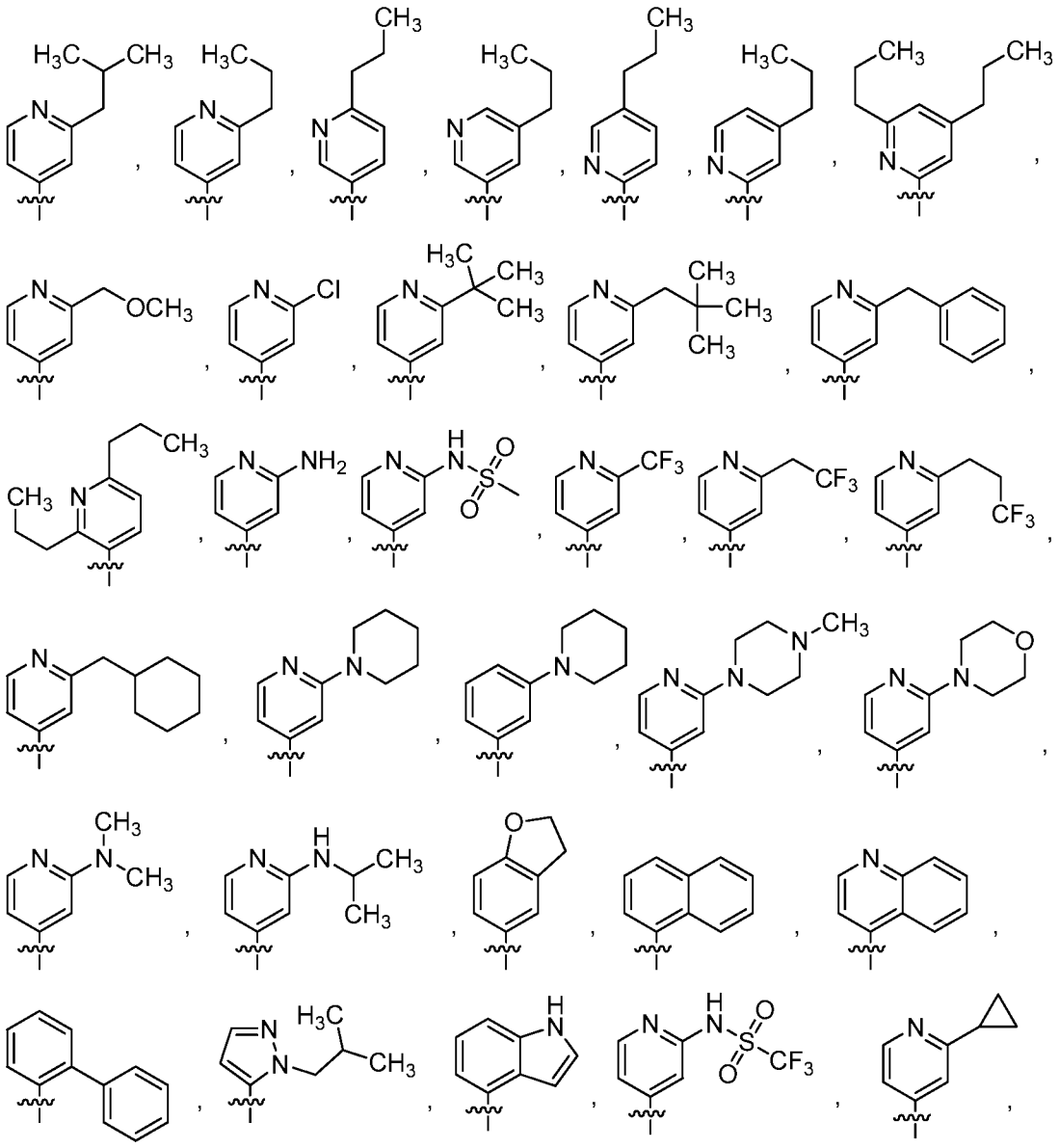
(IIa)

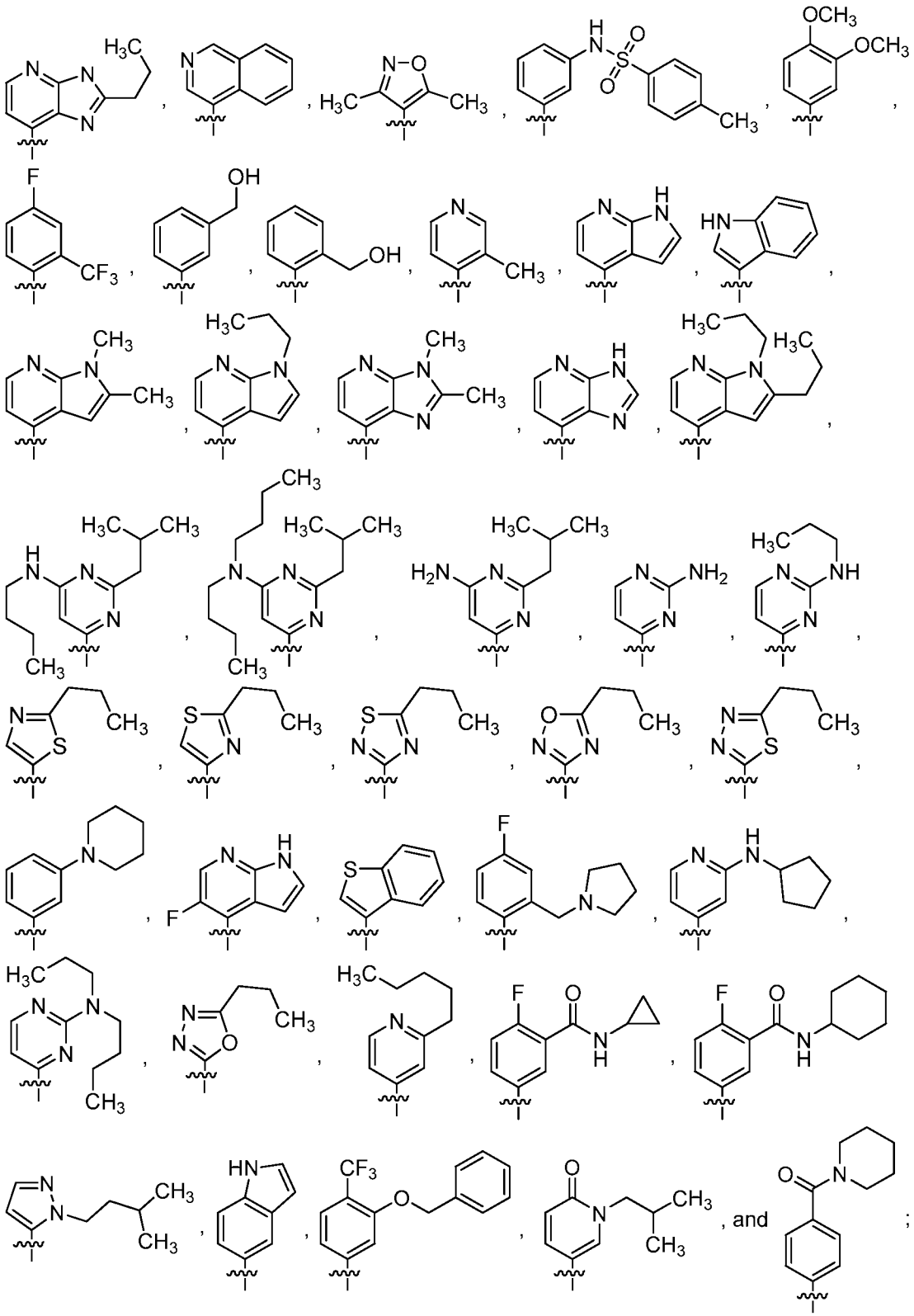


(IIb)

or a pharmaceutically acceptable salt thereof, wherein:

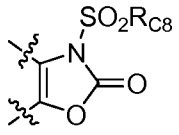
A is a moiety selected from the group consisting of:

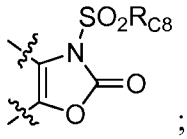




Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6

cycloalkenyl, C1-C3 linear or branched alkoxy, -CO_2H, -CON**R10R11**, or -$NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety  ;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$NR10R11, -CO_2-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$$OPO_3Na_2$, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O($C\mathbf{R_{9a}R_{9b}}$)$_n$O-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O(C=O)-Alkyl, -($C\mathbf{R_{9a}R_{9b}}$)$_m$O($C\mathbf{R_{9a}R_{9b}}$)$_n$O(C=O)-Alkyl, –(C=O)$CH=CH_2$, -$SO_2\mathbf{R_{C8'}}$; or is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety  ;

$\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

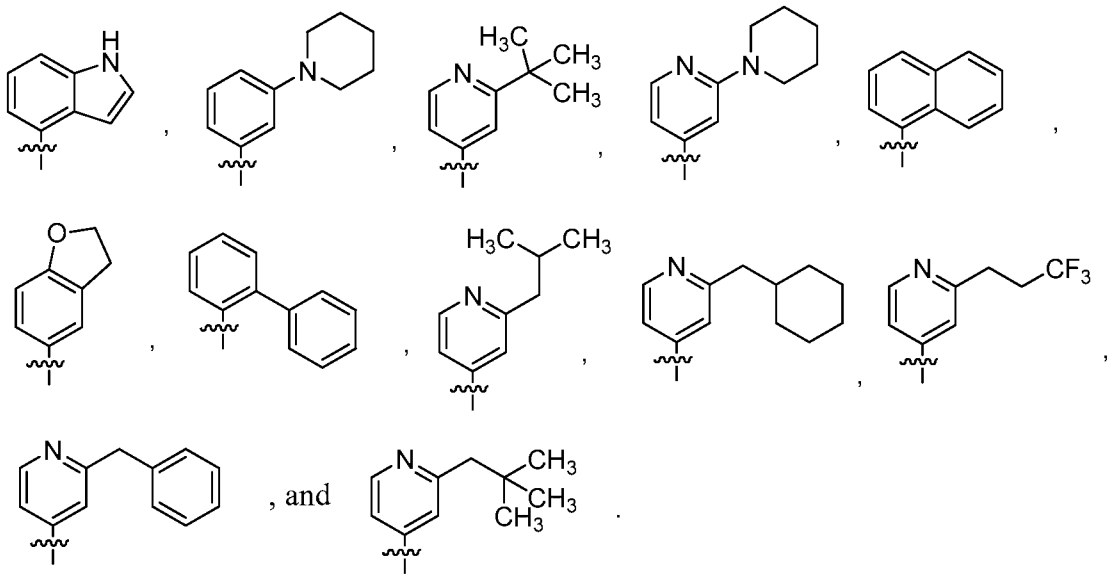
Each $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, -$SO_2\mathbf{R_{C8'}}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

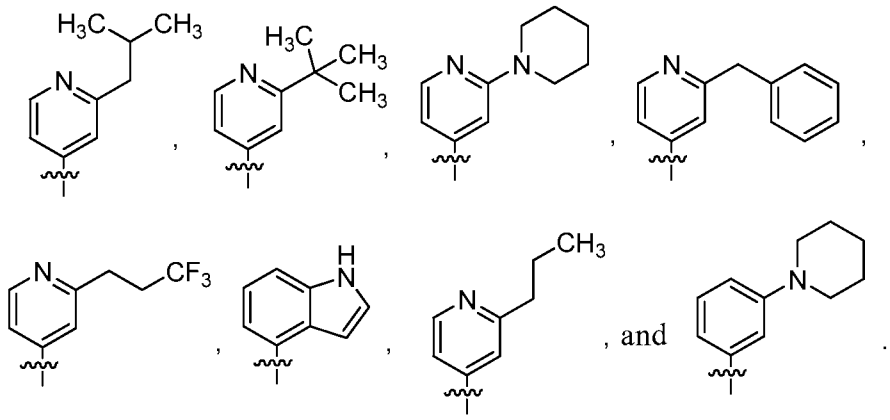
X is a heteroatom selected from S, O; or N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

[042] In some variations of Formulae (IIa) or (IIb), A is a moiety selected from the group consisting of:

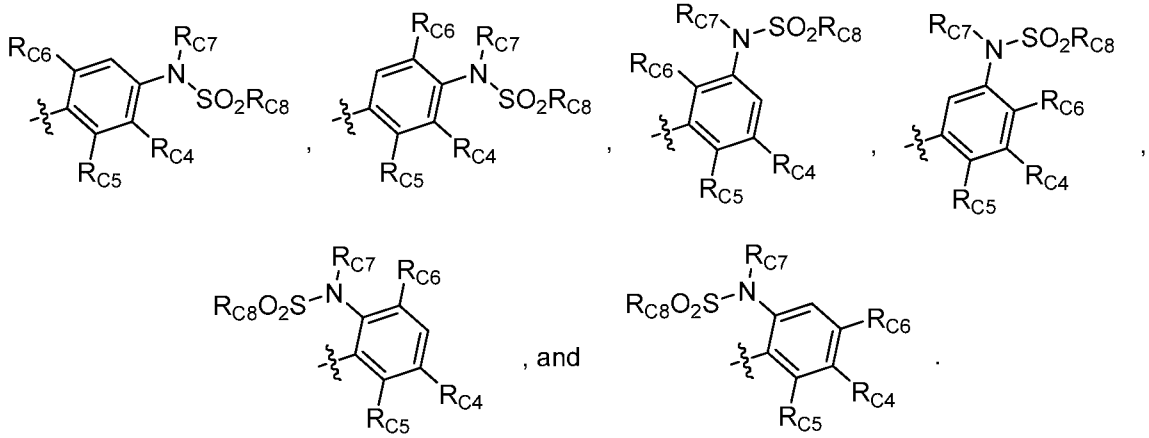


[043] In some variations of Formulae (IIa) or (IIb), A is a moiety selected from the group consisting of:

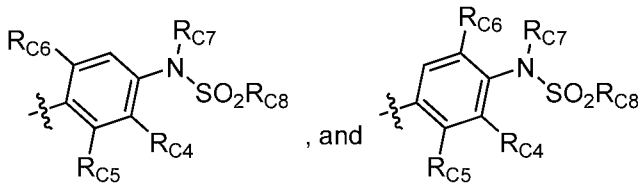


[044] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), X is S. In some variations, X is O. In some variations, X is N$\mathbf{R_B}$, wherein $\mathbf{R_B}$ is hydrogen. In some variations, X is N$\mathbf{R_B}$, wherein $\mathbf{R_B}$ is a linear or branched C1-C6 alkyl. In these variations, $\mathbf{R_B}$ is a linear C1-C6 alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl. In particular variations, $\mathbf{R_B}$ is methyl. In some variations, $\mathbf{R_B}$ is a branched C1-C6 alkyl selected from iso-propyl, iso-pentyl, and tert-butyl.

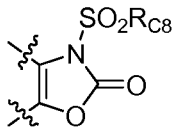
[045] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from:



[046] In particular variations of Formulae (Ia), (Ib), (IIa) or (IIb), the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from:



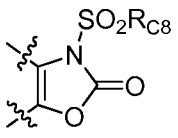
[047] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is hydrogen. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is halogen. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is CN. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is CF_3. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is OH. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is C1-C3 linear or branched alkyl. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is C2-C3 alkenyl. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is C2-C3 alkynyl. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is C3-C6 cycloalkyl. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is C3-C6 cycloalkenyl. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is C1-C3 linear or branched alkoxy. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is $-CON(CH_3)_2$. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is $-CO_2H$. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is $-CONH_2$. In some variations, one

or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is -$NHCONH_2$. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is–$CONHCH_3$. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is taken with $\mathbf{R_{C7}}$ to form the moiety 

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[048] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is hydrogen. In some variations, two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are hydrogen. In some variations, each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is hydrogen. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is methoxy. In some variations, one or more of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is OH.

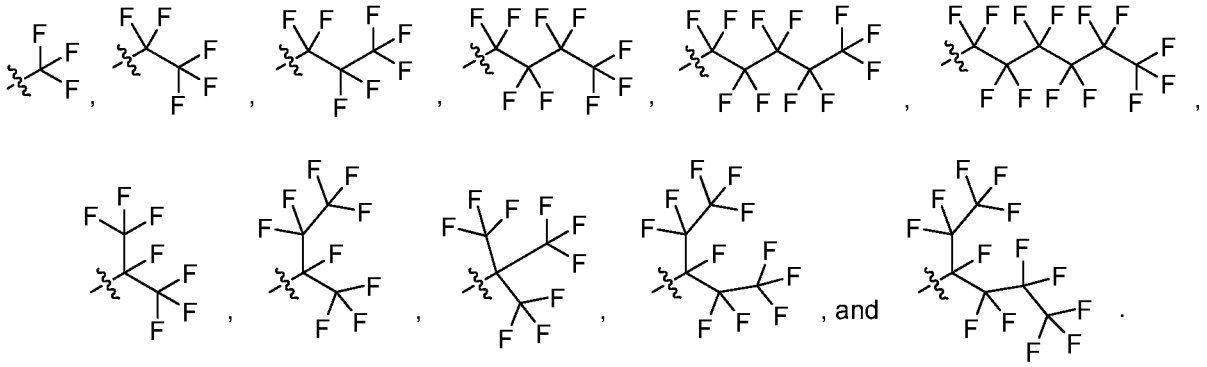
[049] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is halogen. In some variations, two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are halogen. In some variations each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is halogen. In some variations, one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is hydrogen, and the remaining two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are halogen. In some variations, two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are hydrogen, and the remaining one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is halogen. In some variations, $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are each halogen. In some embodiments, one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is fluoro, chloro or bromo. In some embodiments, two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are fluoro, chloro or bromo. In some embodiments, one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is chloro. In some embodiments, one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is chloro and one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is bromo. In some embodiments, $\mathbf{R_{C4}}$ is chloro. In some embodiments, $\mathbf{R_{C5}}$ is chloro. In some embodiments, $\mathbf{R_{C4}}$ is bromo. In some embodiments, $\mathbf{R_{C5}}$ is bromo.

[050] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), $\mathbf{R_{C7}}$ is hydrogen. In some variations, $\mathbf{R_{C7}}$ is C1-C6 linear or branched alkyl. In some variations, $\mathbf{R_{C7}}$ is C1-C6 linear or branched hydroxyalkyl. In some variations, $\mathbf{R_{C7}}$ is -$(\mathbf{CR_{9a}R_{9b}})_m\mathbf{NR10R11}$. In some variations, $\mathbf{R_{C7}}$ is -CO_2-Alkyl. In some variations, $\mathbf{R_{C7}}$ is -$(\mathbf{CR_{9a}R_{9b}})_m$O-Alkyl. In some variations, $\mathbf{R_{C7}}$ is -$(\mathbf{CR_{9a}R_{9b}})_m OPO_3Na_2$. In some variations, $\mathbf{R_{C7}}$ is -$(\mathbf{CR_{9a}R_{9b}})_m O(\mathbf{CR_{9a}R_{9b}})_n$O-Alkyl. In some variations, $\mathbf{R_{C7}}$ is -$(\mathbf{CR_{9a}R_{9b}})_m$O(C=O)-Alkyl. In some variations, $\mathbf{R_{C7}}$ is -$(\mathbf{CR_{9a}R_{9b}})_m O(\mathbf{CR_{9a}R_{9b}})_n$O(C=O)-Alkyl. In some variations, $\mathbf{R_{C7}}$ is –(C=O)$CH=CH_2$. In some variations, $\mathbf{R_{C7}}$ is -$SO_2\mathbf{R_{C8}}$. In some variations, $\mathbf{R_{C7}}$ is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety 

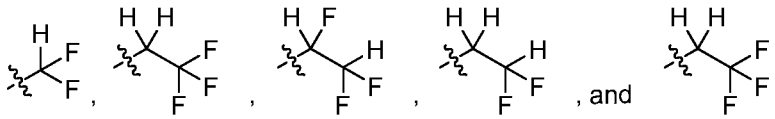
.

[051] In all embodiments, $\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6

alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom. In some embodiments, $\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl. In some embodiments, the C1-C6 perhaloalkyl is a C1-C6 perfluoroalkyl. In some embodiments, the C1-C6 perfluoroalkyl is selected from

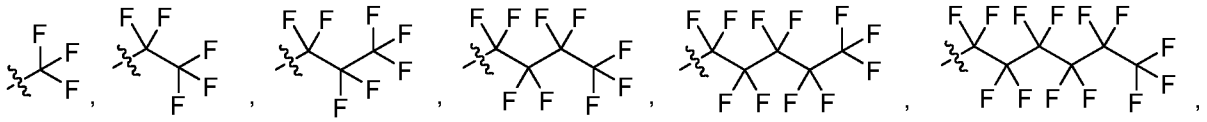


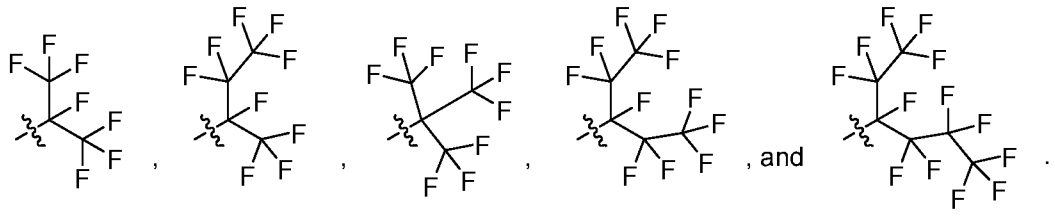
In preferred embodiments, the C1-C6 perfluoroalkyl is $-CF_3$. In some embodiments, $\mathbf{R_{C8}}$ is a linear or branched C1-C6 alkyl having at least two halogen atoms. In some embodiments, $\mathbf{R_{C8}}$ is selected from:



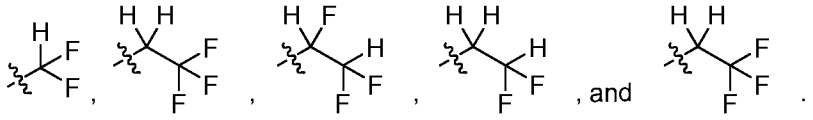
[052] In some embodiments, $\mathbf{R_{C8}}$ is a linear or branched C2-C6 perhaloalkenyl. In some embodiments, $\mathbf{R_{C8}}$ is a linear or branched C2-C6 perhaloalkynyl. In some embodiments, $\mathbf{R_{C8}}$ is a linear or branched C1-C6 alkyl having at least one halogen atom. In some embodiments, $\mathbf{R_{C8}}$ is a linear or branched C2-C6 alkenyl having at least one halogen atom. In some embodiments, $\mathbf{R_{C8}}$ is or a linear or branched C2-C6 alkynyl having at least one halogen atom.

[053] In some embodiments, $\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom. In some embodiments, $\mathbf{R_{C8'}}$ is a linear or branched C1-C6 perhaloalkyl. In some embodiments, the C1-C6 perhaloalkyl is a C1-C6 perfluoroalkyl. In some embodiments, the C1-C6 perfluoroalkyl is selected from





In preferred embodiments, the C1-C6 perfluoroalkyl is $-CF_3$. In some embodiments, $\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl having at least two halogen atoms. In some embodiments, $\mathbf{R_{C8'}}$ is selected from:



[054] In some embodiments, $\mathbf{R_{C8'}}$ is a linear or branched C2-C6 perhaloalkenyl. In some embodiments, $\mathbf{R_{C8'}}$ is a linear or branched C2-C6 perhaloalkynyl. In some embodiments, $\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl having at least one halogen atom. In some embodiments, $\mathbf{R_{C8'}}$ is a linear or branched C2-C6 alkenyl having at least one halogen atom. In some embodiments, $\mathbf{R_{C8'}}$ is or a linear or branched C2-C6 alkynyl having at least one halogen atom.

[055] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), both $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$ are hydrogen. In some embodiments, $\mathbf{R_{9a}}$ is hydrogen, and $\mathbf{R_{9b}}$ is C1-C6 linear or branched alkyl. In some embodiments, both $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$ are C1-C6 linear or branched alkyl. In some embodiments, $\mathbf{R_{9a}}$ is hydrogen, and $\mathbf{R_{9b}}$ is methyl.

[056] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one or both of **R10** and **R11** are hydrogen. In some variations, one or both of **R10** and **R11** are $-SO_2\mathbf{R_{C8'}}$. In some variations, one or both of **R10** and **R11** are C1-C6 linear or branched alkyl. In some variations, one or both of **R10** and **R11** are C2-C6 linear or branched alkenyl. In some variations, one or both of **R10** and **R11** are C3-C6 cycloalkyl. In some variations, one or both of **R10** and **R11** are C3-C6 cycloalkenyl.

[057] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), **R10** and **R11** are taken together with the N to which they are attached to form a C3-C6 heterocycle. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a pyrrolidin-2-one or pyrrolidin-3-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a piperidin-2-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a piperidin-3-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a piperidin-4-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form an

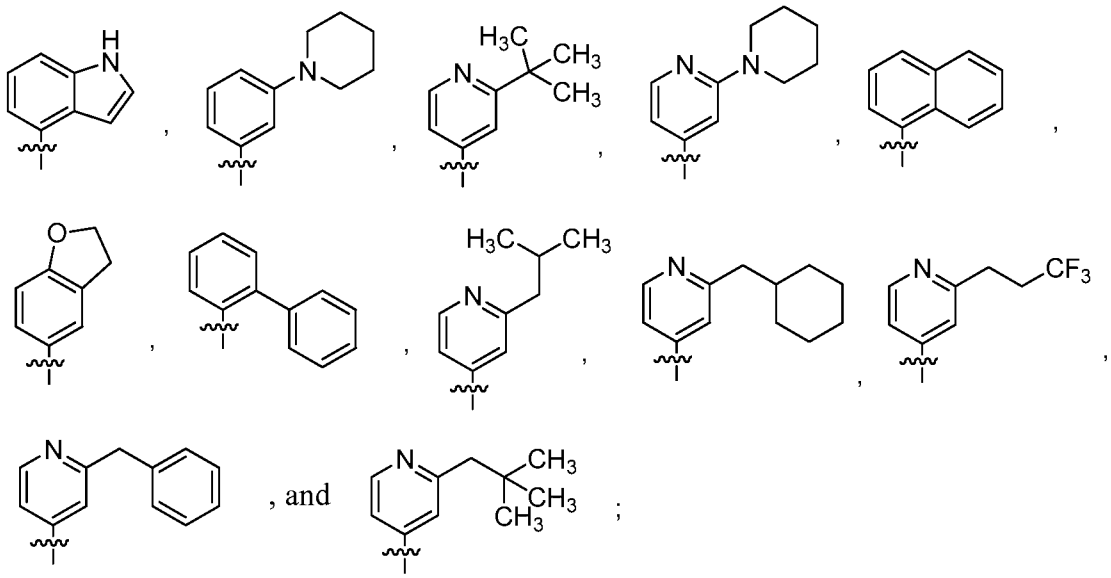
oxazolidinone. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form an oxazinanone. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form an imidazolidinone. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a tetrahydropyrimidin-2(1H)-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a $1\lambda^6$,2-thiazolidine-1,1-dione. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione

[058] In some variations, the compound is of formula (Ia) or (IIa), wherein **X** is a heteroatom selected from S, O; or N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, X is S. In some variations, X is O. In some variations, X is N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, X is N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is a C1-C6 linear or branched alkyl. In some variations, X is N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is C3-C6 cycloalkyl.

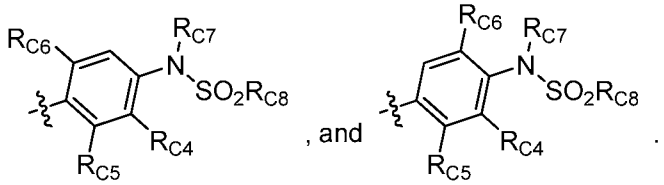
[059] In some variations, the compound is of formula (Ib) or (IIb), wherein **X** is a heteroatom selected from S, O; or N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, X is S. In some variations, X is O. In some variations, X is N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, X is N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is a C1-C6 linear or branched alkyl. In some variations, X is N$\mathbf{R_B}$ wherein $\mathbf{R_B}$ is C3-C6 cycloalkyl.

[060] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), both ***m*** and ***n*** are 1. In some variations, ***m*** is 1 and ***n*** is 2. In some variations, ***m*** is 1 and ***n*** is 3. In some variations, ***m*** is 2 and ***n*** is 1. In some variations, both ***m*** and ***n*** are 2. In some variations, ***m*** is 2 and ***n*** is 3. In some variations, ***m*** is 3 and ***n*** is 1. In some variations, ***m*** is 3 and ***n*** is 2. In some variations, both ***m*** and ***n*** are 3.

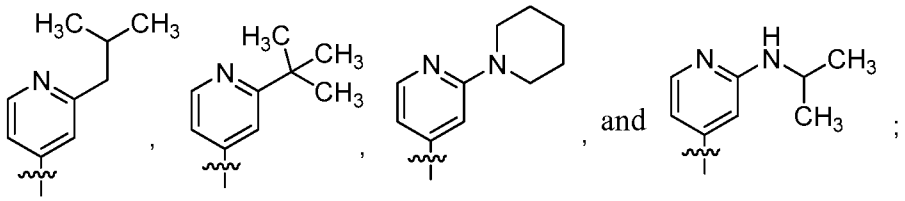
[061] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), A is a moiety selected from



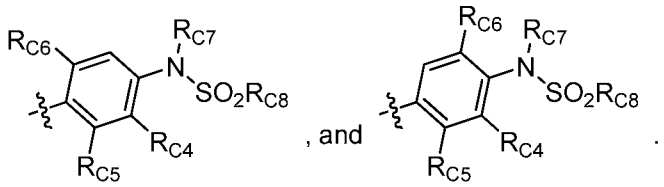
X is S, and the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from:



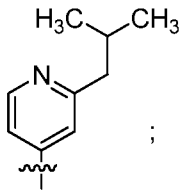
[062] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), A is a moiety selected from



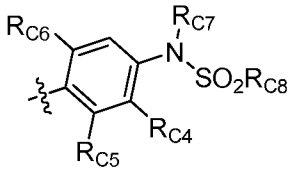
X is S, and the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from

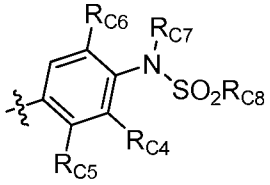


[063] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), A is



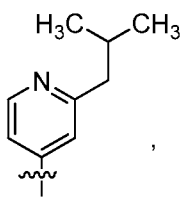
X is S; the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is selected from

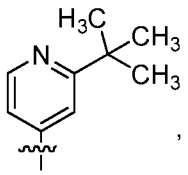


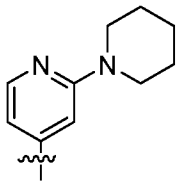
, and


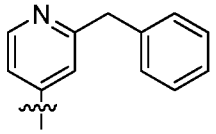
; wherein $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$ are hydrogen or halogen; $\mathbf{R_{C7}}$ is hydrogen; and $\mathbf{R_{C8}}$ is perfluoroalkyl. In some variations $\mathbf{R_{C8}}$ is $-CF_3$.

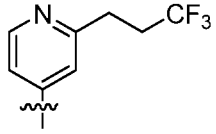
[064] In some variations, the compound is of Formula (Ia), wherein A is a moiety selected from

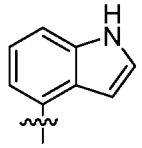


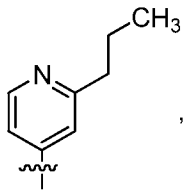
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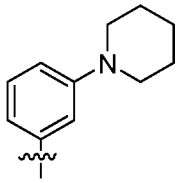
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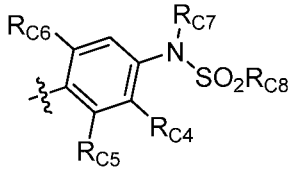
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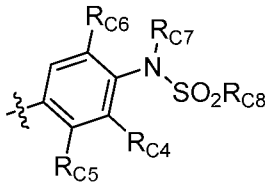
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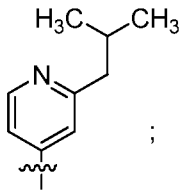
X is S, and the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from



, and


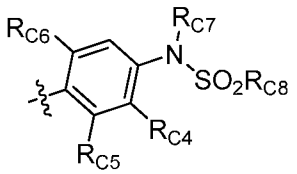
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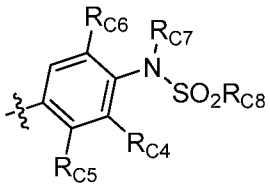
[065] In particular variations, the compound is of Formula (Ia), wherein A is



;

X is S; the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is selected from



, and


; wherein $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$ are hydrogen or halogen; $\mathbf{R_{C7}}$ is hydrogen and $\mathbf{R_{C8}}$ is perfluoroalkyl. In some variations, $\mathbf{R_{C8}}$ is $-CF_3$.

[066] It is intended and understood that each and every variation of A, $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, $\mathbf{R_{C7}}$, $\mathbf{R_{C8}}$, $\mathbf{R_{C8'}}$, $\mathbf{R_{9a}}$, $\mathbf{R_{9b}}$, **R10**, **R11**, **X**, ***m***, and ***n***, where present, described for formulae (Ia) and (Ib), may be combined with each and every variation of A, $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, $\mathbf{R_{C7}}$, $\mathbf{R_{C8}}$, $\mathbf{R_{C8'}}$, $\mathbf{R_{9a}}$, $\mathbf{R_{9b}}$, **R10**, **R11**, **X**, ***m***, and ***n***, as if each and every combination is individually described.

[067] In some embodiments, the compound is selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1-propyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(3-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dipropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(6-(butylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(6-(dibutylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(6-amino-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-aminopyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(propylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dibutylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2'-propyl-2,4'-bithiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,2,4-thiadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,2,4-oxadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2'-propyl-2,5'-bithiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,3,4-thiadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,3,4-oxadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-6-oxo-1,6-dihydropyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-fluoro-3-isobutylphenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3,5-dichloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-(trifluoromethyl)phenyl)methanesulfonamide;

N-(2-cyclopropyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methylphenyl)methanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-isopropylphenyl)methanesulfonamide;

N-(2-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-6-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-6-methylphenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)-1-methyl-1H-imidazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-5-chloro-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)oxazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)oxazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dimethylamino)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(trifluoromethylsulfonyl)acrylamide;

N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(3,3,3-trifluoropropyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-hydroxyphenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethyl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

6-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethylsulfonyl)benzo[d]oxazol-2(3H)-one;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,2,2,2-pentafluoroethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;

1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide;

N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-chloropyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxopyrrolidin-1-yl)ethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxoimidazolidin-1-yl)ethyl)methanesulfonamide;

N-(2-bromo-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethyl acetate;

(2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethoxy)methyl acetate;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-(2-{[4-(3-chlorophenyl)-2-oxo-1,3,2λ^5-dioxaphosphinan-2-yl]oxy}ethyl)-1,1,1-trifluoromethanesulfonamide;

(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl acetate;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(methoxymethyl)methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-({[4-(3-chlorophenyl)-2-oxo-1,3,2λ^5-dioxaphosphinan-2-yl]oxy}methyl)-1,1,1-trifluoromethanesulfonamide;

methyl 4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl(trifluoromethylsulfonyl)carbamate;

sodium (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl phosphate;

1-(N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethylsulfonamido)ethyl isobutyrate;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(diethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(dimethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(3-fluoro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-methylmethanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(2-bromo-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-methyl-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2-butylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide

1,1,1-trifluoro-N-(4-(2-(2-(methoxymethyl)pyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(4,6-dipropylpyridin-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(4-propylpyridin-2-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2,6-dipropylpyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-(cyclohexylmethyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-methoxyphenyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-((trifluoromethylsulfonyl)methyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclopropyl-2-fluorobenzamide;

5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclohexyl-2-fluorobenzamide;

N-(4-(2-(1H-indol-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-5-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide; and

N-(2-bromo-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

[068] In some embodiments, the compound is selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;

1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide;

N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide; and

N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

[069] In some embodiments, the compound is selected from the group consisting of:

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide; and

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide.

[070] In some embodiments, the compound is compound #37: N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

[071] The compounds described below are not intended to be limiting; rather, these embodiments and variations are intended to provide examples of compounds within the scope of Formulae (Ia), (Ib), (IIa) or (IIb).

[072] Representative compounds are presented in Table 1.

Table 1

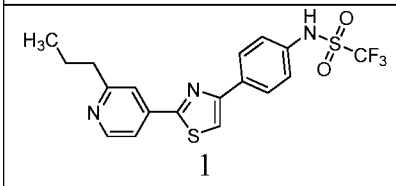
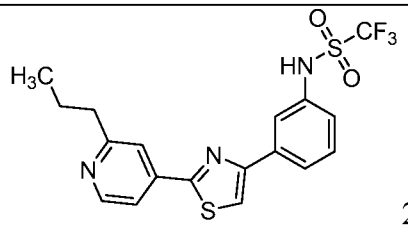
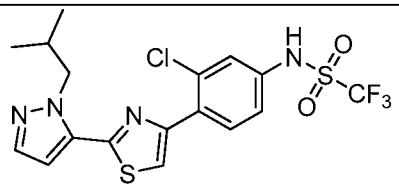
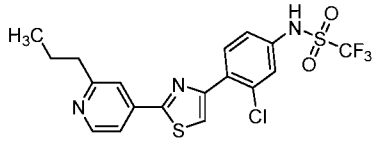
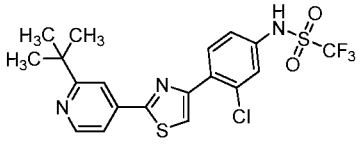
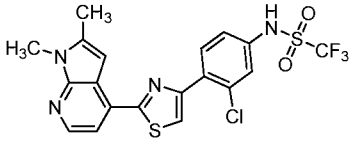
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Table 1

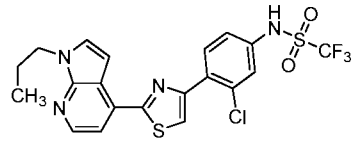
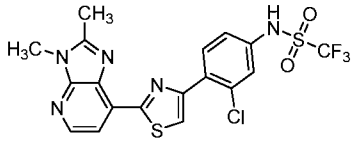
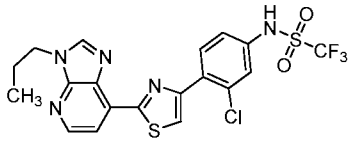
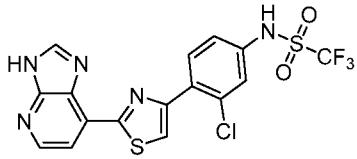
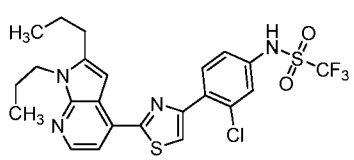
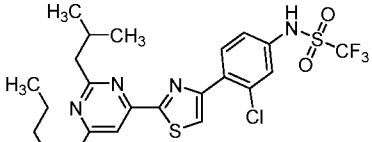
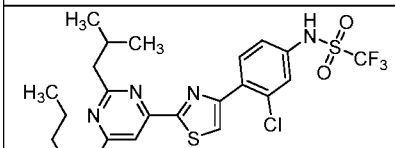
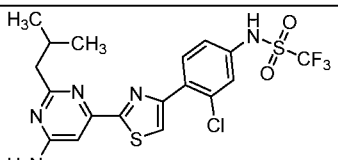
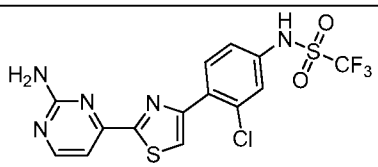
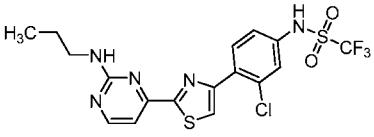
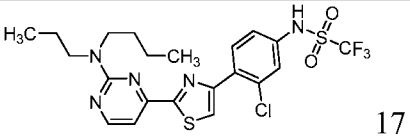
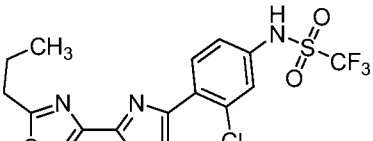
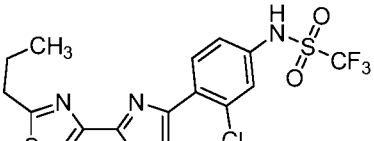
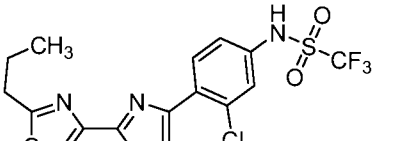
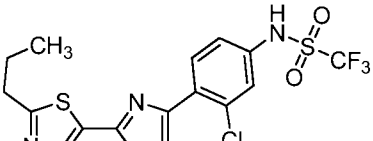
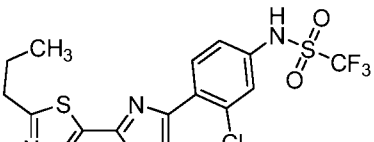
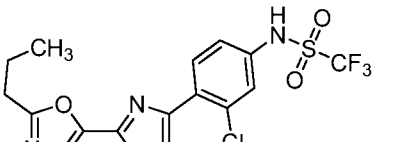
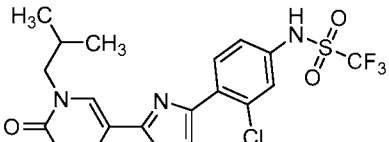
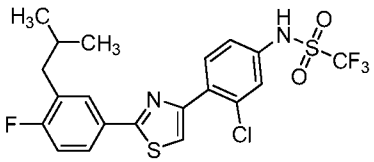
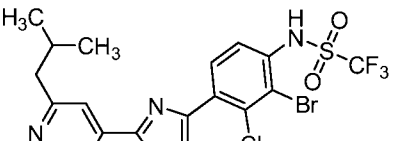
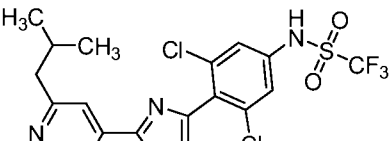
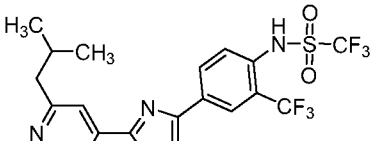
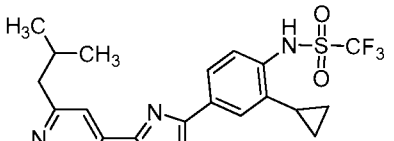
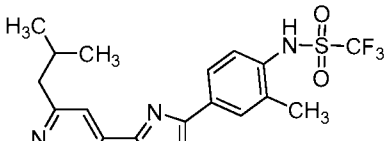
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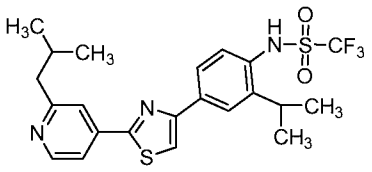
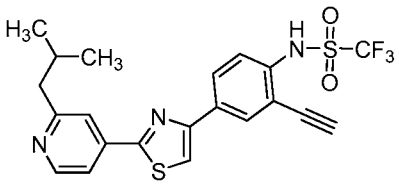
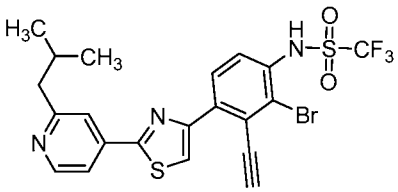
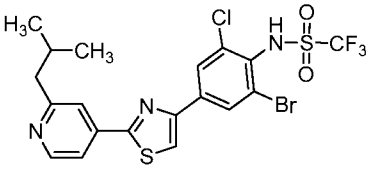
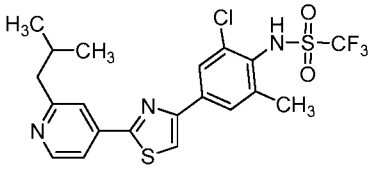
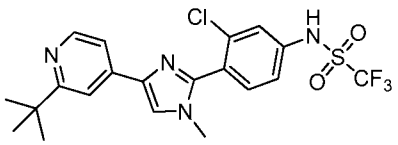
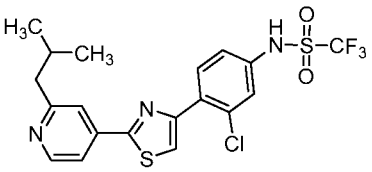
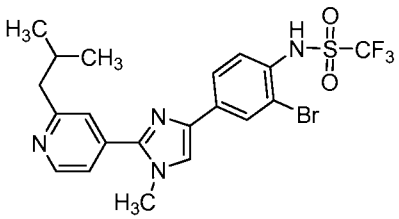
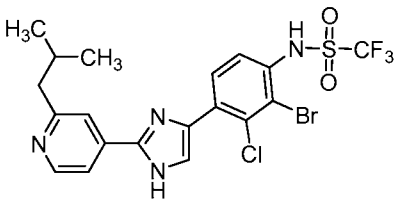
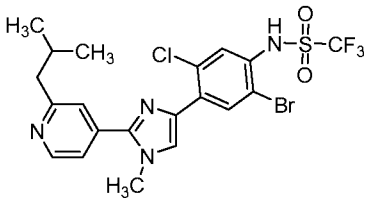
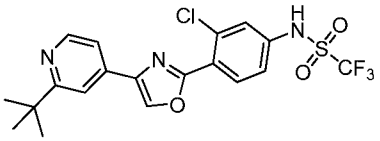
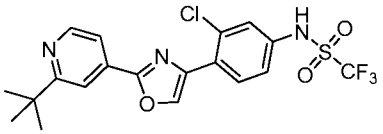
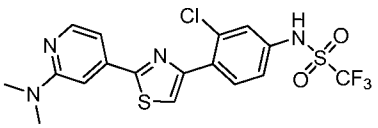
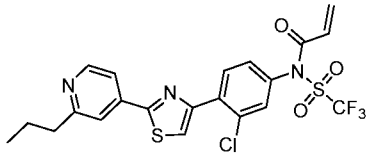
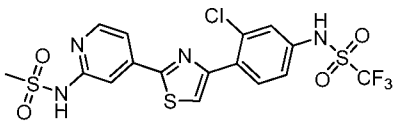
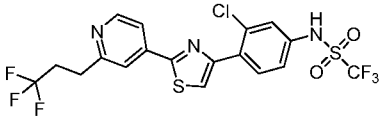
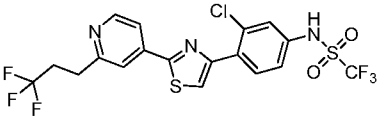
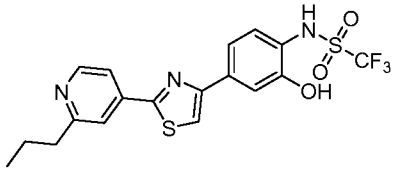
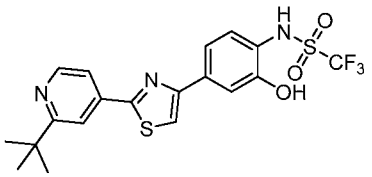
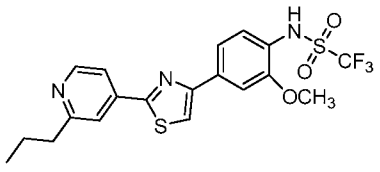
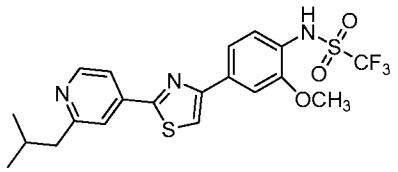
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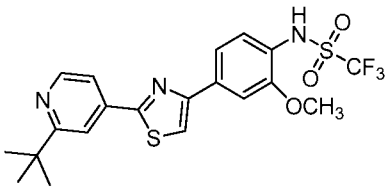
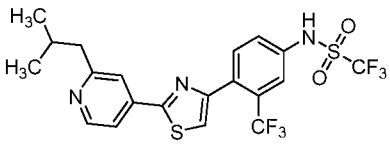
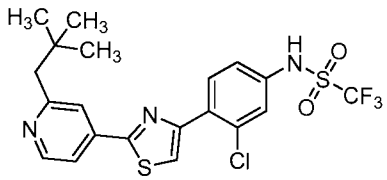
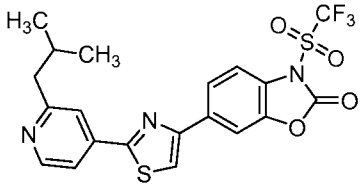
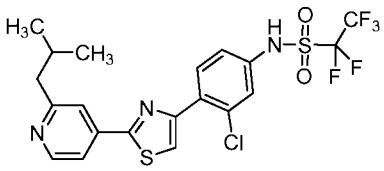
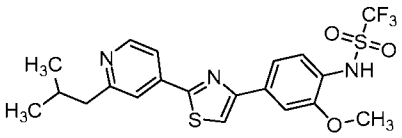
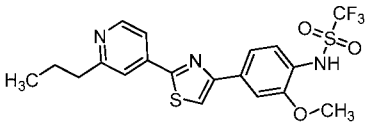
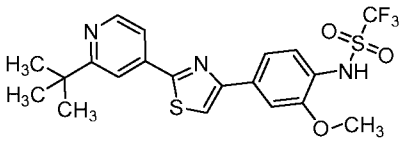
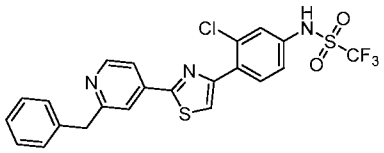
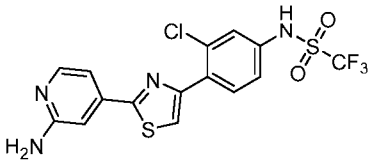
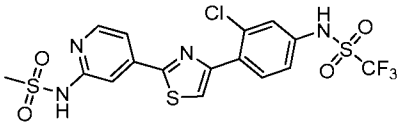
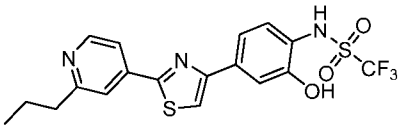
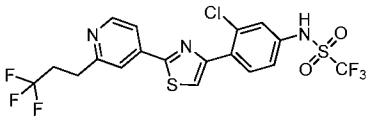
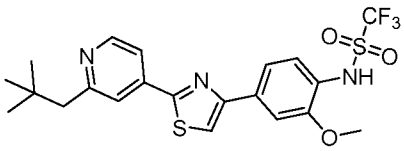
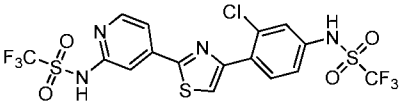
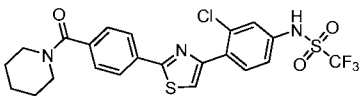
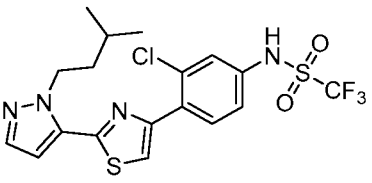
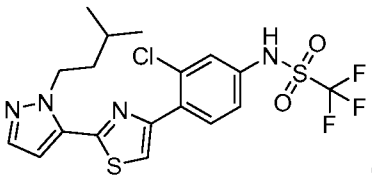
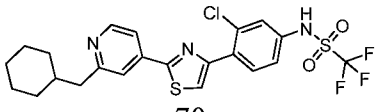
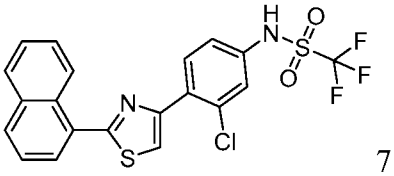
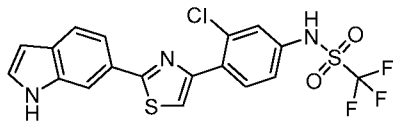
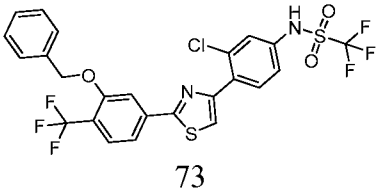
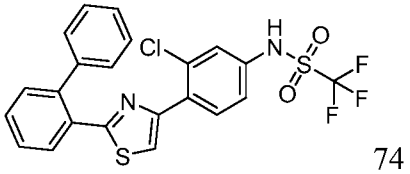
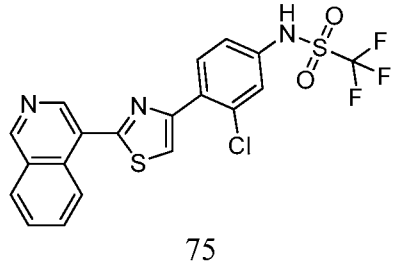
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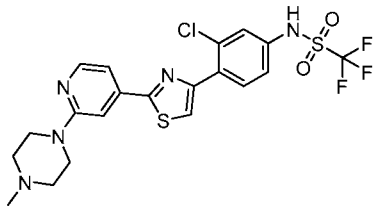
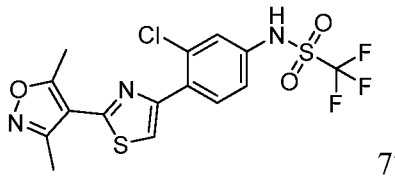
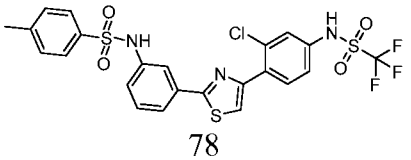
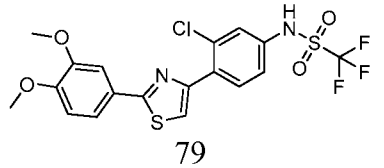
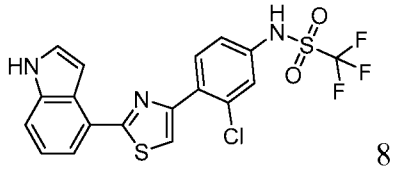
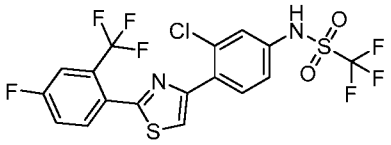
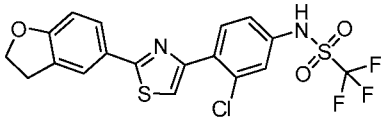
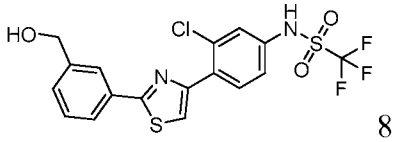
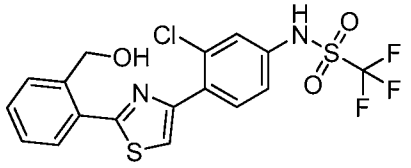
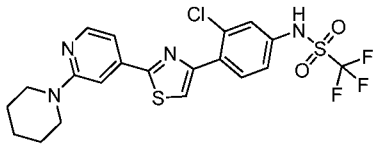
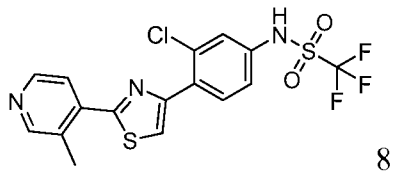
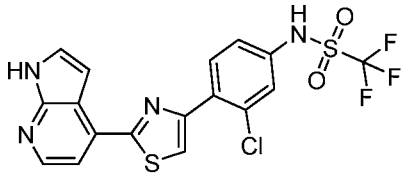
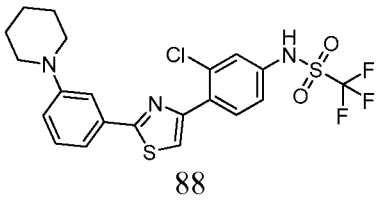
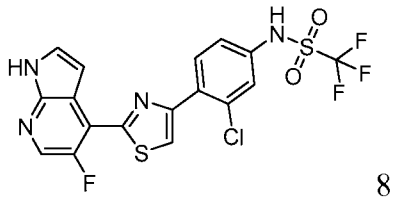
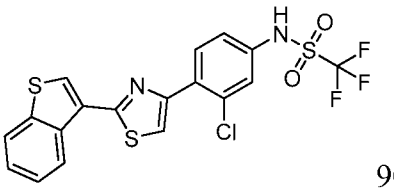
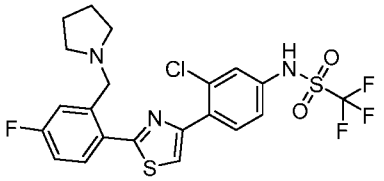
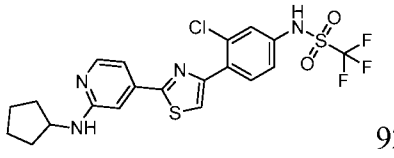
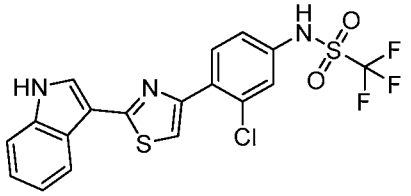
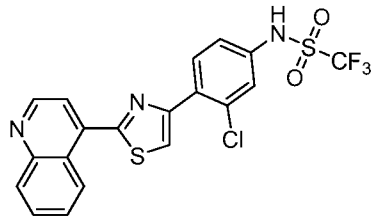
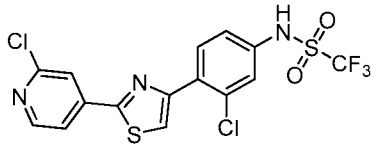
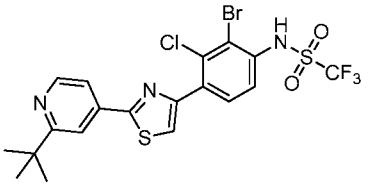
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Table 1

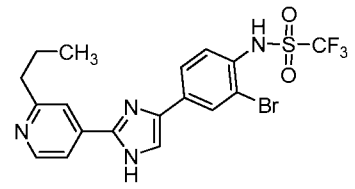
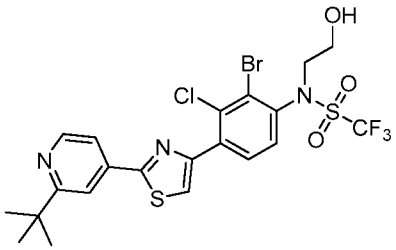
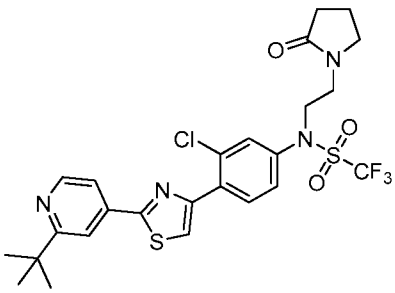
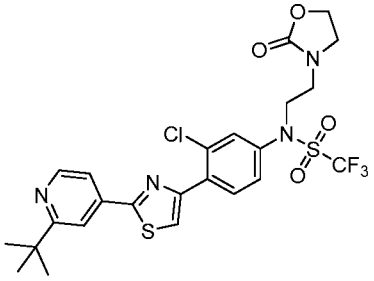
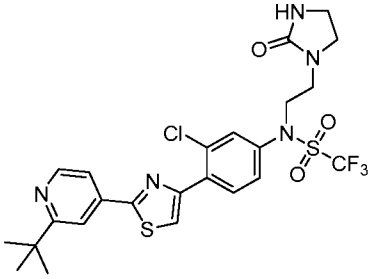
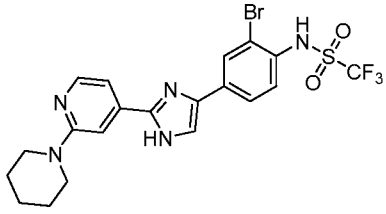
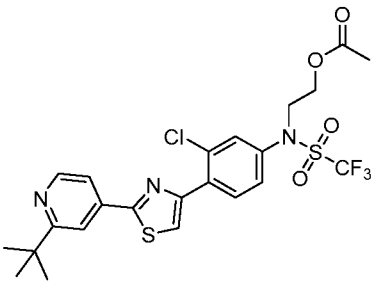
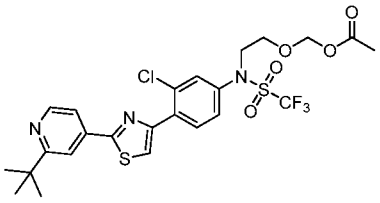
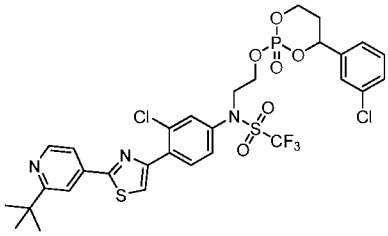
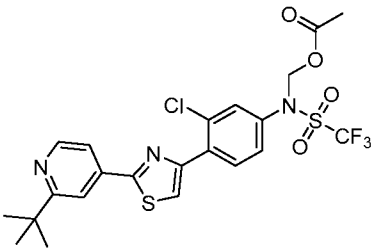
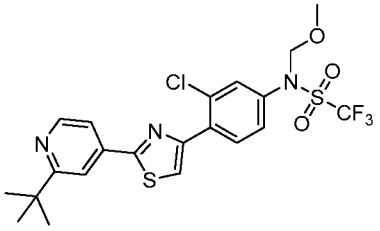
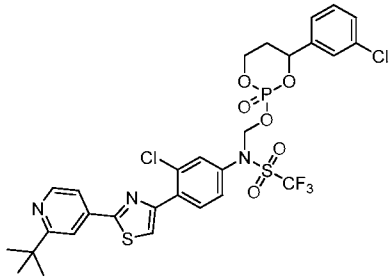
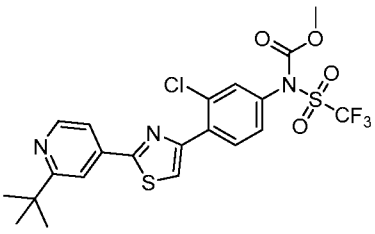
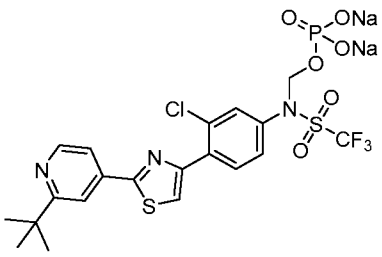
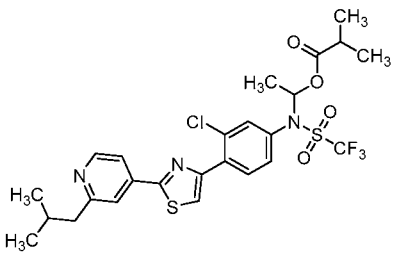
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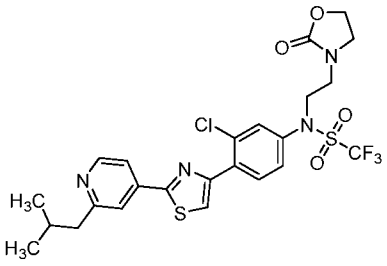
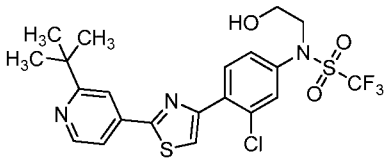
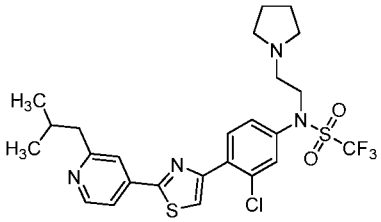
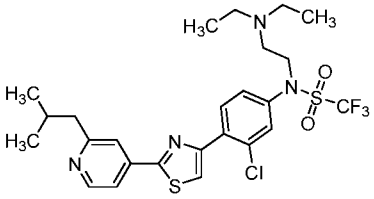
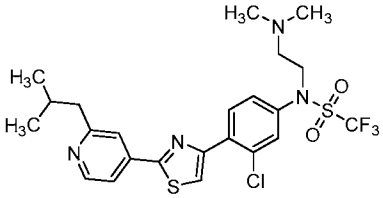
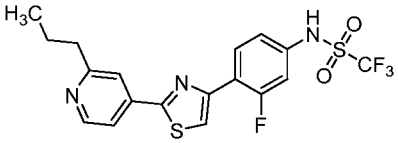
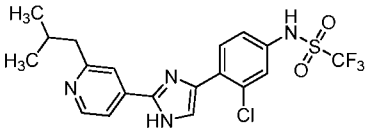
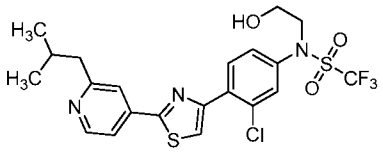
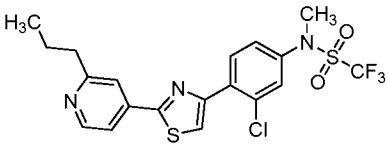
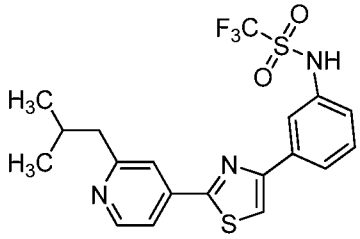
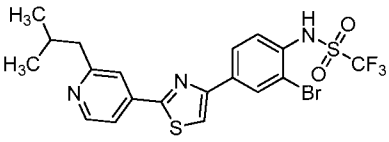
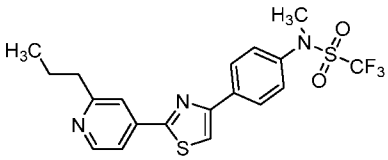
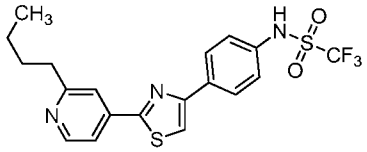
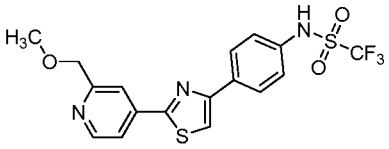
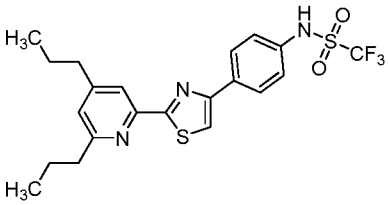
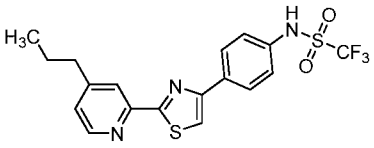
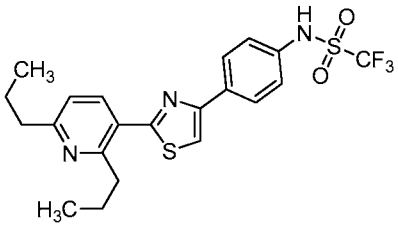
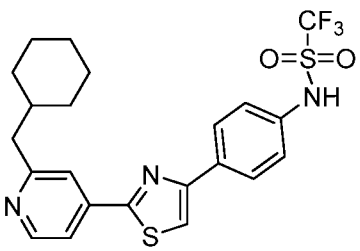
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Table 1

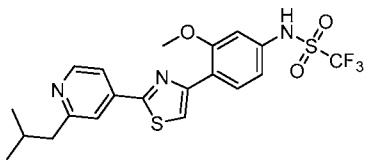
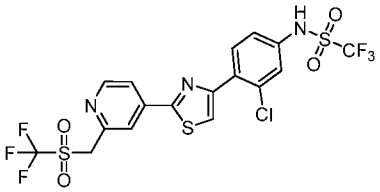
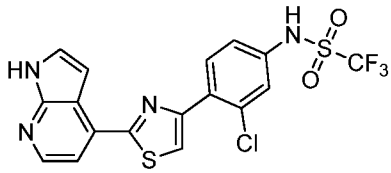
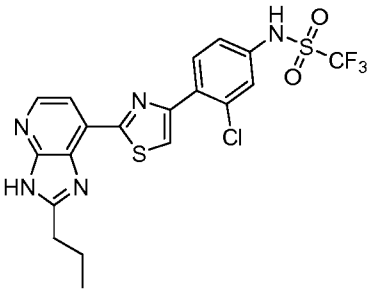
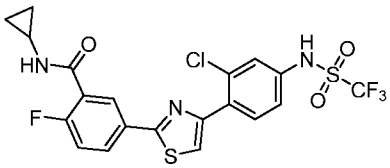
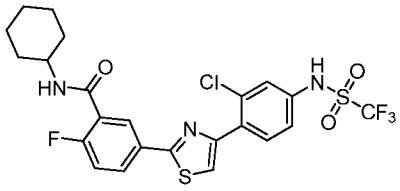
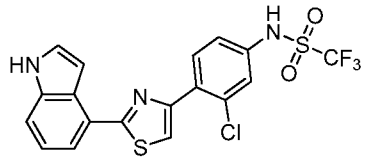
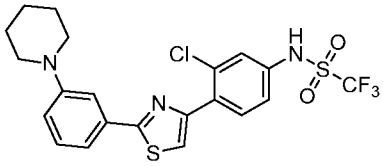
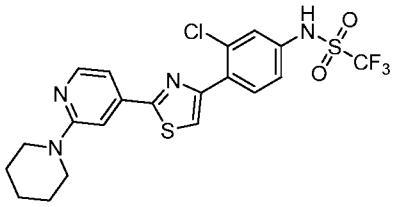
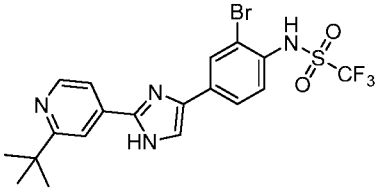
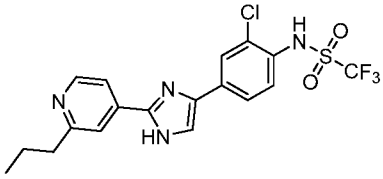
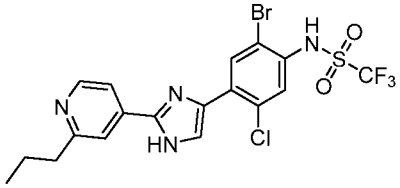
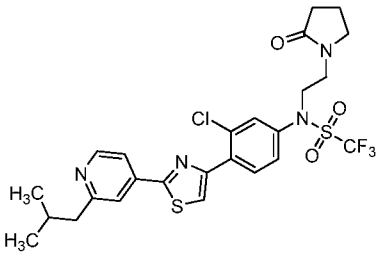
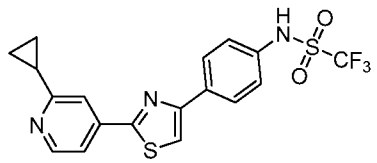
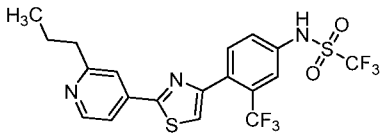
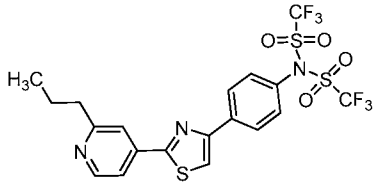
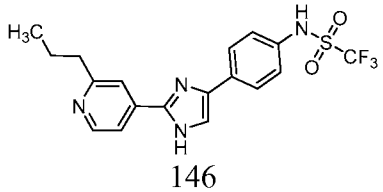
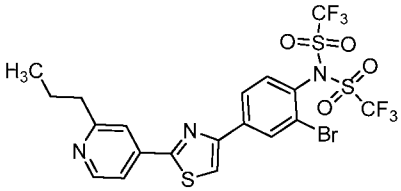
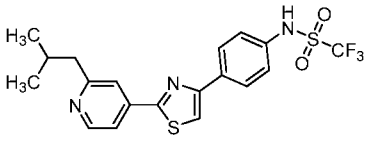
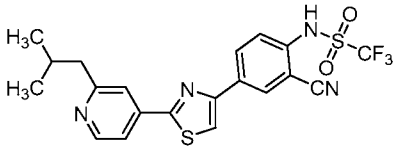
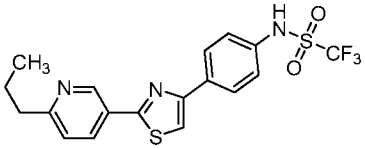
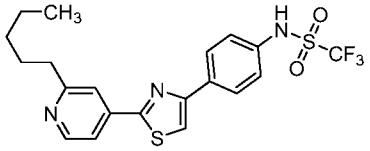
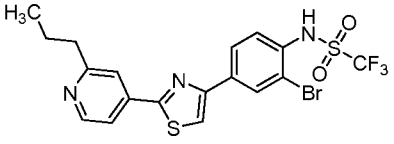
 130	 131	 132
 133	 134	 135
 136	 137	 138
 139	 140	 141
 142	 143	 144
 145	 146	 147

Table 1		
 148	 149	 150
 151	 152	

[073] In some embodiments, the compound is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, or 152.

[074] In some embodiments, the compound is 1, 2, 3, 4, 5, 37, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, or 94.

[075] Representative examples of compounds detailed herein, including intermediates and final compounds, are depicted in Table 1 and elsewhere herein. It is understood that in one aspect, any of the compounds may be used in the methods detailed herein, including, where applicable, intermediate compounds that may be isolated and administered to an individual.

[076] The compounds depicted herein may be present as salts even if salts are not depicted, and it is understood that the compositions and methods provided herein embrace all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds provided herein are pharmaceutically acceptable salts.

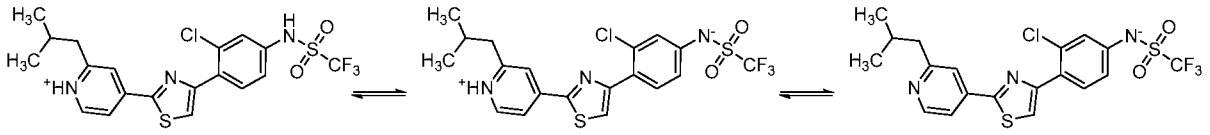
[077] In one embodiment, the compound is a pharmaceutically acceptable salt of a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, or a pharmaceutically acceptable salt thereof.

[078] In some embodiments, certain compounds presented herein are considered to be "prodrug" forms of other compounds herein. Prodrugs are precursor derivatives that, upon administration to a patient, undergo metabolism *in-vivo* such as, for example, hydrolysis to release the active form of the compound – the 'parent' compound. The prodrug form itself is either inactive or less active than the parent. Prodrugs are designed to improve bioavailability or to improve selective administration to particular organs, such as the liver [see, for example, Erion, et al. *PNAS* (2007) 104:39, pp 15490-15495; Erion, et al. *J. Pharmacol. Exp. Ther.* (2005) 312:2, pp 554-560; Meyer, et al. *Patent Publication US 2006-0281695A1*]. Compounds provided herein such as, for example, compound nos. 106-111 can be considered prodrug forms of the 'parent' compound no. 5. In some embodiments, prodrug forms of compounds presented herein

are provided. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *"Design of Prodrugs"*, ed. H. Bundgaard, Elsevier, 1985; Beaumont; K. et al. *Curr. Drug Metab.* (2003) 4, pp 461-485; Mizen, L, et al. *Pharm. Biotechnol.* (1998) 11, pp 345-365. In addition to prodrugs, the invention provides the salts, esters, amides, and other protected or derivatized forms of the described compounds.

[079] As has been described above, the inherent pKa(s) of molecules can be assessed by potentiometric methods known to the skilled artisan, typically UV spectrophotometry [see, for example, Julémont, et al. *J. Med. Chem.* (2002), 45, pp 5182-5185]. In-silico methods can be used as a predictive tool, and software is commercially available from, for example, ACD/Labs, Molecular Discovery, ChemAxon, and other vendors. Without being bound by theory, it is presented that compounds provided herein possess unexpected physicochemical properties presumed to arise from the presence of the trifluoromethylsulfonamide moiety and its effect on the acidity of the remaining structure of the provided compounds as a whole. The compounds provided herein contain several ionizable centers including, for example, the trifluoromethylsulfonamide nitrogen atom; the thiazole ring nitrogen atom; the "ring A" pyridine nitrogen atom, etc.

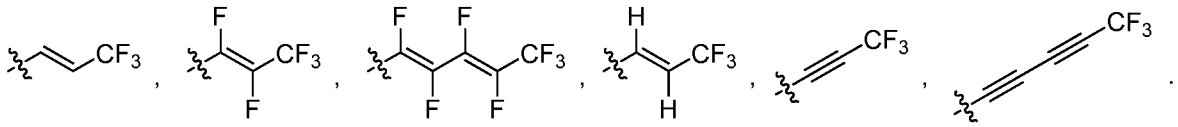
[080] As one example to describe the theory, compound #37 could exist in the following forms:



Other ionized forms are conceivable, but those presented here are a protonated form; a neutral or internal zwitterionic form; and an anionic form. Which form would exist is dependent upon the pH of the aqueous or physiological solution in which the compound is placed. Calculated pKa values of compound #37 [provided by I-Lab 2.0 (ACD/Labs, Inc.)] give two values of 3.4 and 5.4. These values are similar to those experimentally obtained under potentiometric and spectrophotometric methods [courtesy of Pion, Inc.], found to be 3.09 and 5.27. When the CF_3 group is replaced by a CH_3 group, the calculated pKa values become 5.1 and 7.5 – both notably higher. It is postulated that the more electronegative nature of the CF_3 group results in a more highly acidic nature of the compound. Based on the calculated / measured pKa values of the trifluoromethylsulfonamide containing compounds claimed herein, it is likely that at a pH of 6-8, these compounds will predominantly exist in the anionic form, with the above equilibrium lying to the right at higher pH values. The anionic form renders the compound more aqueous soluble and therefore better absorbed. A solubility study [courtesy of Pion, Inc.] showed average

solubilities of 13μg/mL @ pH 6.0, 104μg/mL @ pH 7.0, and >130μg/mL @ pH 8.0. When a compound is dosed orally, most of the absorption occurs in the intestines where the pH ranges from 6-8. Therefore it is likely that the trifluoromethylsulfonamide containing compounds claimed herein will have significantly better solubility and absorption when dose orally relative to the methylsulfonamides which the anionic form would be present to a significantly lower extent at pH 6-8, compared to its neutral/zwitterionic form).

[081] Examples of perhaloalkylsulfonamide groups are presented hereinabove. In some embodiments, also provided are compounds bearing perhaloalkenylsulfonamide groups, perhaloalkynylsulfonamide groups, or alkylsulfonamide groups bearing 1 or more halogen atoms. Such compounds can include, for example, the following:



Without being bound by theory, it is expected that each of these particular groups, and variations therein, has varying degrees of electronegativity, affording subtle changes in pKa, and allowing a tuning of the acidity to compounds of the invention, where required by the skilled artisan.

Pharmaceutically acceptable salts

[082] "Pharmaceutically acceptable salts" are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth metal ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Further examples of pharmaceutically acceptable salts include those listed in Berge *et al.*, Pharmaceutical Salts, *J. Pharm. Sci.* 1977 Jan; 66(1):1-19. Pharmaceutically acceptable salts can be prepared *in situ* in the manufacturing process, or by separately reacting a purified compound disclosed herein in its free acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification. In one embodiment, a

pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

Pharmaceutical Compositions

[083] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, typically is provided in a pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or excipient. A "pharmaceutically acceptable" carrier or excipient is a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to an individual without causing significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition, wherein it is contained. Pharmaceutically acceptable carriers or excipients meet the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[084] A pharmaceutical composition can comprise one or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein. In some embodiments, a pharmaceutical composition further comprises chemotherapeutic agent, as described below.

[085] Preferably a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, is bioavailable orally. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration.

[086] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be used in the preparation of a medicament by combining the compound or compounds as an active ingredient with a pharmacologically acceptable carrier, which is known in the art. Depending on the therapeutic form of the medication, the carrier may be in various forms. In one variation, the manufacture of a medicament is for use in any of the methods disclosed herein.

[087] Methods as provided herein may comprise administering to an individual a pharmacological composition that contains an effective amount of a compound of Formulae (Ia),

(Ib), (IIa) or (IIb), or any variation presented herein, and a pharmaceutically acceptable carrier. The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg.

[088] The compound may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[089] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds as an active ingredient with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, *e.g.*, in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference.

[090] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, *etc*. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[091] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be formulated in a tablet in any dosage form described, for example, a compound as described herein or a pharmaceutically acceptable salt thereof can be formulated as a 10 mg tablet.

[092] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

[093] In some embodiments, a pharmaceutical composition is provided as a unit dosage form, such as a tablet, capsule, or individually packaged container (*e.g.*, an ampoule, syringe, or vial).

[094] In some embodiments, the unit dosage form contains a daily dose of a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein. In some embodiments, the unit dosage form contains a daily sub-dose of the compound.

[095] In some embodiments, the unit dosage form contains a daily dose of each of two or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein. In some embodiments, the unit dosage form contains a daily sub-dose of each of two or more compounds.

[096] In some embodiments, the unit dosage form contains a daily dose of compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, and a daily dose of each of one or more chemotherapeutic agents. In some embodiments, the unit dosage form contains a daily sub-dose of the compound and a daily sub-dose of each of one or more chemotherapeutic agents.

[097] In some embodiments, the unit dosage form contains a daily dose of each of two or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, and a daily

dose of each of one or more chemotherapeutic agents. In some embodiments, the unit dosage form contains a daily sub-dose of each of two or more compounds and a daily dose of each of one or more chemotherapeutic agents.

Kits and Articles of Manufacture

[098] This disclosure also provides kits and articles of manufacture comprising one or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, or a pharmacological composition comprising a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein,. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein or a pharmaceutically acceptable salt thereof.

[099] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[0100] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or a second pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[0101] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the disclosed methods. The instructions included with the kit generally include information as to the components and their administration to an individual.

Therapeutic Uses

[0102] Compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be used to treat hyperproliferative disorders. A "hyperproliferative disorder" is a disorder associated with some degree of abnormal cell proliferation. A hyperproliferative disorder can be benign (including pre-cancerous disorders) or malignant.

[0103] In some embodiments, the hyperproliferative disorder is benign, such as benign prostatic hyperplasia, neurofibromatosis, actinic keratosis, hypertrophic actinic keratosis, Bowenoid actinic keratosis, arsenical keratosis, hydrocarbon keratosis, thermal keratosis, radiation keratosis, chronic scar keratosis, viral keratosis, actinic cheilitis, Bowen's disease, erythroplaquia of queyrat, oral erythroplaquia, leukoplakia, intraepidermal epithelioma, psoriasis, polyps, Barrett's esophagus, atrophic gastritis, cervical dysplasia, benign meningioma, and benign ovarian epithelial tumors (*e.g.*, serous adenomas, mucinous adenomas, Brenner tumors).

[0104] In some embodiments, the hyperproliferative disorder is malignant, *e.g.*, adenocarcinoma, bladder cancer, breast cancer, cervical cancer, cholangiocarcinoma, CNS cancer (*e.g.*, astrocytoma, dendroma, ependymoma, glioma, malignant meningioma, medulloblastoma, neuroblastoma, neuroglioma, oligodendroglioma), gastrointestinal cancer (*e.g.*, gastrointestinal stromal carcinoma, colorectal cancer), kidney cancer, leukemia (*e.g.*, acute lymphocytic leukemia; acute myelogenous leukemia; chronic lymphocytic leukemia; chronic myelogenous leukemia), liver cancer (*e.g.*, hepatic cancer, hepatocellular carcinoma), lung cancer (*e.g.*, lung squamous carcinoma, small-cell lung carcinoma, non-small-cell lung carcinoma, mesothelioma), lymphoma (*e.g.*, Hodgkin lymphoma and non-Hodgkin lymphoma), melanoma, myeloma (*e.g.*, multiple myeloma, plasmacytoma), ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, thyroid cancer, and uterine cancer.

[0105] In some embodiments, the breast cancer is AR+, ER+, and Her2+. In some embodiments, the breast cancer is AR+, ER+, and PR+. In some embodiments, the breast cancer is AR+, ER+, Her2+, and PR+. In some embodiments, the breast cancer is AR-, ER+, and Her2+. In some embodiments, the breast cancer is AR-, ER+, and PR+. In some embodiments, the breast cancer is AR-, ER+, Her2+, and PR+.

[0106] In some embodiments, the breast cancer is ductal carcinoma *in situ*. In some embodiments, the breast cancer is invasive ductal carcinoma. In some embodiments, the breast cancer is triple negative breast cancer (*e.g.*, basal-like type 1 (BL1), basal-like type 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) subtypes). In some embodiments, the breast cancer is inflammatory breast cancer. In some embodiments, the breast cancer is BRCA1-related breast cancer. In some embodiments, the breast cancer is medullary breast cancer, metaplastic breast cancer. In some embodiments, the breast cancer is special histologic type of breast cancer. In some embodiments, the breast cancer is resistant to endocrine therapy.

[0107] In some embodiments, the prostate cancer is hormone-sensitive prostate cancer. In some embodiments, the prostate cancer is castration-resistant prostate cancer.

[0108] In some embodiments, the ovarian cancer is an epithelial carcinoma. In some embodiments, the ovarian cancer is a germ cell tumor. In some embodiments, the ovarian cancer is an ovarian stromal tumor (*e.g.*, granulosa-theca tumors and Sertoli-Leydig cell tumors).

[0109] Compounds disclosed herein also can be used to treat a variety of metabolic disorders, including metabolic disorders that are mediated by genetic factors (*e.g.*, Niemann-Pick disease, Fabry disease, Gaucher disease, Forbe′s disease, Tangier disease) and environmental factors (*e.g.*, diets rich in fat and/or sugar). Compounds also may be useful in the treatment of complications of metabolic diseases, such as cardiovascular disease, non-alcoholic hepatic steatosis, hyperlipemia, and obesity.

[0110] Compounds disclosed herein also can be used to treat pancreatitis.

Treatment Regimens

[0111] Compounds can be administered alone or in conjunction with other therapeutic interventions. The disclosed compounds decrease the synthesis of cholesterol and fatty acids, which are essential components of cell membranes and cell division; accordingly, administration of a compound should decrease the rate of cell division. These effects, coupled with alterations in lipid-mediated cell signaling pathways, induce cell death.

[0112] Administration of a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, “in conjunction with” another therapeutic intervention may include any of the following regimens.

Dosing and Method of Administration

[0113] The dose of a compound administered to an individual (such as a human) may vary with the particular compound or salt thereof, the method of administration, and the particular stage of hyperproliferative or metabolic disorder being treated. For therapeutic purposes, "effective dose" or "effective amount" refers to that amount of each active compound or pharmaceutical agent, alone or in combination, that elicits the biological or medicinal response in a tissue system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. For prophylactic purposes (i.e., preventing or inhibiting the onset or progression of a disorder), the term "effective dose" or "effective amount" refers to that amount of each active compound or pharmaceutical agent, alone or in combination, that inhibits in a subject the onset or progression

of a disorder as being sought by a researcher, veterinarian, medical doctor, or other clinician, the delaying of which disorder is mediated, at least in part, by blocking of SREBP function. The amount should be sufficient to produce a desirable response, such as a therapeutic or prophylactic response against the disorder. In some embodiments, the amount of the compound or salt thereof is a therapeutically effective amount. In some embodiments, the amount of the compound or salt thereof is a prophylactically effective amount. In some embodiments, the amount of compound or salt thereof is below the level that induces a toxicological effect (e.g., an effect above a clinically acceptable level of toxicity) or is at a level where a potential side effect can be controlled or tolerated when the composition is administered to the individual.

[0114] In some embodiments, the amount of compound or salt thereof is an amount sufficient to inhibit cancer cell growth and/or proliferation or increase apoptosis of cancer cells.

[0115] The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg/kg.

[0116] Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a compound provided herein or a salt thereof and a pharmaceutically acceptable excipient.

[0117] A compound or composition provided herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

[0118] The compounds provided herein or a salt thereof may be administered to an individual via various routes, including, e.g., intravenous, intramuscular, subcutaneous, oral and transdermal.

[0119] In one aspect, provided is a method of treating cancer in an individual by parenterally administering to the individual (e.g., a human) an effective amount of a compound or salt thereof. In some embodiments, the route of administration is intravenous, intra-arterial,

intramuscular, or subcutaneous. In some embodiments, the route of administration is oral. In still other embodiments, the route of administration is transdermal. In one aspect are provided compositions (including pharmaceutical compositions) as described herein for the use in treating a hyperproliferative or metabolic disorder, such as cancer (e.g., prostate cancer).

[0120] Also provided are compositions (including pharmaceutical compositions) as described herein for the use in treating, preventing, and/or delaying the onset and/or development of cancer and other methods described herein. In certain embodiments, the composition comprises a pharmaceutical formulation which is present in a unit dosage form.

[0121] Also provided are articles of manufacture, comprising a compound provided herein or a salt thereof, composition, and unit dosages described herein in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

Anti-Proliferative Agents

[0122] An "anti-proliferative agent" is an intervention that increases apoptosis of hyperproliferating cells. In some embodiments, a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, is used in conjunction with an anti-proliferative agent which is a chemotherapeutic agent. Chemotherapeutic agents include any pharmacological agent which is currently approved by the FDA in the U.S. (or elsewhere by any other regulatory body) for use as pharmacological treatment for hyperproliferative disorders, including cancer, or which is currently being used experimentally as part of a clinical trial program.

General Synthetic Methods

[0123] The compounds may be prepared by a number of processes as generally described below in the General Synthetic Schemes and more specifically in the Examples hereinafter. In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

[0124] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

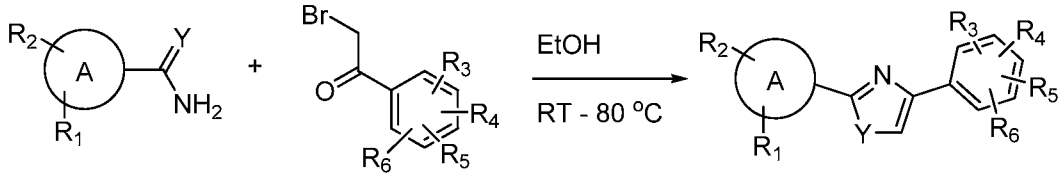
[0125] The following abbreviations are used herein: thin layer chromatography (TLC); hour (h); minute (min); second (sec); ethanol (EtOH); dimethylsulfoxide (DMSO); *N,N*-dimethylformamide (DMF); trifluoroacetic acid (TFA); tetrahydrofuran (THF); Normal(N);

aqueous (aq.); methanol (MeOH); dichloromethane (DCM); ethyl acetate (EtOAc); Retention factor (Rf); room temperature (RT).

[0126] The following General Synthetic Schemes and Examples are provided to illustrate but not to limit the invention. Those skilled in the art will be familiar with many of the reaction steps described. Particular publications are presented to assist with certain steps of the synthetic route.

General Synthetic Scheme 1

[0127] General Synthetic Scheme 1 provides methods to prepare compounds with a thiazole or imidazole B-ring as presented herein. Substituents R_1-R_6 are as exemplified in the Examples below. Syntheses of tricyclic substituted thiazoles, oxazoles and imidazoles, such as those presented herein, will be familiar to those skilled in the art. An example to illustrate a synthesis of a substituted thiazole is presented below. Complete details for syntheses of the compounds presented herein are provided in the Examples.



A = aromatic or heteroaromatic ring
Y = O, S, NH

[0128] **General procedure:** The corresponding substituted pyridine-4-carbothioamide or isonicotinamide and the corresponding substituted 2-bromoacetylbenzene are dissolved in EtOH. The resultant reaction mixture is stirred at between RT and 70 °C for between 30 min and 2 h. The progress of the reaction is monitored by TLC and LCMS. The reaction mixture is cooled to RT, basified with aq. sodium bicarbonate solution and the mixture extracted with EtOAc. The organic layer is dried over sodium sulfate and concentrated to obtain the crude product, which is purified by silica gel (100-200 mesh) column chromatography / by HPLC to obtain the desired product.

EXAMPLES

Example 1. Preparation of Compound No. 1

[0129] Pyridine (0.02 mL, 0.248 mmol) was added to a solution of triflic anhydride (0.05 mL, 0.297 mmol) at 0 °C under nitrogen in DCM (2 mL). After 15 min, 4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)aniline (70 mg, 0.236 mmol) was added dropwise at 0 °C in DCM (3 mL). The reaction was allowed to stir at RT for additional 30 min, monitored by TLC. After completion,

the reaction mixture was diluted with water (10 mL) and the mixture extracted with EtOAc (2x20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by reverse phase preparative HPLC to obtain 17 mg of 1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide (yellow solid). This was treated with 2N aq. HCl for salt formation. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.77 (d, J = 6.2 Hz, 1H), 8.54 (s, 1H), 8.48 (d, J = 6.2 Hz, 1H), 8.36 (s, 1H), 8.13 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 3.18-2.98 (m, 2H), 1.91 (p, J = 7.7 Hz, 2H), 1.10 (t, J = 7.4 Hz, 3H).

Example 2. Preparation of Compound No. 2

[0130] 2-Propylpyridine-4-carbothioamide (50 mg,0.118 mmol) and N-(3-(2,2-dibromoacetyl)phenyl)-1,1,1-trifluoromethanesulfonamide (16.9 mg, 0.09 mmol) were charged in acetic acid (1 mL) and the reaction mixture was stirred at 80 °C for 30 min. The reaction was monitored by LCMS and acetic acid was evaporated under vacuum. The crude reaction mixture was purified using reverse phase chromatography to get 2.4 mg of 1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide. ^{1}H NMR (CD_3OD) δ (ppm): 8.59 (d, J= 5.3 Hz, 1H), 8.08 (s, 1H), 8.00 (s, 1H), 7.94 (m, 2H), 7.49 (m, 1H), 7.33 (d, J=8.1 Hz, 1H), 2.99-2.77 (m, 3H), 1.83 (m, 2H), 1.03 (t, J=7.3 Hz, 3H).

Example 4. Preparation of Compound No. 4

[0131] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50mg, 0.132 mmol) and 2-propylpyridine-4-carbothioamide (23.8 mg, 0.132mmol) were charged in EtOH (10 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated and purified through reverse phase HPLC. Yield: 17 mg TFA salt. ^{1}H NMR (TFA salt, CD_3OD) δ (ppm): 8.72 (d, J=6.0 Hz, 1H), 8.38 (d, J=7.6 Hz, 1H), 8.31 (d, J=6.0 Hz, 2H), 8.07 (d, J=8.5 Hz, 1H), 7.49 (s, 1H), 3.04 (t, J=7.8 Hz, 3H), 1.88 (m, 2H), 1.07 (s, J=7.3 Hz, 3H).

Example 5. Preparation of Compound No. 5

[0132] 2-tert-Butylpyridine-4-carbothioamide (100 mg, 0.26 mmol) and N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (51 mg, 0.26 mmol) were charged in EtOH (5 mL) and the reaction mixture was stirred at 80 °C for 30 min. The reaction was monitored by LCMS, and then the EtOH was evaporated under vacuum. The reaction mixture was purified using reverse phase chromatography to get 43mg of N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide. ^{1}H NMR (HCl salt, CD_3OD) δ (ppm):

8.76 (d, J =6.1 Hz, 1H), 8.50 (s, 1H), 8.43 (m, 2H), 8.06 (d, J=8.5 Hz, 1H), 7.50 (d, J=2.2Hz, 1H), 7.4 (m, 1H), 1.58 (s, 9H).

Example 6. Preparation of Compound No. 57

Synthesis of 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide

Step-1: Synthesis of 3-methoxy-4-nitrobenzoyl chloride

[0133] 3-Methoxy-4-nitrobenzoicacid (5) (3 g) and thionyl chloride (10 mL) were added dropwise at 0 °C. The reaction mixture was allowed to come to RT and heated to reflux overnight. Thionyl chloride was evaporated and ice was added to the reaction mixture. The organic layer was extracted in ethyl acetate (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get 6 g of 3-methoxy-4-nitrobenzoyl chloride.

Step-2: Synthesis of 1-(3-methoxy-4-nitrophenyl)ethanone

[0134] A suspension of anhydrous magnesium chloride (932 mg, 9.8 mmol) in toluene (13 mL) was treated with triethylamine (4.7 mL, 33.4 mmol) and diethylmalonate (2.7 mL, 16.74 mmol). The reaction mixture was stirred at RT for 1.5 h. Finally, 3-methoxy-4-nitrobenzoyl chloride (6) (3 g, 13.9 mmol) was added and the reaction mixture was stirred at RT for 18 h. Concentrated hydrochloric acid (10 mL) was added and the organic layer was separated. DMSO (11.5 mL) and water (0.5 mL) were added and the mixture was heated to reflux for 2 h. The reaction mixture was allowed to come to RT and partitioned between water and EtOAc. The organic phase was washed subsequently with saturated sodium bicarbonate solution and brine and concentrated to get 2.5 g of 1-(3-methoxy-4-nitrophenyl)ethanone.

Step-3: Synthesis of 1-(4-amino-3-methoxyphenyl)ethanone

[0135] 1-(3-Methoxy-4-nitrophenyl)ethanone (2 g, 10.25 mmol) was charged in MeOH (30 mL). Iron powder (1.72 g, 30.76 mmol) was added and concentrated HCl (10 mL) was added dropwise with constant stirring. The reaction mixture was heated at 60 °C for 1 h. The iron powder was filtered off and MeOH was concentrated. Water (10 mL) was added and the organic layer was extracted in EtOAc (3x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get 1.2 g of 1-(4-amino-3-methoxyphenyl)ethanone.

Step-4: Synthesis of N-(4-acetyl-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0136] Triflic anhydride (0.6ml 3.6 mmol) was charged in DCM (20 mL). The reaction mixture was cooled to 0 °C and pyridine was added dropwise with constant stirring. After 15 min, 1-(4-

amino-3-methoxyphenyl)ethanone (500mg, 3.03 mmol) was dissolved in DCM (10 mL) and added slowly to the reaction mixture. The reaction mixture was allowed to come to RT and the reaction mixture was stirred at RT for 1 h. The reaction was monitored by TLC. Water (15 mL) was added and the organic layer was extracted in DCM (3x100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get 700 mg of N-(4-acetyl-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide.

Step-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0137] N-(4-Acetyl-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide (700 mg, 2.35 mmol) was charged in chloroform (50 mL) and the reaction mixture was cooled to 0 °C. Liquid bromine (0.125 mL, 2.35 mmol) was added dropwise and the reaction mixture was stirred at RT for 18 h. A saturated solution of sodium thiosulfate (20 mL) was added and the chloroform layer was isolated and concentrated under reduced pressure to get 525 mg of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide.

Step-6: Synthesis of 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)methanesulfonamide

[0138] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-isobutylpyridine-4-carbothioamide compound (20.6 mg, 0.10 mmol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified through reverse phase HPLC to get 16 mg of 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide. ^{1}H NMR (400 MHz, Methanol-d4) : δ (ppm): 8.56 (d, J = 5.2 Hz, 1H), 7.96 – 7.70 (m, 3H), 7.58 (d, J = 1.9 Hz, 1H), 7.48 (dd, J = 8.3, 1.9 Hz, 1H), 7.33 (dd, J = 8.3, 2.1 Hz, 2H), 3.92 (s, 3H), 2.76 (d, J = 7.3 Hz, 2H), 2.12 (td, J = 14.0, 7.2 Hz, 1H), 0.98 (d, J = 6.6 Hz, 6H). LCMS: 473.2 (M+1).

Example 7. Preparation of Compound No. 58

Steps 1-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0139] See Example 6.

Step-6: Synthesis of N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4 yl)phenyl)methanesulfonamide:

[0140] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-propylpyridine-4-carbothioamide (18 mg, 0.1 mmol) were charged in ethanol (10 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified through reverse phase HPLC to get 17 mg of N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4 yl)phenyl)methanesulfonamide. ^{1}H NMR (400 MHz, Methanol-d4) : δ (ppm): 8.68 (d, J = 5.8 Hz, 1H), 8.28 (d, J = 5.9 Hz, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.4, 1.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 4.02 (s, 3H), 3.01 (m, 2H), 1.87 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H). LCMS: (M+1) 458.3.

Example 8. Preparation of Compound No. 59

Steps 1-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0141] See Example 6.

Step-6: Synthesis of N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0142] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-tert-butylpyridine-4-carbothioamide (20.6 mg, 0.10 mmol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified through reverse phase HPLC to get 15 mg of N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide. ^{1}H NMR (400 MHz, Methanol-d4): δ (ppm): 8.61 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 3.3 Hz, 2H), 7.82 (dd, J = 5.2, 1.6 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 8.3, 1.9 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 3.98 (s, 3H), 1.45 (s, 9H). LCMS: (M+1) 472.5.

Example 9. Preparation of Compound No. 60

[0143] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1,trifluoromethane sulfonamide (100 mg, 0.263 mol) and 2-benzylpyridine-4-carbothioamide (54.1 mg, 0.237 mol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. A yellow solid reaction mixture was obtained, which was filtered and the residue was washed with diethyl ether (15 mL) to get N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide (33 mg) as a brown solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.85-8.68 (d, J = 6.2 Hz, 1H), 8.55-8.39 (m, 2H), 8.03 (d, J=8.5 Hz, 1H), 7.49 (d, J=2.3 Hz, 1H), 7.48-7.31 (m, 7H), 4.51 (s, 2H). LCMS (M+1): 510.1.

Example 10. Preparation of Compound No. 61

Step-1: Synthesis of 2-aminopyridine-4-carbothioamide

[0144] To a solution of 2-aminoisonicotinamide (100 mg, 0.0729 mol, 1 eq.) in pyridine (3 mL), phosphorus pentasulfide (83 mg, 0.0365 mol, 0.5 eq.) was added. The reaction was heated at 100 ° C for 3 h. The reaction was monitored by LCMS. After completion, pyridine was concentrated under reduced pressure and residue was dissolved in water (5 mL) and the mixture extracted with EtOAc (3x15 mL). The EtOAc extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to get 33 mg of 2-aminopyridine-4-carbothioamide as a yellow solid.

Step-2: Synthesis of 2-chloro-4-nitrobenzoyl chloride

[0145] To a two neck RBF (1 liter) placed in ice bath, 2-chloro-4-nitrobenzoic acid (50 g, 0.248 mol, 1 eq.) was charged. Thionyl chloride (110 mL, 1.51 mol, 6.1 eq.) was added dropwise at 0 °C. The reaction mixture was allowed to come to RT and then heated to reflux. The reflux was continued overnight. Thionyl chloride was evaporated and ice (approx. 150 g) was added into the reaction mixture. The aqueous reaction mass was extracted with DCM (2x200 mL). The DCM extracts were combined dried over anhydrous sodium sulfate and concentrated under vacuum to get 50 g (91.7 %) of 2-chloro-4-nitrobenzoyl chloride as a light yellow liquid.

Step-3: Synthesis of 1-(2-chloro-4-nitrophenyl) ethanone

[0146] A suspension of anhydrous magnesium chloride (47 g, 0.214 mol, 0.7 eq.) in toluene (300 mL) was treated with triethylamine (75.04 mL, 0.535 mol, 2.5 eq.) and diethylmalonate (41.09 g, 0.257 mol, 1.2 eq.). The reaction mixture was stirred at RT for 1.5 h. To this was added 2-chloro-4-nitrobenzoyl chloride (4) (47 g, 0.214 mol, 1 eq.) was added dropwise (an exothermic reaction up to 50 °C was observed during addition). Toluene (50 mL) was used for complete transfer of 2-chloro-4-nitrobenzoyl chloride to the reaction mixture. The reaction mixture was stirred at RT for 18 h. The reaction was monitored by TLC and NMR. After complete consumption of starting material, concentrated hydrochloric acid (35 % solution) (300 mL) was added and the upper toluene layer was separated. Toluene was evaporated under reduced pressure below 50 °C. To the residue after concentration, DMSO (200 mL) and water (10 mL) were added and the mixture was heated at 160 °C for 12 h. The reaction was monitored by TLC and NMR. The reaction mixture was allowed to come to RT and water (40 mL) was added to the reaction mixture. The reaction mixture was extracted with EtOAc (3x200 mL). The EtOAc extracts were combined was washed brine solution (3x300 mL) and dried over anhydrous sodium

sulfate. The EtOAc layer was concentrated to get 43 g (100%) of 1-(2-chloro-4-nitrophenyl) ethanone as a yellow liquid which solidified upon refrigeration.

Step-4: Synthesis of 1-(4-amino-2-chlorophenyl) ethanone

[0147] 1-(2-Chloro-4-nitrophenyl) ethanone (126 g, 0.63 mole 1 eq.) was dissolved in MeOH (600 mL). Iron powder (105.8 g, 1.89 mol, 3 eq.) was added to the solution. Concentrated HCl (130 mL, 1.89 mol, 3 eq.) was added dropwise with constant stirring. The reaction mixture was then heated at 70 °C for 12 h. The reaction was monitored by TLC and NMR. The reaction mixture showed presence of starting material. The same quantity of iron powder and concentrated HCl were added again at 70 °C and the heating was continued at 70 °C for 4 h. The reaction mixture was again monitored by TLC and NMR. After completion of reaction, Iron powder was filtered through a celite bed and the MeOH filtrate was concentrated. Water (100 mL) was added and the reaction mixture was extracted in EtOAc (5x300 mL). The EtOAc extracts were combined, dried over anhydrous sodium sulfate and concentrated to get 100 g of crude product. 71 g of the crude product was purified through silica column (#100-200) using 0-20% EtOAc: hexane as eluant to get 38.6 g (52.5 %) of 1-(4-amino-3-methoxyphenyl) ethanone (6) as pink solid. ^{1}H NMR (400 MHz, Chloroform-d): δ (ppm): 7.62 (d, J = 8.5 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 6.54 (dd, J =8.5, 2.3 Hz, 1H), 4.07 (s, 2H), 2.61 (s, 3H).

Step-5: Synthesis of N-(4-acetyl-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide

[0148] A solution of triflic anhydride (75.1 g, 0.266 mol, 1.5 eq.) in DCM (600 mL) was cooled to 0 °C. Pyridine (21.4 mL, 0.266 mol, 1.5 eq.) was added dropwise with constant stirring over 30 min. The reaction mixture was stirred at same temperature for 1 h. A solution of 1-(4-amino-2-chlorophenyl)ethanone (30 g, 0.177 mol, 1 eq.) in DCM (400 mL) was added dropwise maintaining the temperature 0 °C with constant stirring over a period of 45 min. The reaction mixture was then allowed to come to RT and stirred for 1 h at RT. The reaction was monitored by TLC and NMR. Upon completion, ice water (500 mL) was added and the DCM layer was separated. The aqueous layer was again extracted with DCM (2x100 mL). The DCM extracts were combined washed with ice water (2x500 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure below 40 °C to obtain the crude product. Diethyl ether (200 mL) and pentane (600 mL) were added into the reaction mixture and stirred for 30 min. The reaction mixture was filtered and the mother liquor was concentrated and triturated in pentane to get 28 g (52.8%) of N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide as a light pink solid.

Step-6: Synthesis of N-(4-(2-bromoacetyl)-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide

[0149] A solution of N-(4-acetyl-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide (21 g, 0.07 mol, 1 eq.) in chloroform (600 mL) was cooled to 0 °C. Liquid bromine (2.9 mL, 0.004 mol, 0.8 eq.) dissolved in chloroform (400 mL) was added dropwise over a period of 40 min, maintaining the temperature between 0-10 °C. The reaction mixture was allowed to come to RT and was stirred at RT for 18 h. The reaction was monitored by TLC and NMR, which indicated the presence of starting material and desired compound along with some amount of N-(3-chloro-4-(2,2-dibromoacetyl)phenyl)-1,1,1-trifluoromethanesulfonamide (dibromo impurity). A saturated solution of sodium thiosulfate (200 mL) was added and the chloroform layer was separated. The aqueous layer was extracted with chloroform (2x100 mL). The main chloroform layer and the chloroform extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. A clear liquid was obtained as a residue. To this were added diethylether (50 mL) and pentane (250 mL) and the mixture stirred for 10 min. The reaction mixture was filtered off and mother liquor was concentrated. The crude product obtained was triturated with pentane (~50 mL) to obtain a white solid. The white solid obtained was filtered off and dried under vacuum to get 20 g of N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide with contained approximately 35% of starting material i.e. N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide by NMR. The mixture of both was directly used in the next step.

Step-7: Synthesis of N-(4-(2-(2-aminopyridin-4-yl)thiazol-5-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide:

[0150] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50 mg, 0. 132 mmol, 1 eq.) and 2-aminopyridine-4-carbothioamide (32.8 mg, 0.132 mmol, 1 eq.) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated and purified by reverse phase chromatography to get 6.8 mg of N-(4-(2-(2-aminopyridin-4-yl) thiazol-5-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide. ^{1}H NMR (400 MHz, Methanol-d4): δ (ppm): 8.25 (s, 1H), 8.01 – 7.89 (m, 2H), 7.55 (d, J = 1.6 Hz, 1H), 7.46 – 7.40(m, 1H), 7.33 (dd, J = 8.5, 2.2 Hz, 1H). LCMS: (M+1) 435.1.

Example 11. Preparation of Compound No. 62

Steps 1-7: Synthesis of N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide

[0151] See Example 10.

Step-8: Synthesis of N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-5-yl)phenyl)-1,1,1-trifluoromethanesulfonamide

[0152] N-(4-(2-(2-Aminopyridin-4-yl)thiazol-5-yl)-3-chlorophenyl)-1,1,1-trifluoro methane sulfonamide (50 mg, 0.115 mmol, 1 eq.) was charged in pyridine (3 mL). The reaction mixture was cooled to 0 °C and methane sulfonyl chloride (0.01 mL, 0.115 mol, 1 eq.) was added dropwise with constant stirring. The reaction mixture was allowed to come to RT and the reaction mixture was stirred at RT for 1 h. Pyridine was evaporated and water was added and the mixture extracted in EtOAc (3x100 mL). The combined organic layer was concentrated and purified using reverse phase chromatography to get 1.3 mg of N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-5-yl)phenyl)-1,1,1-trifluoromethanesulfonamide. ^{1}H NMR (400 MHz, Methanol-d4): δ (ppm): 8.32 (d, J = 5.6 Hz, 1H), 8.17 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.59 (dd, J = 5.6, 1.6 Hz, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.6, 2.3 Hz, 1H), 3.2 (s, 1H). LCMS: 513 (M+1).

Example 12. Preparation of Compound No. 63

Steps 1-6: Synthesis of N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4 yl)phenyl)methanesulfonamide:

[0153] See Example 7.

Step-7: Synthesis of 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide

[0154] 1,1,1-Trifluoro-N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide (17 mg, 0.037 mmol, 1 eq.) charged in DCM (5 mL) and the reaction mixture was cooled at 0 °C. A 1M solution of boron tribromide (0.12 mL, 0.11mmol) was added dropwise. The reaction mixture was allowed to come to RT and stirred at RT for 12 h. The reaction was monitored by LCMS. A saturated sodium bicarbonate was added and the mixture extracted in EtOAc (3x25 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure and the crude reaction mixture was purified using reverse phase HPLC to get (1.5 mg) of 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide as the TFA salt. ^{1}H NMR (400 MHz, Methanol-d4): δ (ppm): 8.63 (d, J = 5.6 Hz, 1H), 8.13 – 8.00 (m, 2H), 7.63 (d, J = 1.9 Hz, 1H), 7.53 – 7.38 (m, 2H), 2.94 (t, J = 7.7 Hz, 2H), 1.84 (p, J = 7.5 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H) LCMS (M+1): 444.4.

Example 13. Preparation of Compound No. 64

[0155] N-(4-(2-Bromoacetyl)-3-chlorophenyl)1,1,1-trifluoro methane sulfonamide (100 mg, 0.263 mol) and 2-(3,3,3-trifluoropropyl) pyridine-4-carbothioamide (55.5 mg, 0.237 mol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1h. The resultant reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (27 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.84 (d, J = 6.2 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.52 (d, J = 6.1 Hz, 1H), 8.42 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 2.3Hz, 1H), 7.40 (d, J = 8.5Hz, 1H), 3.42 (m 2H), 2.87 (m, 2H). LCMS (M+1): 516.1.

Example 14. Preparation of Compound No. 65

Steps 1-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0156] See Example 6

Step-6: Synthesis of 1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide

[0157] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-neopentylpyridine-4-carbothioamide (50 mg, 0.10 mmol) was charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified through reverse phase HPLC to get 14 mg of 1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide. ^{1}H NMR (400 MHz, Methanol-d4): δ (ppm): 8.71 (d, J = 5.8 Hz, 1H), 8.33 – 8.14 (m, 2H), 7.76 (d, J = 1.9 Hz, 1H), 7.68 (dd, J = 8.4, 1.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 4.01 (s, 3H), 2.95 (s, 2H), 1.06 (s, 9H). LCMS: 486 (M+1).

Example 15. Preparation of Compound No. 66

[0158] A solution of triflic anhydride (0.03ml, 0.17 mmol, 1.5 eq.) in DCM (8 mL) was cooled to 0 °C. Pyridine (0.01 mL, 0.17 mmol, 1.5 eq.) was added dropwise with constant stirring over 30 min. A solution of N-(4-(2-(2-aminopyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50 mg, 0.115 mmol, 1 eq.) in DCM (2 mL) was added dropwise maintaining the temperature at 0 °C with constant stirring over a period of 5 min. The reaction mixture was then allowed to come to RT and stirred for 1 h at RT. The reaction was monitored by LCMS and NMR. Upon completion, ice water (10 mL) was added and the DCM layer was

separated. The aqueous layer was again extracted with DCM (2x20 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure and purified using reverse phase chromatography to get 9.26 mg of N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide. ^{1}H NMR (400 MHz, Methanol-d4): δ (ppm): 8.40 – 8.22 (m, 2H), 8.06 (dd, J = 7.6, 3.6 Hz, 2H), 7.72 (dd, J =6.6, 1.7 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.6, 2.3 Hz, 1H). LCMS (M+1): 566.8.

Example 16. Preparation of Compound No. 67

[0159] N-[4-(2-Bromothiazol-4-yl)-3-chloro-phenyl]-1,1,1-trifluoro-methanesulfonamide (300 mg, 0.71 mmol, 1 eq.), [4-(piperidine-1-carbonyl)phenyl]boronic acid (233 mg, 1.4 eq.) and sodium carbonate (189 mg, 2.5 eq. in 1 mL water) were charged in 5 mL of DMF in a 25 mL glass bottle and aerated with nitrogen gas for 7 min. After adding $Pd(PPh_3)_4$ (82.5 mg, 0.1 mmol) the mixture was further purged for 3 min and was heated to 100 °C overnight. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (4x50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[4-(piperidine-1-carbonyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (207 mg) as a white solid as the free base. ^{1}H NMR (400 MHz, Chloroform-d) δ (ppm): 7.98 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.82 (s, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 2.2 Hz, 1H), 6.98 (dd, J = 8.5, 2.3 Hz, 1H), 3.78 (s, 2H), 3.37 (s, 2H), 1.72 (s, 4H), 1.55 (s, 2H). LCMS (M+1): 530.1.

Example 17. Preparation of Compound No. 68

[0160] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (200 mg, 0.4761 mmol) and 1-isopentyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (150.9 mg, 0.5714 mmol), sodium carbonate (100 mg, 0.952 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (55 mg, 0.0476 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-

yl}phenyl)-1,1,1-trifluoromethanesulfonamide (135 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.05 (s, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 4.75 (m, 2H), 1.77 (m, J = 9.4 Hz, 2H), 1.60 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H). LCMS (M+1): 479.1.

Example 18. Preparation of Compound No. 69

Step-1: Synthesis of N-[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] methanesulfonamide

[0161] 3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (506 mg, 1 mmol, 1 eq.) was suspended in DCM (18 mL) then TEA (808 mg, 4 eq.) added and stirred for 5 min at RT. The mixture was maintained at ice-bath condition and mesyl chloride (458 mg, 2 eq.) was added dropwise and stirred for 2 h at the same temperature. The reaction was monitored by 1H-NMR. After completion of the reaction, the solvent was evaporated to get the desired product as a solid which was used for next step without any further purification.

Step-2: Synthesis of 4-(4-bromo-2-thienyl)-2-tert-butyl-pyridine

[0162] 2,4-Dibromothiophene (150 mg, 0.62 mmol), 2-tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (242 mg, 1.5 equiv) and sodium carbonate (164 mg, 1.54 mmol, 2.5 eq. in 1.0 mL water) in dimethyl formamide (5 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 8 min. After adding $Pd(PPh_3)_4$ (35 mg, 0.05 mmol) and Xantphos (35.8 mg, 0.1 eq.), the mixture was further purged for 3 min, and was heated to 100 °C overnight. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude 4-(4-bromo-2-thienyl)-2-tert-butyl-pyridine, which was used as such for the next step of synthesis without any further purification.

Step-3: Synthesis of N-[4-[5-(2-tert-butyl-4-pyridyl)-3-thienyl]-3-chloro-phenyl]methanesulfonamide

[0163] 4-(4-Bromo-2-thienyl)-2-tert-butyl-pyridine (170 mg, 0.576 mmol, 1 eq.), N-[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] methanesulfonamide (286 mg, 1.5 eq.) and sodium carbonate (152 mg, 2.5 equiv) were charged in DMF (5 mL) in a 25 mL glass bottle and aerated with nitrogen gas for 7 min. After adding $Pd(PPh_3)_4$ (66 mg, 0.1 mmol) the mixture was further purged for 3 min and was heated to 100 °C overnight. The reaction was monitored by LCMS. The reaction mixture was allowed to come to RT, water (10 mL) was added and the

mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide (64 mg) as a light yellow solid as the formate salt. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.53 (d, J = 5.2 Hz, 1H), 7.99 (s, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.57 (d, J= 8.4 Hz, 1H), 7.47 (d, J = 5.2 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 8.2, 2.1 Hz, 1H), 3.07 (s, 3H), 1.36 (s, 9H). LCMS (M+1): 421.1.

Example 19. Preparation of Compound No. 70

[0164] N-(4-(2-Bromoacetyl)-3-chlorophenyl) 1, 1, 1-trifluoro methane sulfonamide (200 mg, 0.527 mol) and 2-(cyclohexylmethyl) pyridine-4-carbothioamide (111 .2 mg, 0.475 mol) were charged in ethanol (10 mL) and the reaction mixture was heated at 80 °C for 1h. The resultant reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (45 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.75 (d, J = 6.2 Hz, 1H), 8.46-8.36 (m, 3H), 8.07 (d, j=8.5 Hz, 1H), 7.49 (d, J=2.3Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 2.98 (d, J = 7.3Hz, 2H), 1.88 (m, J = 10.9Hz, 1H), 1.76 (m 5H), 1.35 (m, 5H). LCMS (M+1): 516.1.

Example 20. Preparation of Compound No. 71

[0165] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and naphthalene-1-yl-boronic acid (61.3 mg, 0.3571 mmol), cesium carbonate (155 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (40 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.69-8.60 (d, J = 6.2 Hz, 1H), 8.18 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.04-7.96 (m, 2H), 7.92 (d, J = 7.2 Hz, 1H), 7.6 (m, 3H), 7.53 (d, J = 2.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H). LCMS (M+1): 469.0.

Example 21. Preparation of Compound No. 72

[0166] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1H-indole-6-yl-boronic acid (57.4 mg, 0.357mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the reaction mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (43 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.10 (d, J = 6.2 Hz, 1H), 8.04 (d, J = 1.9 Hz, 1H), 7.88 (s, 1H), 7.65 (m, 2H), 7.48 (d, J = 2.2 Hz, 1H), 7.39 (m, 2H), 6.52 (d, J = 7.2 Hz, 1H). LCMS (M+1): 457.9.

Example 22. Preparation of Compound No. 73

[0167] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 3-(benzyloxy)-4-(trifluoromethyl)phenylboronic acid (105.7 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (10 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.06-7.94 (m, 2H), 7.91-7.80 (d, J = 1.9 Hz, 1H), 7.71-7.67 (d, J = 1.9 Hz, 1H), 7.65-7.60 (m, 1H), 7.48-7.40 (m, 3H), 7.38-7.27 (m, 4H), 3.33 (d, J = 15.4 Hz, 2H). LCMS (M+1): 593.2.

Example 23. Preparation of Compound No. 74

[0168] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and biphenyl-2-ylboronic acid (70 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.238

mol), the mixture was heated to 100 °C for 18h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (18 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 7.92 (d, J =7.8 Hz, 2H), 7.72-7.59 (m, 2H), 7.57-7.47 (m, 2H), 7.43 (d, J =2.2 Hz 1H), 7.43-7.35 (m, 3H), 7.28 (m, 3H). LCMS (M+1): 495.

Example 24. Preparation of Compound No. 75

[0169] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and isoquinolin-4-ylboronic acid (61.7mg, 0.357 mmol),potassium carbonate (65 mg,0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (18 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 9.41 (s, 1H), 9.08 (d, J = 8.5 Hz, 1H) 8.95 (s, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.28 (s, 1H), 7.98-8.12 (m, 2H), 7.88 (m, 1H)), 7.58 (s, 1H), 7.39 (d, J = 5.5 Hz, 1H). LCMS (M+1): 469.9.

Example 25. Preparation of Compound No. 76

[0170] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-yl)piperazine (108 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-

trifluoromethanesulfonamide (54.2 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.28 (d, J = 5.6 Hz, 1H), 8.19 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.67 (s, 1H), 7.52-7.43 (m, 2H), 7.38 (d, J =8.4, Hz, 1H), 4.60 (d, J =14.5 Hz, 2H), 3.67 (d, J =12.5 Hz, 2H), 3.42 (s, 2H), 3.22 (d, J =10.5 Hz, 2H), 2.99 (s, 3H). LCMS (M+1): 518.06.

Example 26. Preparation of Compound No. 77

[0171] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (79.6 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (3.2 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.20 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.41 (d, J =2.2 Hz, 1H), 7.32 (d, J =8.5 Hz, 1H), 2.73 (s, 3H), 2.52 (s, 3H). LCMS (M+1): 437.9.

Example 27. Preparation of Compound No. 78

[0172] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 4-methyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzenesulfonamide (133 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide (35.2 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.48 (s, 1H), 8.11 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.78-7.66 (m, 3H), 7.62 (d, J =7.8 Hz, 1H), 7.43-7.34 (m, 2H), 7.37-7.27 (m, 2H), 7.23 (d, J =8.0 Hz, 1H), 2.32 (s, 3H). LCMS (M+1): 588.

Example 28. Preparation of Compound No. 79

[0173] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and (3,4-dimethoxy phenyl) boronic acid (64.9 mg, 0.3571 mmol), cesium carbonate (155 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (11 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 7.70 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.90(s, 3H). LCMS (M+1): 479.0.

Example 29. Preparation of Compound No. 80

[0174] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1H-indole-4-yl-boronic acid (57.5 mg, 0.3571 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (30 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.10 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.72 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.43 (t, J =2. 8 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 5.4 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H). LCMS (M+1): 457.7.

Example 30. Preparation of Compound No. 81

Step-1: Synthesis of 4-fluoro-2-(trifluoromethyl)benzamide

[0175] A solution of 4-fluoro-2-(trifluoromethyl)benzonitrile (100 mg, 0.528 mmol) in conc. sulfuric acid (1.2 mL) and glacial acetic acid (0.8 mL) was heated at 120 °C for 0.5h, monitored

by TLC. The reaction was diluted with water and the mixture extracted with EtOAc (2x30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 80 mg of 4-fluoro-2-(trifluoromethyl)benzamide as an off-white solid.

Step-2: Synthesis of 4-fluoro-2-(trifluoromethyl)benzenecarbothioamide

[0176] A solution of 4-fluoro-2-(trifluoromethyl)benzamide (500 mg, 2.414 mmol) and Lawesson's Reagent (1.95 g, 4.821 mmol) in toluene (30 mL) was heated at 80 °C for 1h. The progress of the reaction was monitored by TLC. The reaction was diluted with water (30 mL) and the mixture extracted with EtOAc (2x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude product, which was purified by column chromatography (silica-gel, 230-400 mesh) using 10 % EtOAc in hexane as eluent to obtain 100 mg of 4-fluoro-2-(trifluoromethyl)benzenecarbothioamide as a yellow sticky compound.

Step-3: Synthesis of N-[3-chloro-4-[2-[4-fluoro-2-(trifluoromethyl)phenyl]thiazol-4-yl]phenyl]-1,1,1-trifluoro-methanesulfonamide

[0177] A solution of 4-fluoro-2-(trifluoromethyl)benzenecarbothioamide (50 mg, 0224 mmol) and N-[4-(2-bromoacetyl)-3-chloro-phenyl]-1,1,1-trifluoro-methanesulfonamide (170 mg, 0.446 mmol) in ethanol (10 mL) was heated at 70 °C for 40 min, monitored by TLC. The reaction was diluted with aqueous saturated $NaHCO_3$ solution (25 mL) and the mixture extracted with EtOAc (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude product, which was purified by reverse phase preparative HPLC to obtain N-[3-chloro-4-[2-[4-fluoro-2-(trifluoromethyl)phenyl]thiazol-4-yl]phenyl]-1,1,1-trifluoro-methanesulfonamide (22 mg) as an off-white solid. ^{1}H NMR (400 MHz, Methanol-d4): δ (ppm): 7.98 (s, 1H), 7.81 (dd, J = 8.6, 5.4 Hz, 1H), 7.68 (dd, J = 8.9, 3.0 Hz, 2H), 7.53 (td, J = 8.4, 2.6 Hz 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H).

Example 31. Preparation of Compound No. 82

[0178] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 2,3-dihydrobenzofuran-5-boronic acid (58.5 mg, 0.3571 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with

water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (15 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 7.97 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.63 (t, J = 8.7 Hz, 2H), 2.17 (t, J = 9.3 Hz, 2H). LCMS (M+1): 460.6.

Example 32. Preparation of Compound No. 83

[0179] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [3-(bromomethyl)phenyl]boronic acid (61.3 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol), the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (9 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.13 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.97 – 7.79 (m, 1H), 7.51 – 7.43 (m, 2H), 7.41 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.6, 2.2 Hz, 1H), 4.59 (s, 2H). LCMS (M+1): 448.9.

Example 33. Preparation of Compound No. 84

[0180] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [2-(bromomethyl)phenyl]boronic acid (56 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (25 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.20 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.79 – 7.71 (m, 1H), 7.54 (dd, J = 7.5,

1.3 Hz, 1H), 7.43 (dt, J = 3.7, 1.9 Hz, 2H), 7.35 (dd, J = 8.5, 2.3 Hz, 1H), 4.87 (s, 2H). LCMS (M+1): 449.1.

Example 34. Preparation of Compound No. 85

[0181] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [2-(1-piperidyl)-4-pyridyl]boronic acid (53 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (56 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.23 – 8.07 (m, 2H), 7. 38 (s, 1H) 7.83 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.19 –7.09 (m, 2H), 3.62 (t, J = 5.1 Hz, 4H), 3.17 (s, 2H), 1.60 (dt, J = 9.7, 5.7 Hz, 4H). LCMS (M+1): 504.0.

Example 35. Preparation of Compound No. 86

[0182] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and (3-methyl-4-pyridyl)boronic acid (35 mg, 0. 0.261 mmol), sodium carbonate (63 mg, 0. 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (13 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.80 (s, 1H), 8.70 (s, 1H), 8.41 (s, 2H), 8.04 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 2.86 (s, 3H). LCMS (M+1): 434.4.

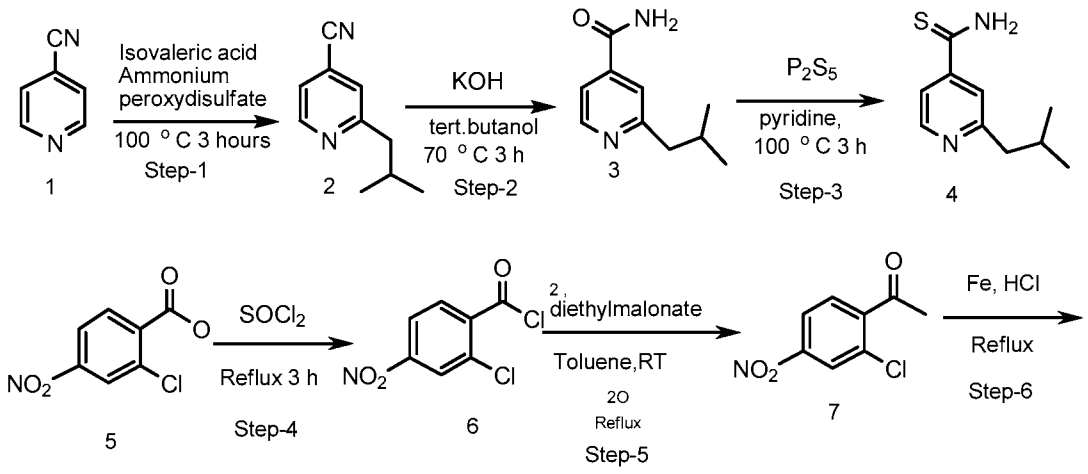
Example 36. Preparation of Compound No. 87

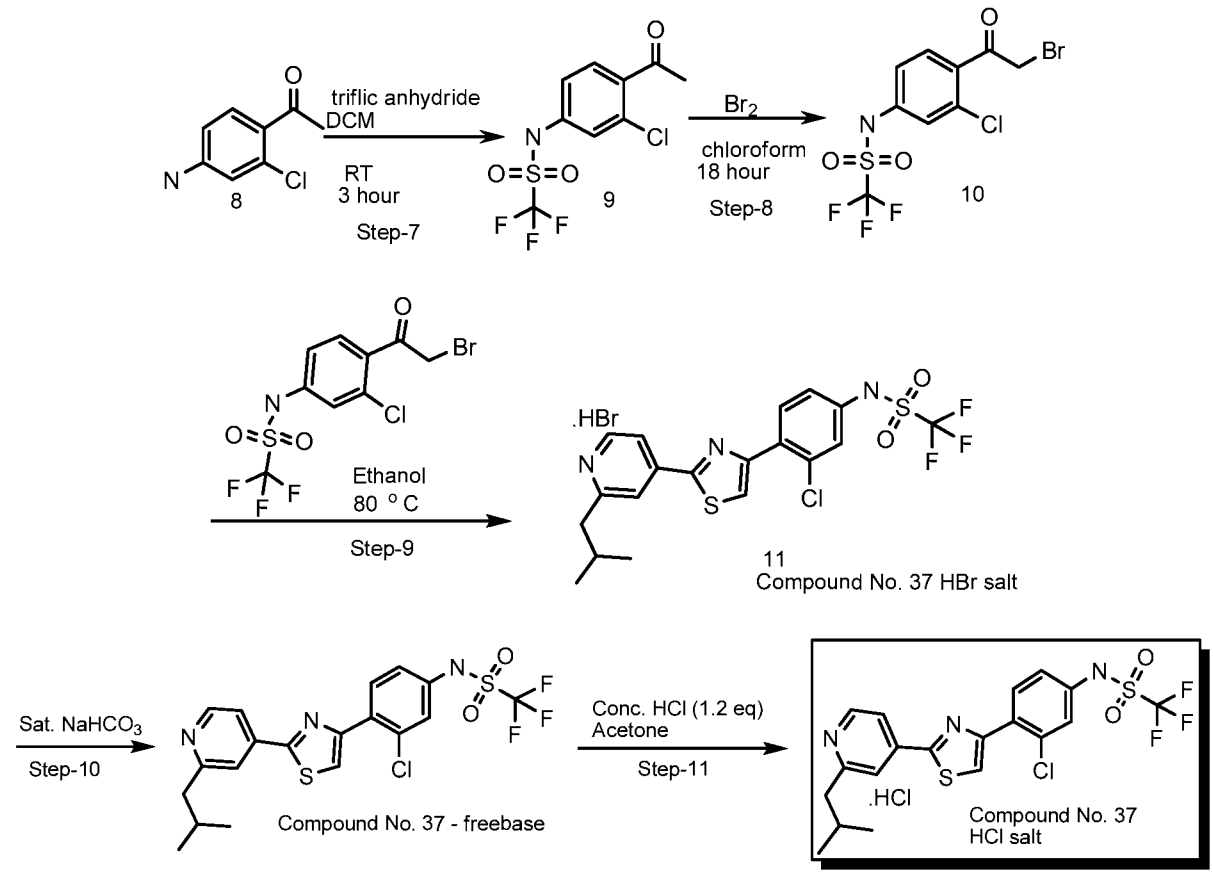
[0183] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (63 mg, 0. 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide (37 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.39 (d, J = 5.6 Hz, 1H), 8.29 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 3.5 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.43 – 7.33 (m, 2H). LCMS (M+1): 459.5.

Example 37. Preparation of Compound No. 37

[0184] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50mg, 0.132 mmol) and 2-isobutylpyridine-4-carbothioamide (25.34 mg, 0.132mmol) were charged in EtOH (10 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated and purified through reverse phase HPLC. (Yield: 17 mg TFA salt). ^{1}H NMR (TFA salt, CD_3OD) δ (ppm): 8.73 (d, J=5.9 Hz, 1H), 8.38 (d, J=2.9 Hz, 1H), 8.31 (d, J = 6.2 Hz, 1H), 8.07 (d, J= 8.5 Hz, 1H), 7.49 (s, 1H), 7.39 (d, J=8.2 Hz, 1H), 2.94 (d, J=7.3 Hz, 2H), 2.19 (m, 2H), 1.07 (d, J=6.6 Hz, 6H).

Complete synthesis of Compound No. 37





Step 1: Synthesis of 2-isobutylpyridine-4-carbonitrile (2)

[0185] To a suspension of 4-cyano pyridine **(1)** (30 g, 0.288 mol, 1 equiv.) in water (210 mL), concentrated sulfuric acid (15.3 mL, 0.288 mol, 1 equiv.) was added dropwise maintaining the temperature at 20-25 °C. After formation of a clear solution, $AgNO_3$ (4.9 g, 0.028 mmol, 0.0001 equiv.) followed by isovaleric acid (160 mL, 1.47 mol, 5 equiv.) were added in to the reaction mixture. A white hazy solution formed. Ammonium peroxydisulfate (66 g, 0.288 mol, 1 equiv.) dissolved in water (90 mL) was then added. A black clear solution formed. The reaction mixture was then heated to reflux at 100 °C for 3 h. The reaction was monitored by TLC. After completion, the reaction mixture was basified (pH = 7-8) using a saturated solution of sodium bicarbonate, and extracted with EtOAc (3x750 mL). The extracts were combined and were washed with brine (3x300 mL) and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel: #100-200) using 0-6 % EtOAc in hexane as eluant to afford 2-isobutylpyridine-4-carbonitrile **(2)** (15 g (32.5 % yield)) as a pale yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.78 – 8.63 (m, 1H), 7.41 – 7.27 (m, 2H), 2.72 (d, J = 7.2 Hz, 2H), 1.35 – 1.23 (m, 1H), 0.94 (d, J = 6.6 Hz, 6H).

Step 2: Synthesis of 2-isobutylpyridine-4-carboxamide (3)

[0186] 2-Isobutylpyridine-4-carbonitrile **(2)** (15 g, 0.093 mol, 1 equiv.) and KOH (15.7 g, 0.281 mol, 3 equiv.) was dissolved in *tert*-butanol (160 mL). The reaction mixture was stirred at 70 °C for 90 min. The reaction was monitored by TLC. After completion, the *tert*-butanol was removed under reduced pressure; the residue was dissolved in water and extracted with EtOAc (3x275 mL). The extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was triturated with *n*-hexane (3x200 mL). To the residue was added diethyl ether (50 mL) and then concentrated under reduced pressure to afford 2-isobutylpyridine-4-carboxamide **(3)** (13.5 g (81.3 % yield)) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.68 (d, *J* = 5.1 Hz, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 5.1 Hz, 1H), 6.14(s, 1H), 5.81 (s, 1H), 2.73 (d, *J* = 7.3 Hz, 2H), 2.13 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 6H).

Step 3: Synthesis of 2-isobutylpyridine-4-carbothioamide (4)

[0187] To a solution of 2-isobutylpyridine-4-carboxamide **(3)** (13.5 g, 0.075mol, 1 equiv.) in pyridine (135 ml), was added P_2S_5 (8.45 g, 0.037 mol, 0.5 equiv.). The reaction was heated at 100 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the pyridine was evaporated under reduced pressure; the residue was dissolved in water (100 mL) and extracted with EtOAc (3x250 mL). The EtOAc extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product obtained was triturated with *n*-hexane (3x200 mL) to afford 2-isobutylpyridine-4-carbothioamide **(4)** (8 g (54.4 % yield)) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.62 (d, *J* = 5.1 Hz, 1H), 7.73 – 7.64 (broad, 1H), 7.52 – 7.40 (m, 2H), 7.32 – 7.25 (m, 1H), 2.72 (d, *J* = 7.2 Hz, 2H), 2.13 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H).

Step 4: Synthesis of 2-chloro-4-nitrobenzoyl chloride (6)

[0188] To a two neck flask (1L) placed in ice bath was placed 2-chloro-4-nitrobenzoic acid **(5)** (50 g, 0.248 mol, 1 equiv.). Thionyl chloride (110 ml, 1.51 mol, 6.1 equiv.) was added dropwise at 0 °C. The reaction mixture was allowed to come to RT and then heated to reflux. The heating was continued overnight. The thionyl chloride was evaporated and ice (approx. 150 g) was added to the reaction mixture. The aqueous reaction mixture was extracted with DCM (2x200 mL). The DCM extracts were combined dried over anhydrous sodium sulfate and concentrated under vacuum to get 2-chloro-4-nitrobenzoyl chloride **(6)** (50 g (91.7 % yield)) as a light yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.37 (d, *J* = 2.2 Hz, 1H), 8.25 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H).

Step 5: Synthesis of 1-(2-chloro-4-nitrophenyl)ethanone (7)

[0189] A suspension of anhydrous magnesium chloride (47 g, 0.214 mol, 0.7 equiv.) in toluene (300 mL) was treated with triethylamine (75.04 mL, 0.535 mol, 2.5 equiv.) and diethylmalonate (41.09 g, 0.257 mol, 1.2 equiv.). The reaction mixture was stirred at RT for 1.5 h. To this was added 2-chloro-4-nitrobenzoyl chloride **(6)** (47 g, 0.214 mol, 1 equiv.) dropwise (an exothermic reaction up to 50 °C was observed during addition). Toluene (50 mL) was used for complete transfer of 2-chloro-4-nitrobenzoyl chloride to the reaction mixture. The reaction mixture was stirred at RT for 18 h. The reaction was monitored by TLC and NMR. After complete consumption of starting material, concentrated hydrochloric acid (35 % solution) (300 mL) was added and the upper toluene layer was separated. The toluene was evaporated under reduced pressure below 50 °C. To the residue were added DMSO (200 mL) and water (10 mL), and the mixture heated at 160 °C for 12 h. The reaction was monitored by TLC and NMR. The reaction mixture was allowed to come to RT and water (40 mL) was added. The reaction mixture was extracted with EtOAc (3x200 mL). The EtOAc extracts were combined and washed with brine solution (3x300 mL) and dried over anhydrous sodium sulfate. The EtOAc layer was concentrated to get 1-(2-chloro-4-nitrophenyl) ethanone **(7)** (43 g (84 % yield)) as a yellow liquid which solidified upon refrigeration. ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.29 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.65 (d, *J* =8.4 Hz, 1H), 2.66 (s, 3H).

Step 6: Synthesis of 1-(4-amino-2-chlorophenyl) ethanone (8)

[0190] 1-(2-Chloro-4-nitrophenyl) ethanone (87.8 g, 0.43 mol, 1 equiv.) was charged in methanol (600 mL). The reaction mixture was heated to 70 °C and concentrated HCl (131 mL, 1.29 mol, 3 equiv.) was added dropwise with constant stirring. After the completion of addition, iron powder (98.2 g, 1.75 mol, 4 equiv.) was added in four parts at 5 minute intervals. The reaction mixture was heated at 70 °C for 7 h and the reaction monitored by TLC and NMR. After completion of reaction, the mixture was allowed to come to RT and then filtered through a celite bed. The filtrate was concentrated under reduced pressure and celite bed was washed with EtOAc to obtain further crude product. Both portions were combined and water (200 mL) was added. The EtOAc layer was separated and aqueous layer was extracted with EtOAc (2x500 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get crude product (57 g). This crude product was precipitated in pentane to get 1-(4-amino-3-methoxyphenyl) ethanone (**8**) (50g (67 % yield)) as a pink solid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 7.62 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.54 (dd, *J* =8.5, 2.3 Hz, 1H), 4.07 (s, 2H), 2.61 (s, 3H).

Step 7: Synthesis of N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (9)

[0191] A solution of triflic anhydride (75.1 g, 0.266 mol, 1.5 equiv.) in DCM (600 mL) was cooled to 0 °C. Pyridine (23.4 mL, 0.266 mol, 1.5 equiv.) was added dropwise with constant stirring over 30 min. The reaction mixture was stirred at the same temperature for 1 h. A solution of 1-(4-amino-2-chlorophenyl)ethanone **(8)** (30 g, 0.177 mol, 1 equiv.) in DCM (400 mL) was added dropwise maintaining the temperature at 0 °C with constant stirring over a period of 45 min. The reaction mixture was then allowed to come to RT and stirred for 1 h at RT. The reaction was monitored by TLC and NMR. Upon completion, ice cold water (500 mL) was added and the DCM layer was separated. The aqueous layer was again extracted with DCM (2x100 mL). The DCM extracts were combined washed with ice cold water (2x500 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure below 40 °C to obtain the crude product. Diethyl ether (200 mL) and pentane (600 mL) were added to the mixture which was then stirred for 30 min. The mixture was filtered and the filtrate concentrated and triturated in pentane to get N-(4-acetyl-3-chlorophenyl)-1, 1,1-trifluoromethanesulfonamide **(9)** (28 g (52.8% yield)) as a light pink solid**.** ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 7.63 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.28 – 7.21(m, 1H), 2.66 (s, 3H).

Step 8: Synthesis of N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (10)

[0192] A solution of N-(4-acetyl-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide **(9)** (21 g, 0.07 mol, 1 equiv.) in chloroform (600 mL) was cooled to 0 °C. Liquid bromine (2.9 mL, 0.004 mol, 0.8 equiv.) dissolved in chloroform (400 mL) was added dropwise over a period of 40 min, maintaining the reaction temperature between 0-10 °C. The mixture was allowed to come to RT and then stirred at RT for 18 h. The reaction was monitored by TLC and NMR. There was an indication of the presence of starting material and desired compound along with some amount of N-(3-chloro-4-(2,2-dibromoacetyl)phenyl)-1,1,1-trifluoromethanesulfonamide (dibromo impurity). A saturated solution of sodium thiosulfate (200 mL) was added and the chloroform layer was separated. The aqueous layer was extracted with chloroform (2x100 mL). The main chloroform layer and the chloroform extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. A clear liquid was obtained as the residue. To this were added diethylether (50 mL) and pentane (250 mL) and the mixture stirred for 10 min. The reaction mixture was filtered and the filtrate concentrated. The crude product obtained was triturated with pentane (~50 mL) to obtain a white solid. This white solid was filtered and dried under vacuum to get N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide

(10) (20 g) which contained approximately 35% of starting material i.e. N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide **(9)** by NMR. The mixture of products was directly used for the next step without any further purification. ^{1}H NMR (400 MHz, Chloroform-*d*): δ (ppm): 7.64 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.30 –7.27 (m, 1H), 4.51 (s, 2H).

Step 9: Synthesis of N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide (11)

[0193] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide **(10)** (15.5 g, 0.041 mol, 1 equiv.) and 2-isobutylpyridine-4-carbothioamide (5.2 g, 0.027 mol, 0.65 equiv.) were charged in ethanol (40 mL) and the reaction mixture was heated at 80 °C for 30 min. The reaction mixture was cooled in an ice bath and stirred at 0 °C for 30 min. The solid obtained was isolated by filtration and washed with cold ethanol (2x5 mL). The solid obtained was dried under vacuum to get N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide **(11)** (10.2 g (53.6% yield)) as the hydrobromide salt. ^{1}H NMR (400 MHz, Methanol-*d*4): δ (ppm): 8.80 (d, *J* = 6.3 Hz, 1H), 8.57 – 8.45 (m, 3H), 8.08 (d, *J* = 8.5 Hz, 1H),7.50 (d, *J* = 2.2 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.01 (d, *J* = 7.4 Hz, 2H), 2.21 (m,1H), 1.06 (d, *J* = 6.6 Hz, 6H). UPLC: In method, Column Type : ACQUITY BEH SHIELD C18, Column ID:2.1*50 mm, 1.7µ; Flow Rate - 0.35 mL/min, Mobile Phase A: 0.05% TFA; Mobile Phase B: acetonitrile. Gradient: 10% B To 50% B in 1min., hold for 0.5 min, 50% B to 90% B in 0.1 min, hold for 1 min, 90% B to 10% B in 0.4 min compound eluted at a retention time of 2.66 min.

Step 10: Synthesis of N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide - free base (12)

[0194] N-(3-Chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide hydrobromide salt (**11**) (88.5. g) was charged in a flask and a saturated solution of sodium bicarbonate (300 mL) was added so that the pH became slightly basic (pH=7-8). EtOAc (3x500 mL) was added and the reaction mixture was stirred at RT until the mixture became clear. The organic layer was separated and washed with water (50 mL). The EtOAc layer was dried over anhydrous sodium sulfate and concentrated to get N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide (**12**) (46.3g (61% yield)) as the free base. ^{1}H NMR (400 MHz, Methanol-d): δ (ppm): 8.56 (d, J = 5.3 Hz, 1H), 8.10 (s , 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.92 – 7.80 (m, 2H), 7.44 (d, J= 2.2 Hz, 1H), 7.31 (dd, J = 8.5, 2.3 Hz, 1H), 3.06 (s , 3H), 2.86 (dd, J = 8.6, 6.7 Hz, 2H), 1.88 – 1.74 (m, 2H), 1.01 (t, J = 7.4 Hz,3H).

Step 11: Synthesis of N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide Hydrochloride (13)

[0195] N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide - free base (**12**) (46.4 g, 0.097 mol, 1 equiv.) was charged in acetone (1.5 L) and stirred at RT for 5-10 min until a clear solution was obtained. A solution of concentrated hydrochloric acid [~35% v/v] (13.3 mL, 0.126 mol, 1.3 equiv.) in acetone (85 mL) was added dropwise with constant stirring. After addition, the pH of the reaction mixture was 1-2. The reaction mixture was stirred for 30 min at RT. The solid obtained was filtered under vacuum and washed with acetone (3x100 mL) (the washing was performed without vacuum and once acetone was absorbed by the solid, the solvent was removed by vacuum filtration). The washing was repeated until the filtrate was colorless. The light yellow solid obtained was dried at 50 °C under reduced pressure for 2 h to get N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide - hydrochloride salt (13) (44 g (88 % yield)). ^{1}H NMR (400 MHz, Methanol-*d*4): δ (ppm): 8.81 (d, *J* = 6.3 Hz, 1H), 8.58 – 8.45 (m, 3H), 8.08 (d, *J* = 8.5 Hz,1H), 7.49 (t, *J* = 2.8 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.4 Hz, 1H), 3.02 (d, *J* = 7.3 Hz, 2H), 2.22 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 6H). Melting point: 165 °C – 173 °C (FB). LCMS – (M+1):475.9 (99.5%). In method, Column type : HYPERSILGOLD,C18, Column_ID: 4.6*50 mm, 5μ; Mobile Phase A: 0.05% formic acid in H_2O; Mobile Phase B: 0.01% formic acid in acetonitrile. Gradient: 10% B to 90% B From 0.2 to 2 min, hold for 2.5 min, 10%B in 0.1 min. Flow: 0.7 mL/min. The desired compound has RT of 4.514 min. UPLC – In method, Column Type: ACQUITY BEH C18; Column ID: 2.1*50 mm, 1.7μ; Flow Rate: 0.35 mL/min. Mobile phase A: 0.05% TFA Mobile phase B: Acetonitrile, Gradient: 10% B to 90% B in 2.5 min, hold for 1 min, 90% B to 10% B in 0.3 min. The desired compound had RT of 2.793 min. Melting point: 220 °C - 227 °C (Hydrochloride salt).

Example 38. Preparation of Compound No. 88

[0196] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [3-(1-piperidyl)phenyl]boronic acid (53 mg, 0. 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4mL), water(1.0 mL)were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd-acetate (8 mg, 0.035 mmol) and xantphos (27.5 mg, .0476 mmol), the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and

concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (25 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.23 (s, 1H), 8.11 – 7.94 (m, 3H), 7.71 – 7.59 (m, 2H), 7.47 (d, J = 2.2 Hz, 1H), 7.37 (dd, J = 8.6, 2.2 Hz, 1H), 3.63 (t, J = 5.5 Hz, 4H), 2.01 (q, J = 6.2 Hz, 4H), 1.80 (q, J = 6.0 Hz, 2H). LCMS (M+1): 502.5.

Example 39. Preparation of Compound No. 89

[0197] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-b]pyridin-1-yl]-triisopropyl-silane (109 mg, 0. 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide (35 mg) as a white color solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 12.10 (s, 1H), 8.43 (d, J = 2.2 Hz, 2H), 8.08 (d, J = 8.5 Hz, 1H), 7.74 (t, J = 3.0 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.45 – 7.36 (m, 2H). LCMS (M+1): 477.1.

Example 40. Preparation of Compound No. 90

[0198] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380mmol) and benzothiophen-3-ylboronic acid (47 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide (59 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.80 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H), 8.08 (d,

J = 8.5 Hz, 1H), 7.99 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.51 – 7.43 (m, 2H), 7.38 (dd, J = 8.6, 2.3 Hz, 1H). LCMS (M+1): 475.

Example 41. Preparation of Compound No. 91

[0199] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1-[[5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]pyrrolidine (80 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (80 mg) as a pale red solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.11 (dd, J = 8.7, 5.4 Hz, 1H), 7.98 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.56 (dd, J = 9.0, 2.7 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.33 (dd, J = 8.4, 2.2 Hz, 1H), 4.61 (s, 2H), 3.43 (t, 2H), 3.25 (t, 2H), 2.17 (m, 2H), 1.97 (m, 2H). LCMS (M+1): 521.4.

Example 42. Preparation of Compound No. 92

[0200] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and N-cyclopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine (76 mg, 0. 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (96 mg) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.25 (s, 1H), 7.94 (dd, J = 14.6, 7.6 Hz, 2H), 7.57 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.38 – 7.29 (m, 1H), 4.11 (q, J = 6.1 Hz, 1H),

2.14 (dt, J = 13.2, 6.4 Hz, 2H), 1.84 (dt, J = 6.6 Hz, 2H), 1.71 (tt, J = 24.6, 11.7, 6.0 Hz, 4H). LCMS (M+1): 503.8.

Example 43. Preparation of Compound No. 93

[0201] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (64 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (42 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 8.24 – 8.19 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.50 – 7.45 (m, 2H), 7.36 (dd, J = 8.5, 2.3 Hz, 1H), 7.26 – 7.20 (m, 2H). LCMS (M+1): 458.3.

Example 44. Preparation of Compound No. 94

[0202] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 4-quinolyl boronic acid (61.7 mg, 0.3571 mol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding $Pd(PPh_3)_4$ (27.4 mg, 0.0238 mmol) re-purged the mixture for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-[3-chloro-4-[2-(4-quinolyl)thiazol-4-yl]phenyl]-1,1,1-trifluoro-methanesulfonamide (37 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ (ppm): 7.94 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.46 – 7.38 (m, 4H), 7.31 (dd, J = 8.5, 2.3 Hz, 2H), 6.16 (s, 1H), 5.64 (s, 1H). LCMS (M+1): 445.3.

Example 45. Preparation of Compound Nos. 6-36, 38-56, and 95-152

[0203] Compound nos. 6-36, 38-56, and 95-152 can be prepared using conditions analogous to those in both the General Methods and Examples provided above.

Example B1. Effect of Compounds on SREBP2 Cleavage and Cell Viability in HEPG2 Cells.

[0204] Average SREBP2 cleavage in HEPG2 cells was measured in the presence of compounds disclosed in Table 1. HepG2 cells were seeded at 500,000 cells per well in 6-well plates in DMEM supplemented with 10% FBS. After 2 days, cells were treated with compounds (20 μM) for 1 day in DMEM without FBS. Western blots were normalized with respect to actin.

[0205] For viability measurements, HepG2 cells were seeded at 5,000 cells per well in 96-well plates in DMEM supplemented with 10% FBS. After 1 day in culture, cells were treated with compounds (20 μM & 5 μM) for 3 days in DMEM without FBS. Viability was measured by MTS. Treatment with compounds (20μM & 5 μM) was carried out in medium without FBS, and viability was measured by MTS.

[0206] The results are shown in Table 3 as percent inhibition @ 20 μM, and in Table 4 as percent inhibition @ 5 μM.

Table 3 (20 μM)

Compound No.	Average SREBP2 cleavage (% Inhibition, n=3)	Average Viability (% Inhibition, n=3)
1	73.7	92.07
2	73	80.5
4	96.07	94.38
5	81.7	99.2
37	94.59	95.03
57	46.9	56.4
58	29.4	67.9
59	60.6	99.8
60	99.0	100.0
61	2.0	43.0
62	0.0	0.0
63	39.0	47.0
64	97.0	100.0
66	0.0	11.0
67	3.0	20.0

Table 4 (5 μM)		
Compound No.	**Average SREBP2 cleavage (% Inhibition, n=3)**	**Average Viability (% Inhibition, n=3)**
37	75	94
70	73	100
71	77	97
72	61	94
73	64	99
74	76	97
75	55	88
76	7	3
77	56	41
78	38	87
79	65	74
80	90	86
81	44	88
82	77	82
83	2	0
84	20	18
85	82	93
86	54	27
87	50	9
88	90	19
89	53	5100
90	64	99
91	16	4
92	59	94
93	28	82
94	35	84
95	39	86

[0207] Compound #37 was further tested at several concentrations to obtain an IC_{50} for SREBP2 cleavage of 4.6 μM and Viability of 2.15 μM, as shown in **FIG. 1**.

Example B2. Effect of compounds on a human LnCap xenograft.

[0208] LnCap cells were inoculated in male nude mice. Animals were randomized into 3 treatment groups (n=10 per group) when tumor size reached 100mm^3. One group was treated by oral gavage with the vehicle solution twice a day; and another group was treated at 40 mg/kg/po/bid compound #37. Tumor volume was measured by caliper measurements twice a week during the course of the experiment (4 weeks). The results are shown in **FIG. 2**.

Example B3. Effect of compounds in various cell lines.

Cytotoxicity and IC_{50} determination

[0209] Cell plating: Cells were cultured in medium with 10% regular FBS. Cells were harvested respectively during the logarithmic growth period and counted using Countstar. Cells were split to two sets: one set was cultured in medium+5% regular FBS and the other set was cultured in medium+5% LDFBS (lipid reduced FBS). Cell concentrations were adjusted to 2.22×104 cells/mL with respective culture medium for 3-day CTG assay. (The cell density was optimized before actual study; cell density used in the test may vary for different cell lines). For each serum condition, 90µl cell suspensions were added to two 96-well plates (plate A and B) with the final cell density of 2×103 cells/well for 3-day CTG assay (The cell density was optimized before actual study; cell density used in the test may vary for different cell lines). 10 µl of culture medium was added to each well of plate A group for T0 reading. All plates were incubated (A and B groups) overnight in humidified incubator at 37°C with 5% CO2.

[0210] Day 0: T0 reading: For plate A group, CellTiter-Glo® Reagent was added at equal volume of cell culture medium present in each well (e.g., add 100µl of reagent to 100µl of medium containing cells for a 96 -well plate). Contents were mixed for 2 min on an orbital shaker to facilitate cell lysis. The plate was allowed to incubate at RT for 10 min to stabilize luminescent signal. Note: Uneven luminescent signal within standard plates can be caused by temperature gradients, uneven seeding of cells or edge effects in multiwall plates. A Backseal black sticker was affixed to the bottom of each plate. Luminescence was recorded (T0) using EnVision Multi Label Reader.

[0211] Day 0: compound treatment: Test compounds and positive controls were dissolved with PBS as stock solution at the concentration indicated at Test Article Dilution map. A 500× solution was prepared in DMSO, then diluted with appropriate culture media (1:50) into 10×working solutions. 10µl (10×) drug solutions were dispensed in each well (triplicate for each drug concentration) of the plate B group according to plate inoculation map. The test plates were incubated for 3 days in the humidified incubator at 37°C with 5% CO2.

[0212] Day3: Plate B group reading. CellTiter-Glo® Reagent was added at equal volume of cell culture medium present in each well (e.g., add 100µl of reagent to 100µl of medium containing cells for a 96 -well plate). Contents were mixed for 2 min on an orbital shaker to induce cell lysis. The plate was allowed to incubate at RT for 10 min to stabilize luminescent signal. Note: Uneven luminescent signal within standard plates can be caused by temperature gradients, uneven seeding of cells or edge effects in multiwall plates. A Backseal black sticker was affixed

to the bottom of each plate. Record luminescence using EnVision Multi Label Reader. IC_{50} values were calculated for each Compound for each cell line. The results are shown in **FIG. 3** for Compound #37.

Example B4. PK data for representative compounds.

[0213] Standard PK parameters were collected in Mouse and Dog for Compound #37 in mouse (**FIG. 4A**) and dog (**FIG. 4B**). Data for additional compounds was collected and is presented in Table B4:

Table B4: PK parameters for representative compounds

Cpd No.	i.v. @ 2 mg/kg					p.o. @ 10 mg/kg				Bioavailability
	Cmax (μM)	AUC_{last} (μM*h)	Terminal $t_{1/2}$ (h)	CL (L/h/kg)	V_d (L/kg)	C_{max} (μM)	T_{max} (h)	AUC_{last} (μM*h)	Terminal $t_{1/2}$ (h)	
5	10.2	41	2.51	0.095	0.345	20.3	1	302	6.96	149.0%
60	3.38	12.6	3.08	0.288	1.28	6.58	4	57.1	>8hrs	90.20%
64	7.13	38.5		0.055	1.95	32.1	24	526	>8hrs	273%
70	4	2.2	1.1	3.28	5.22	2.2	0.5	5.19	1.04	46.4%
71	3.57	13.6	3.5	0.251	1.27	7.57	4	51.5	>8hrs	75.9%
80	3.63	8.94	2.8	4.25	1.72	20.6	4	130	>8hrs	291.0%
82	12.6	25.4	3.64	0.137	0.719	25.8	4	175	>8hrs	138.0%
85	0.241	0.655	4.08	4.63	27.3	0.45	2	2.27	>8hrs	69.3%
88	3.44	10.6	3.35	0.3	1.45	8.41	2	51.5	>8hrs	96.8%

Example B5. Effect of compounds on a human in-vivo MDA-MB-453 xenograft.

[0214] Cell line: Human breast cancer cell line MD-MB-453 was purchased from ATCC (Manassas, VA). Cells were grown at atmospheric $C0_2$ in L-15 media containing 10% fetal bovine serum, penicillin streptomycin, L-glutamine, and sodium pyruvate. Cells were spun down and resuspended at a concentration of 6.0E07 cells/mL in serum-free medium without additives, then combined 1:1 with Matrigel™ (Trevigen, Gaithersburg, MD).

[0215] Surgical implantation of DHT pellets: One week after castration, the animals were anesthetized with a mixture of isoflurane and oxygen and the surgical area was sterilized using iodine and alcohol. Each animal was implanted with 12.5 mg 5α-DHT 60-day slow release pellets (Innovative Research of America, Sarasota, FL) on the lateral side of the neck between the ear and the shoulder. The skin was closed with a 6-0 silk suture.

[0216] Injection of orthotopic cells: Two days after pellet implantation, the mice were inoculated by injection underneath the nipple of the number 4 mammary fat pad with 200 μL (6.0E06 cells) per mouse of the freshly prepared MD-MB-453:Matrigel mixture. All procedures were carried out in HEPA-filtered laminar-flow hoods.

[0217] Study design: When the tumors reached a mean volume of approximately 100 mm^3, sixty animals with established tumors and moderate body weights were randomized into 6 treatment groups (Group 1-6, n=10 mice each). Group 1 was treated once daily with vehicle (20% HPBCD). Groups 2 to 5 were treated once daily with Compound #37 with (respectively) 1, 3, 10, or 30 mg/kg. Group 6 was treated twice daily (at intervals of ~8-10 h) with Compound #37 at 10 mg/kg. All treatments were administered as oral gavage (PO) at a dose volume of 5 mL/kg. Doses were administered starting on the staging day and continued for 42 days (Days 0-41).

[0218] Tumor volume was measured by caliper measurements twice a week during the course of the experiment (4 weeks). The results are shown in **FIG. 5**.

Example B6. Effect of compounds on an in-vivo LnCAP human prostate adenocarcinoma xenograft.

[0219] An efficacy study of Compound #37 on LnCap Cancer Xenograft in SCID Mice was performed by MuriGenics, Inc.

[0220] Experimental animals: Ninety-five male Beige Severe Combined Immune Deficiency (SCID) mice were purchased from Charles River (Hollister, CA) as 6- to 7-week-old mice. Following arrival, animals were weighed using an electronic balance (Ohaus SCOUT® PRO, Parsippany, NJ), given a clinical examination to ensure that the animals were in good condition, and housed 5 per cage. The animals were maintained in a HEPA-filtered environment in a Modular Animal Caging System (MACS) full-ventilation rodent housing system (Alternative Design, Arkansas). Animal room controls were set to maintain temperature and relative humidity at 22 °C ± 4 °C and 50% ± 20%, respectively. Housing rooms were on a 12:12 light/dark cycle. Cages were autoclaved. Water was autoclaved and supplied ad libitum to each cage via water bottles. Irradiated 2016 Teklad Global 16% Protein Rodent Diet and SaniChip irradiated bedding 7090A were obtained from Harlan Teklad (Hayward, CA).

[0221] Compound formulation: Dose suspensions of Compound #37 were formulated in 20% HPCD at 5.0, 15.0, 50.0, and 150 mg/mL (for administration at 1, 3, 10, and 30 mg/kg (mg/kg), respectively). Specifically, vehicle was dispensed into a vial containing a measured amount of test article powder and the vial was vortexed and sonicated until the test article was suspended completely, approximately 5-15 minutes. The vial contents then were brought to the required volume with additional vehicle, and the solution was vortexed and sonicated for an additional 2-5

minutes. The dosing suspensions (test article in 20% HPCD) were prepared freshly and used within one hour of formulation.

[0222] Cell line: Human prostate adenoma cancer cell line LnCaP was purchased from ATCC (Manassas, VA). Cells were grown in 1640 RPMI containing 10% fetal bovine serum,. Cells were spun down and resuspended at a concentration of 5.0E07 cells/mL in serum-free medium without additives, then combined 1:1 with Matrigel™ (Trevigen, Gaithersburg, MD).

[0223] Injection of cells: At approximately 5 weeks before the projected initiation of dosing, each mouse was implanted, under isoflurane anesthesia, by injection into the left flank with 200 µL (5.0E06 cells) per mouse of the freshly prepared LnCaP:Matrigel mixture(50:50). All procedures were carried out in HEPA-filtered laminar-flow hoods.

[0224] Study design: Study design and treatments of all groups are shown in B6.

Table B6. Study Design

Group	Treatment Phase (Days 0-39)			
	Agent	Dose (mg/kg, PO)	Frequency	n
1	Vehicle	0	QD	10
2	Compound #37	1	QD	10
3	Compound #37	3	QD	10
4	Compound #37	10	QD	10
5	Compound #37	30	QD	10
6	Compound #37	10	BID	10

[0225] When the tumors reached a mean volume of approximately 100 mm^3, sixty animals with established tumors and moderate body weights were randomized into 6 treatment groups (Group 1-6, n=10 mice each). Group 1 was treated once daily with vehicle. Groups 2 to 5 were treated once daily with Compound #37 with (respectively) 1, 3, 10, or 30 mg/kg. Group 6 was treated twice daily (at intervals of ~8-10 hr) with Compound #37 at 10 mg/kg. All treatments were administered as oral gavage (PO) at a dose volume of 5 mL/kg. Doses were administered starting on the staging day and continued for 40 days (Days 0-39).

[0226] Body weights were measured twice per week using an electronic balance (Ohaus SCOUT® PRO). Tumor sizes were measured twice per week using microcalipers (Mitutoyo, Aurora, Illinois) to measure the perpendicular minor dimension (W) and major dimension (L). Tumor volume (mm^3) was calculated using the formula L x W x H/2.

[0227] At 1 hr after the final dose administration on Day 39, animals were subjected to terminal cardiocentesis and euthanized. For each animal, blood was collected as K_2EDTA plasma, split into 2 aliquots (minimum 50 μL each), and frozen at -80 °C. One aliquot from each animal was submitted to Integrated Analytical Solutions, Inc. (Berkeley, CA), for assessment of test article exposure; the remaining aliquot was retained at -80 °C at MuriGenics pending further instructions from the client. At necropsy, terminal body weights were recorded, and tumors were excised, weighed, and split in two. Separate halves of each specimen were flash-frozen on dry ice and stored at -80 °C or drop-fixed in 10% neutral buffered formalin (NBF) pending further analyses.

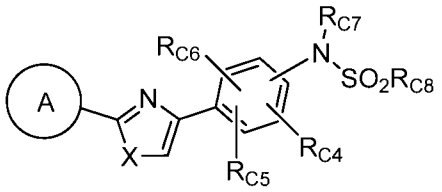
[0228] Statistical analysis: Descriptive and inferential analyses were performed using the corresponding functions of Excel 2010 (Microsoft, Redmond, WA). Inferential analysis consisted of t-test comparisons (two-tailed, heteroscedasticity assumed) to data from the vehicle-dosed (Group-1) animals. Values of $p \leq 0.05$ were considered statistically significant. The results on the effect of Compound #37 on tumor volumes are presented in **FIGS. 6A and 6B**.

Example B7. Effect of compounds in a mouse liver steatosis model.

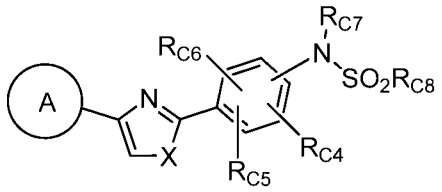
[0229] The effects of Compounds of the invention in a non-alcoholic steatohepatitis (NASH) mouse screening model will be determined, provided by Physiogenex. Male C57BL/6J mice (n=40), 8 weeks old, are fed a high fat/cholesterol/cholic acid diet ("Paigen" diet) for up to 21 days, and compounds of the invention are dosed once daily at both 5 mg/kg and 20 mg/kg. Parameters to be determined include plasma biochemistry (ALT, AST, triglycerides, total cholesterol, fatty acids, IL-6), liver biochemistry (triglycerides, total cholesterol, fatty acids, 15 gene expression by RT-qPCR to assess lipid metabolism, cholesterol metabolism, SREBP proteolysis, ER stress, oxidative stress, inflammation, and fibrosis), and liver histology (H/E, Red Oil with quantification). Changes in liver weight, cholesterol, triglycerides, fatty acids, and enzymes will be assessed.

CLAIMS

1. A compound of Formulae (Ia) or (Ib):



(Ia)



(Ib)

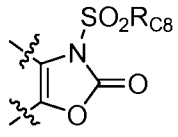
or a pharmaceutically acceptable salt thereof, wherein:

A is either:

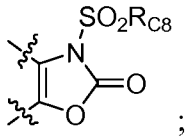
i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -OBn, -CO_2H, -CO_2-Alkyl, -N**R10R11**, and -CON**R10R11**; or

ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -$(CH_2)_mCF_3$, =O, -CH_2OCH_3, -CH_2OH, -OBn, -CO_2H, -CO_2-Alkyl, -N**R10R11**, and -CON**R10R11**;

Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO_2H, -CON**R10R11**, or -$NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety  ;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -$(C\mathbf{R_{9a}R_{9b}})_mN$**R10R11**, -$CO_2$-Alkyl, -$(C\mathbf{R_{9a}R_{9b}})_m$O-Alkyl, -$(C\mathbf{R_{9a}R_{9b}})_m OPO_3Na_2$, -$(C\mathbf{R_{9a}R_{9b}})_m O(C\mathbf{R_{9a}R_{9b}})_n$O-Alkyl, -$(C\mathbf{R_{9a}R_{9b}})_m$O(C=O)-Alkyl, -

$(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$-Alkyl, $-(C=O)CH=CH_2$, $-SO_2R_{C8'}$; or is taken with one of R_{C4}, R_{C5} or R_{C6} to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$R_{C8'}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

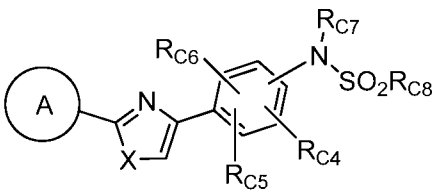
Each R_{9a} and R_{9b}, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, $-SO_2R_{C8'}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

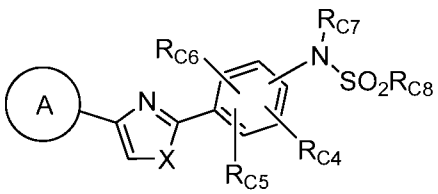
X is a heteroatom selected from S, O; or NR_B wherein R_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

2. The compound of claim 1, wherein compound is of formulae (IIa) or (IIb):



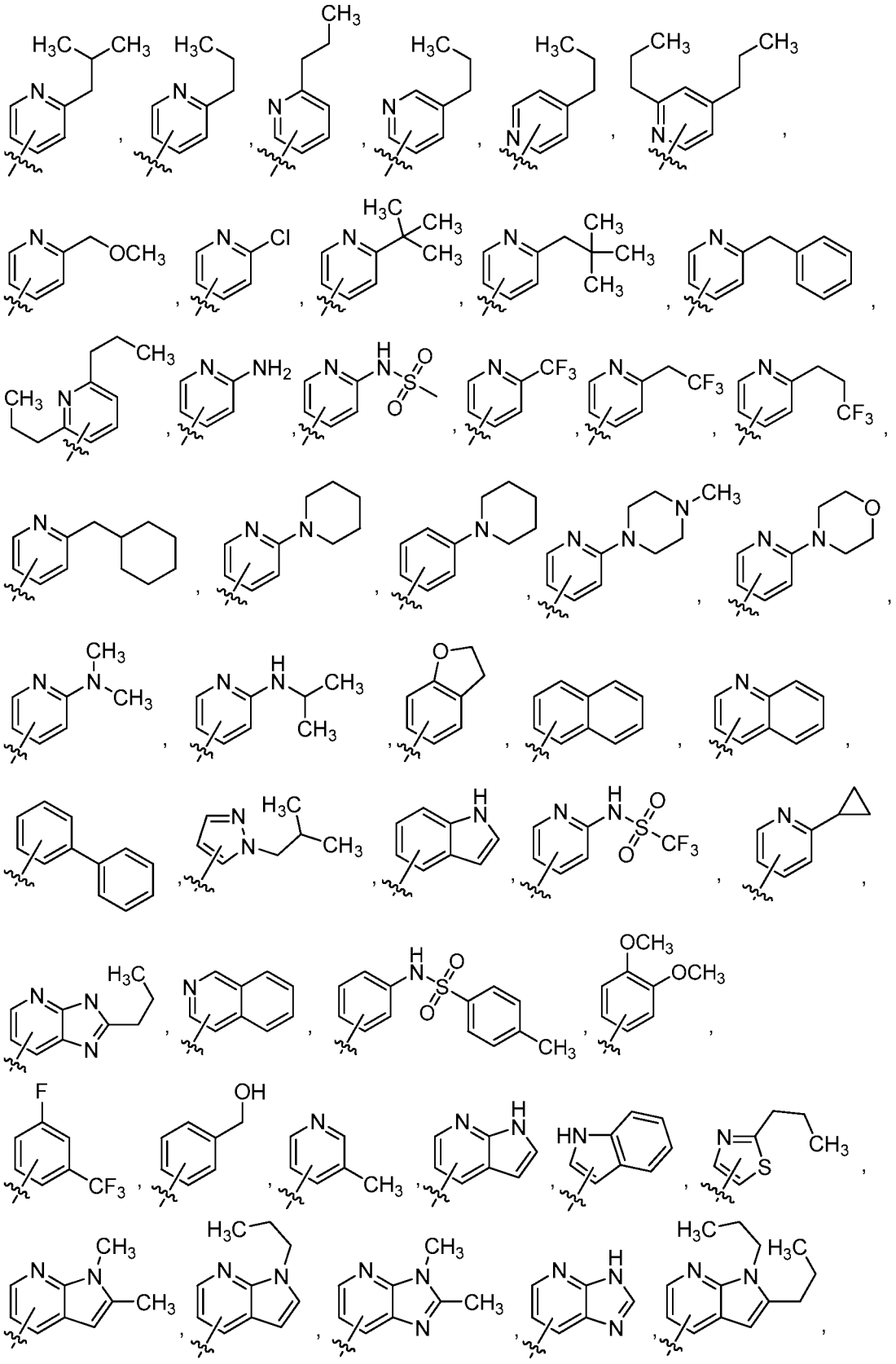
(IIa)

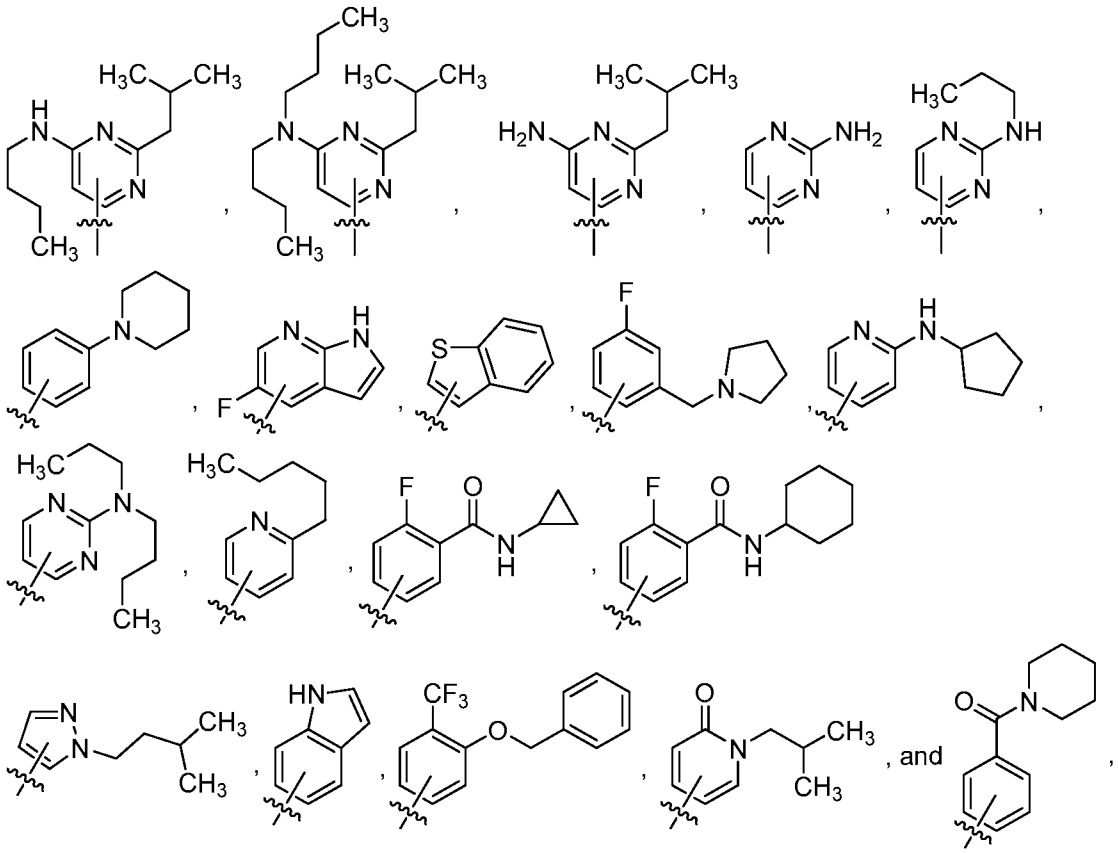


(IIb)

or a pharmaceutically acceptable salt thereof, wherein:

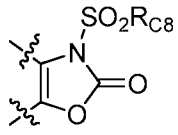
A is a moiety selected from the group consisting of:

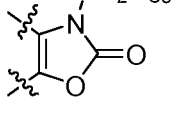




wherein the ring containing X is linked to ring A at any available position on ring A;

Each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-CO_2H$, -CON**R10R11**, or $-NHCONH_2$;

or is taken with $\mathbf{R_{C7}}$ to form the moiety  ;

$\mathbf{R_{C7}}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, $-(CR_{9a}R_{9b})_mNR10R11$, $-CO_2$-Alkyl, $-(CR_{9a}R_{9b})_mO$-Alkyl, $-(CR_{9a}R_{9b})_mOPO_3Na_2$, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$-Alkyl, $-(CR_{9a}R_{9b})_mO(C=O)$-Alkyl, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$-Alkyl, $-(C=O)CH=CH_2$, $-SO_2R_{C8}$; or is taken with one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ or $\mathbf{R_{C6}}$ to form the moiety  ;

$\mathbf{R_{C8}}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least

one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\mathbf{R_{C8'}}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

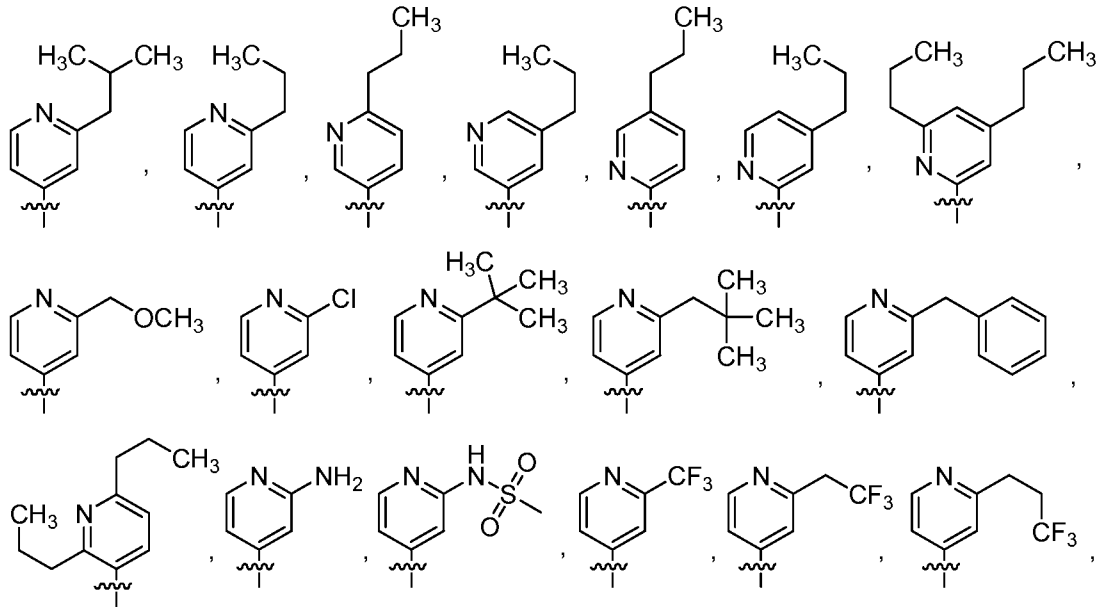
Each $\mathbf{R_{9a}}$ and $\mathbf{R_{9b}}$, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

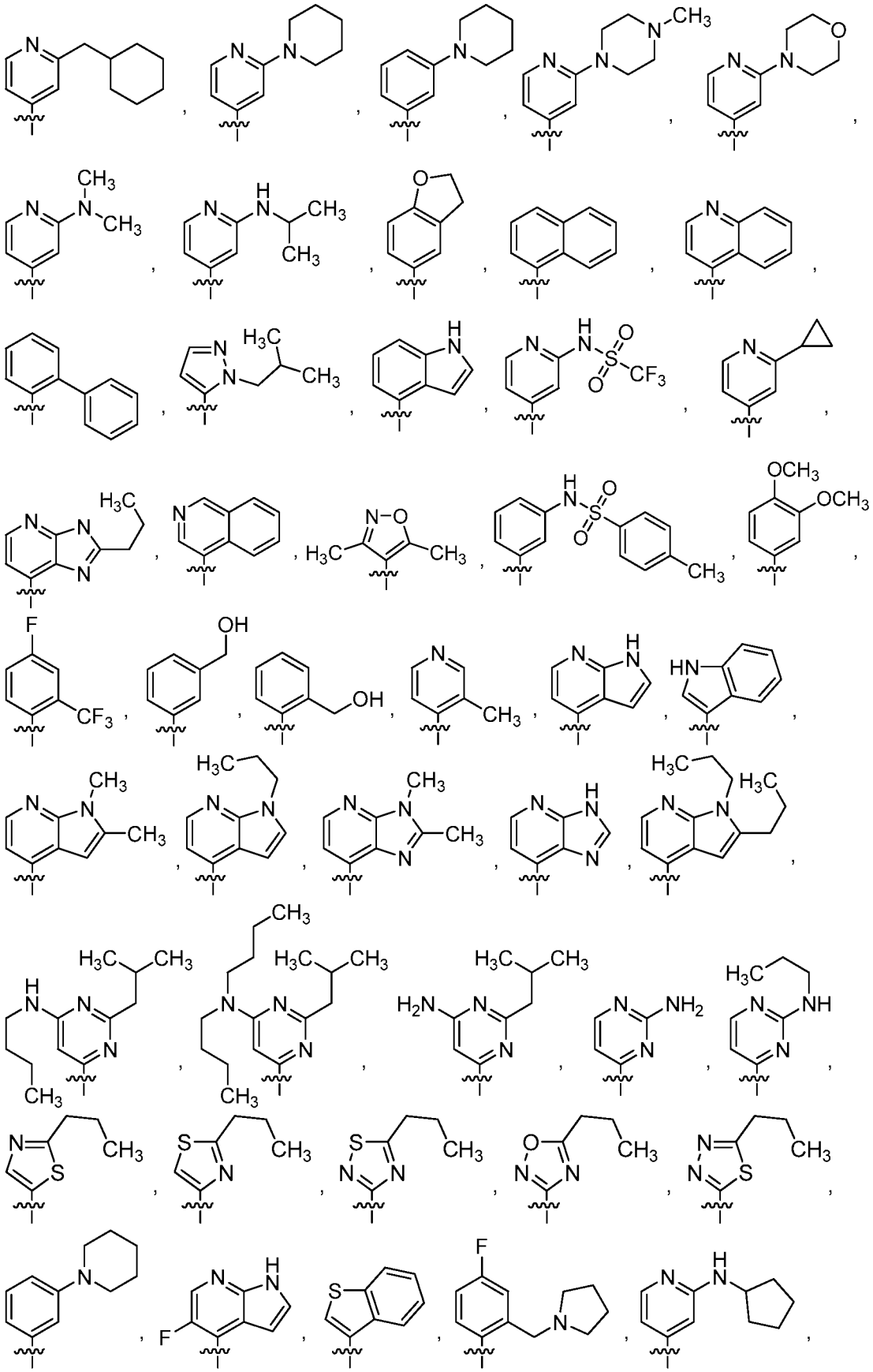
R10 and **R11** are independently hydrogen, $-SO_2\mathbf{R_{C8'}}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

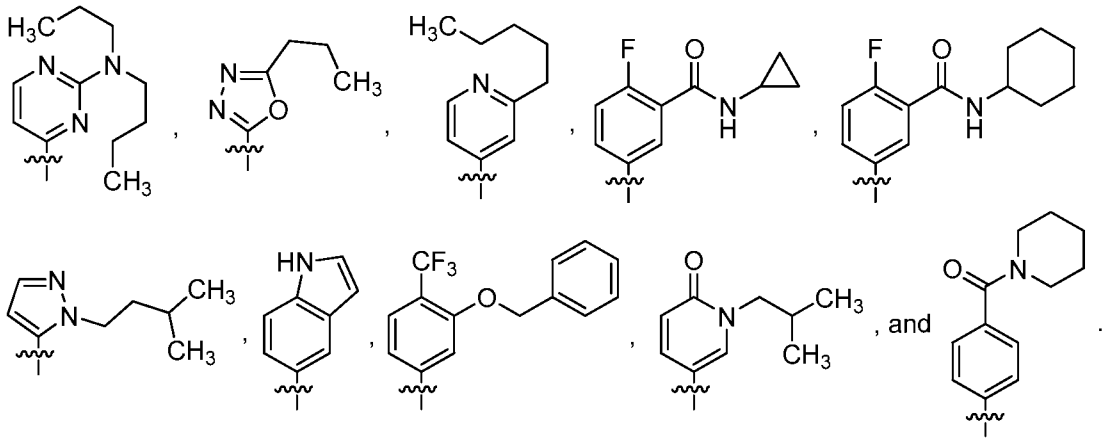
X is a heteroatom selected from S, O; or $N\mathbf{R_B}$ wherein $\mathbf{R_B}$ is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each ***m*** and ***n*** is 1, 2 or 3.

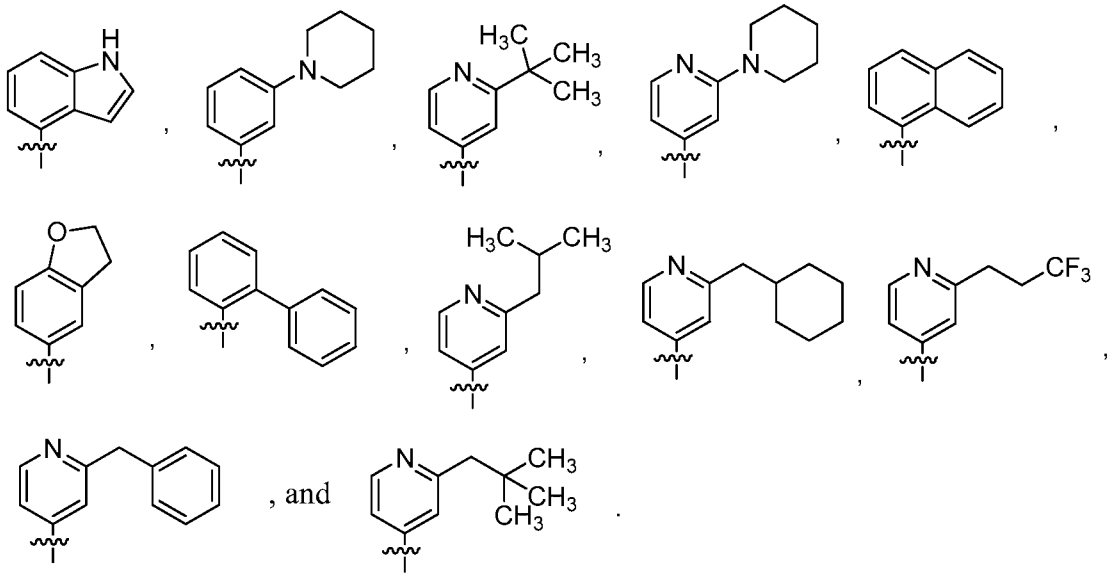
3. The compound of claim 2, wherein A is a moiety selected from the group consisting of:



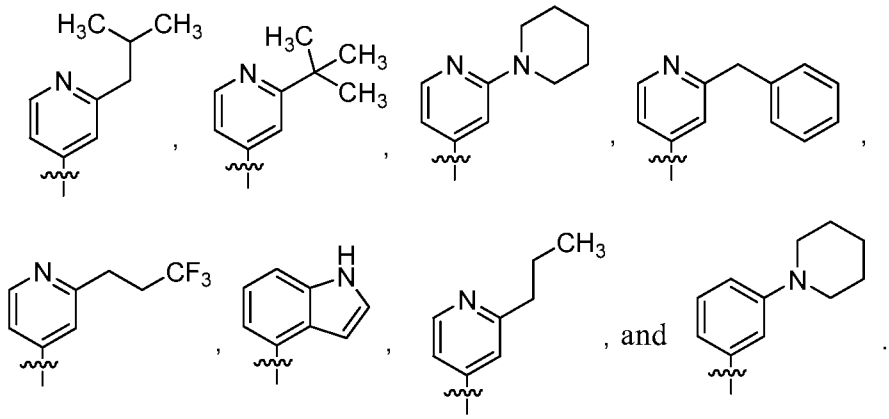




4. The compound of claim 3, wherein A is a moiety selected from the group consisting of:



5. The compound of claim 4, wherein A is a moiety selected from the group consisting of:



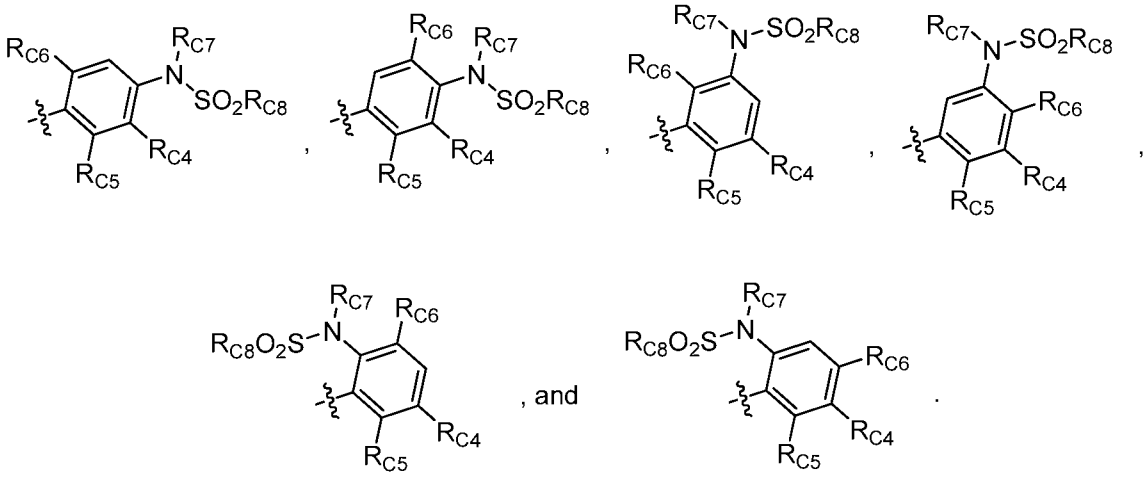
6. The compound of any of claims 1-4, wherein X is S.

7. The compound of any of claims 1-4, wherein X is NR_B, wherein R_B is a linear or branched C1-C6 alkyl.

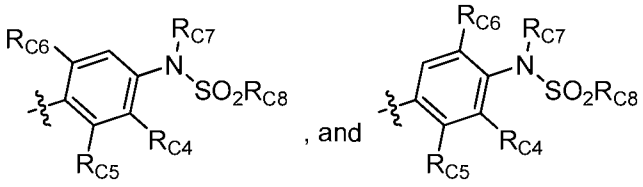
8. The compound of claim 7, wherein R_B is a linear C1-C6 alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl.

9. The compound of claim 7, wherein R_B is a branched C1-C6 alkyl selected from iso-propyl, iso-pentyl, and tert-butyl.

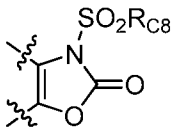
10. The compound of any of claims 1-9, wherein the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from:



11. The compound of claim 10, wherein the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from:



12. The compound of any of claims 1-11, wherein each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$, is independently hydrogen, halogen, CN, CF_3, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO_2H, -CON**R10R11**, or -$NHCONH_2$; or is taken with $\mathbf{R_{C7}}$ to form the moiety



13. The compound of any of claims 1-12, wherein at least one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is hydrogen.

14. The compound of claim 13, wherein two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are hydrogen.

15. The compound of claim 13, wherein each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is hydrogen.

16. The compound of any of claims 1-12, wherein at least one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is halogen.

17. The compound of claim 16, wherein two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are halogen.

18. The compound of claim 16, wherein each $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is halogen.

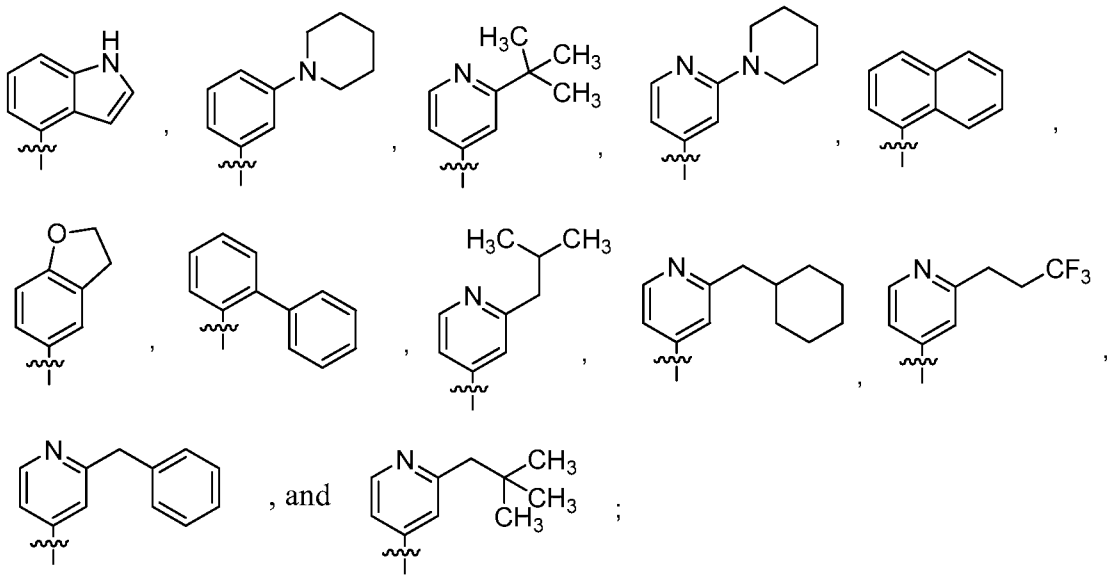
19. The compound of any of claims 1-12, wherein one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is hydrogen, and the remaining two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are halogen.

20. The compound of any of claims 1-12, wherein two of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are hydrogen, and the remaining one of $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ is halogen.

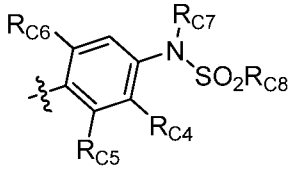
21. The compound of any of claims 1-12, wherein $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$ and $\mathbf{R_{C6}}$ are each halogen.

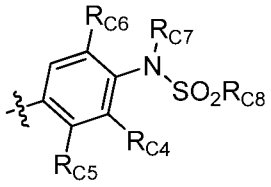
22. The compound of any of claims 1 or 6-21, wherein:

A is a moiety selected from



X is S, and

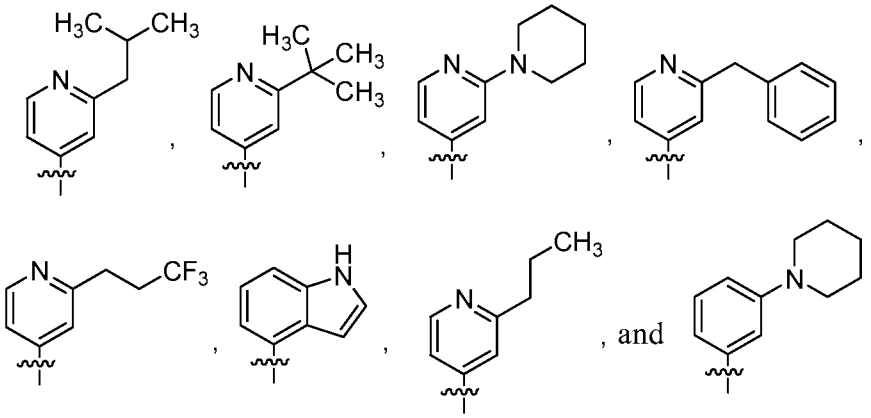
the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $\mathbf{-NR_{C7}SO_2R_{C8}}$, is a moiety selected from: 

, and 

.

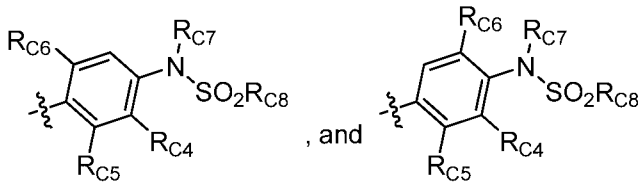
23. The compound of any of claims 1 or 6-21, wherein:

A is a moiety selected from

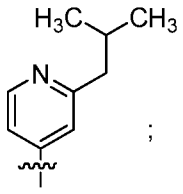


X is S, and

the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$ and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is a moiety selected from

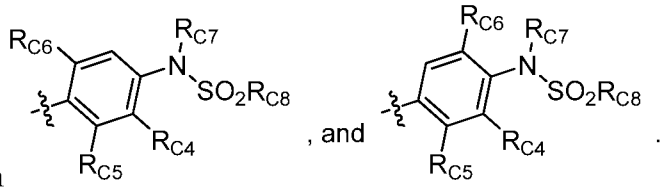


24. The compound of any of claims 1-23, wherein:

A is  ;

X is S, and

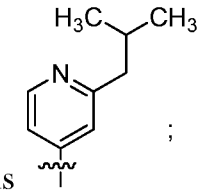
the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is selected from



25. The compound of any of claims 1-24, wherein the compound is of Formula (IIa).

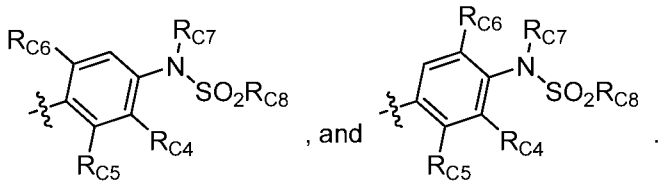
26. The compound of any of claims 1-24, wherein the compound is of Formula (IIb).

27. The compound of any of claims 1-25, wherein the compound is of Formula (IIa), wherein:

A is  ;

X is S;

the phenyl ring containing the groups $\mathbf{R_{C4}}$, $\mathbf{R_{C5}}$, $\mathbf{R_{C6}}$, and $-\mathbf{NR_{C7}SO_2R_{C8}}$, is selected from



28. A compound selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1-propyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(3-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dipropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(6-(butylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(6-(dibutylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(6-amino-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-aminopyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(propylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dibutylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2'-propyl-2,4'-bithiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,2,4-thiadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,2,4-oxadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2'-propyl-2,5'-bithiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,3,4-thiadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,3,4-oxadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-6-oxo-1,6-dihydropyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-fluoro-3-isobutylphenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3,5-dichloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-(trifluoromethyl)phenyl)methanesulfonamide;

N-(2-cyclopropyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methylphenyl)methanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-isopropylphenyl)methanesulfonamide;

N-(2-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-6-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-6-methylphenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)-1-methyl-1H-imidazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-5-chloro-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)oxazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)oxazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dimethylamino)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(trifluoromethylsulfonyl)acrylamide;

N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(3,3,3-trifluoropropyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-hydroxyphenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethyl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

6-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethylsulfonyl)benzo[d]oxazol-2(3H)-one;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,2,2,2-pentafluoroethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;

1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide;

N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-chloropyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxopyrrolidin-1-yl)ethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxoimidazolidin-1-yl)ethyl)methanesulfonamide;

N-(2-bromo-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethyl acetate;

(2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethoxy)methyl acetate;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-(2-{[4-(3-chlorophenyl)-2-oxo-1,3,2λ^5-dioxaphosphinan-2-yl]oxy}ethyl)-1,1,1-trifluoromethanesulfonamide;

(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl acetate;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(methoxymethyl)methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-({[4-(3-chlorophenyl)-2-oxo-1,3,2λ^5-dioxaphosphinan-2-yl]oxy}methyl)-1,1,1-trifluoromethanesulfonamide;

methyl 4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl(trifluoromethylsulfonyl)carbamate;

sodium (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl phosphate;

1-(N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethylsulfonamido)ethyl isobutyrate;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(diethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(dimethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(3-fluoro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-methylmethanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(2-bromo-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-methyl-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2-butylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide

1,1,1-trifluoro-N-(4-(2-(2-(methoxymethyl)pyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(4,6-dipropylpyridin-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(4-propylpyridin-2-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2,6-dipropylpyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-(cyclohexylmethyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-methoxyphenyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-((trifluoromethylsulfonyl)methyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclopropyl-2-fluorobenzamide;

5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclohexyl-2-fluorobenzamide;

N-(4-(2-(1H-indol-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-5-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide; and

N-(2-bromo-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

29. The compound of claim 28, wherein the compound is selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;

1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide;

N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide; and

N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

30. The compound of claim 29, wherein the compound is selected from the group consisting of:

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide; and

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide.

31. A compound N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

32. A pharmaceutical composition comprising a compound of any of claims 1-31 and a pharmaceutically acceptable vehicle.

33. A method of treating a metabolic disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of any of claims 1-31.

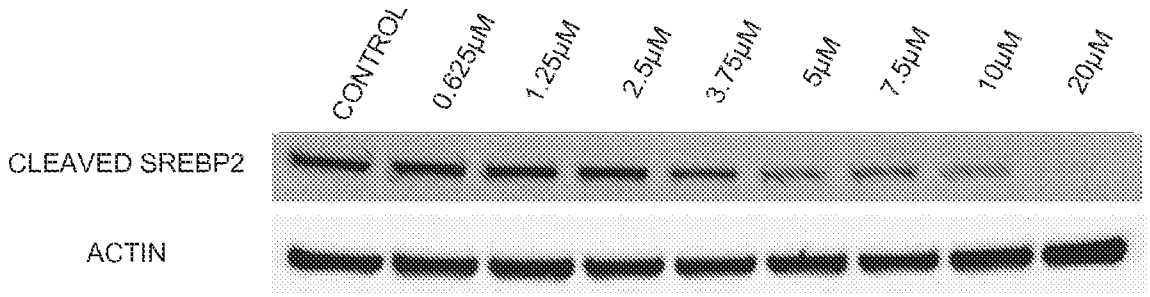
34. A method of treating a hyperproliferative disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of any of claims 1-31.

35. The method of claim 34, wherein the hyperproliferative disorder is cancer.

36. The method of claim 35, wherein the cancer is breast cancer, prostate cancer, or ovarian cancer.

37. Use of a compound of any of claims 1-31 in the manufacture of a medicament for treating a metabolic disorder or a hyperproliferative disorder.

38. Use of a compound of any of claims 1-31 to treat a metabolic disorder or a hyperproliferative disorder.


CONTROL
0.625μM
1.25μM
2.5μM
3.75μM
5μM
7.5μM
10μM
20μM
CLEAVED SREBP2
ACTIN

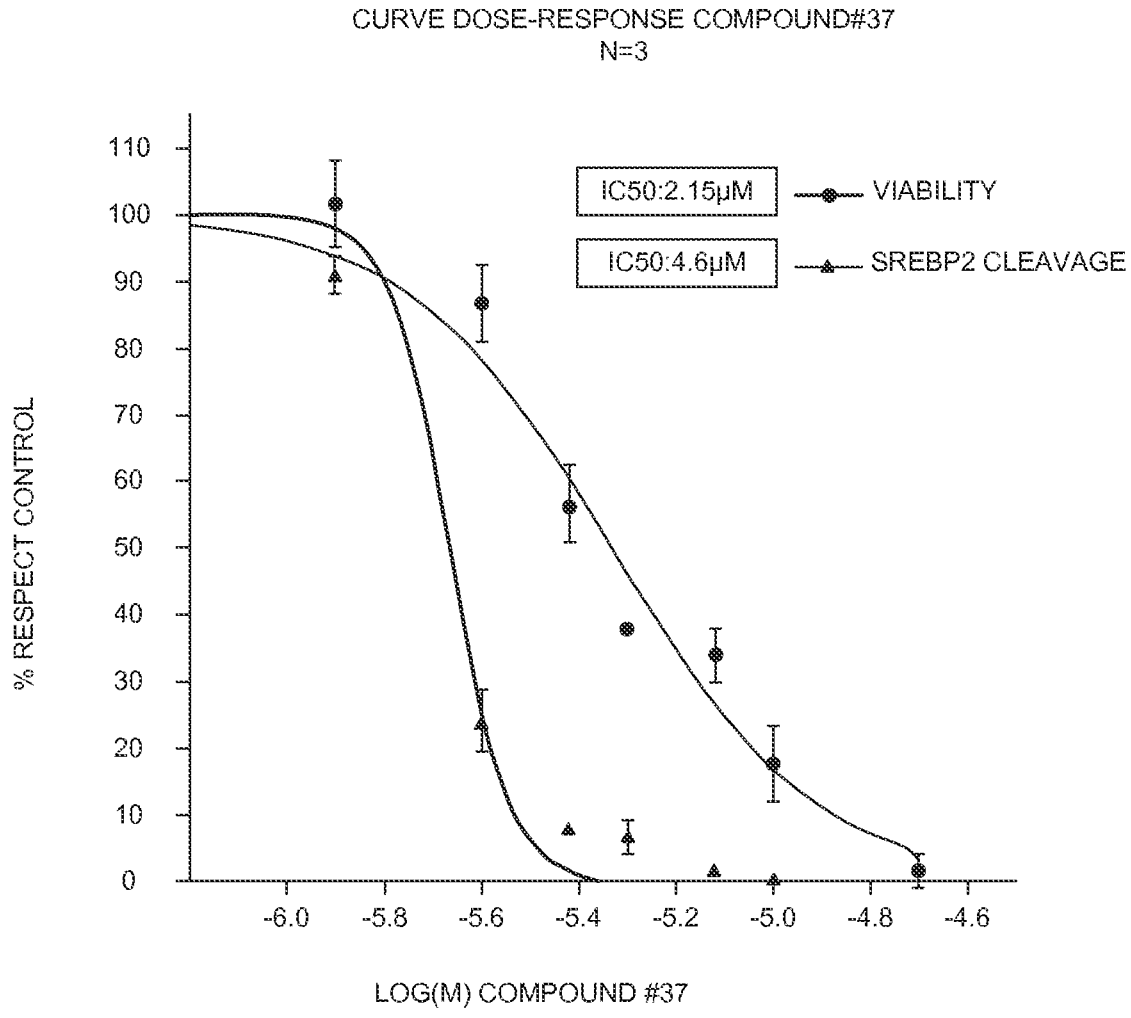

CURVE DOSE-RESPONSE COMPOUND#37
N=3
IC50:2.15μM
VIABILITY
IC50:4.6μM
SREBP2 CLEAVAGE
% RESPECT CONTROL
110
100
90
80
70
60
50
40
30
20
10
0
-6.0
-5.8
-5.6
-5.4
-5.2
-5.0
-4.8
-4.6
LOG(M) COMPOUND #37

FIG. 1

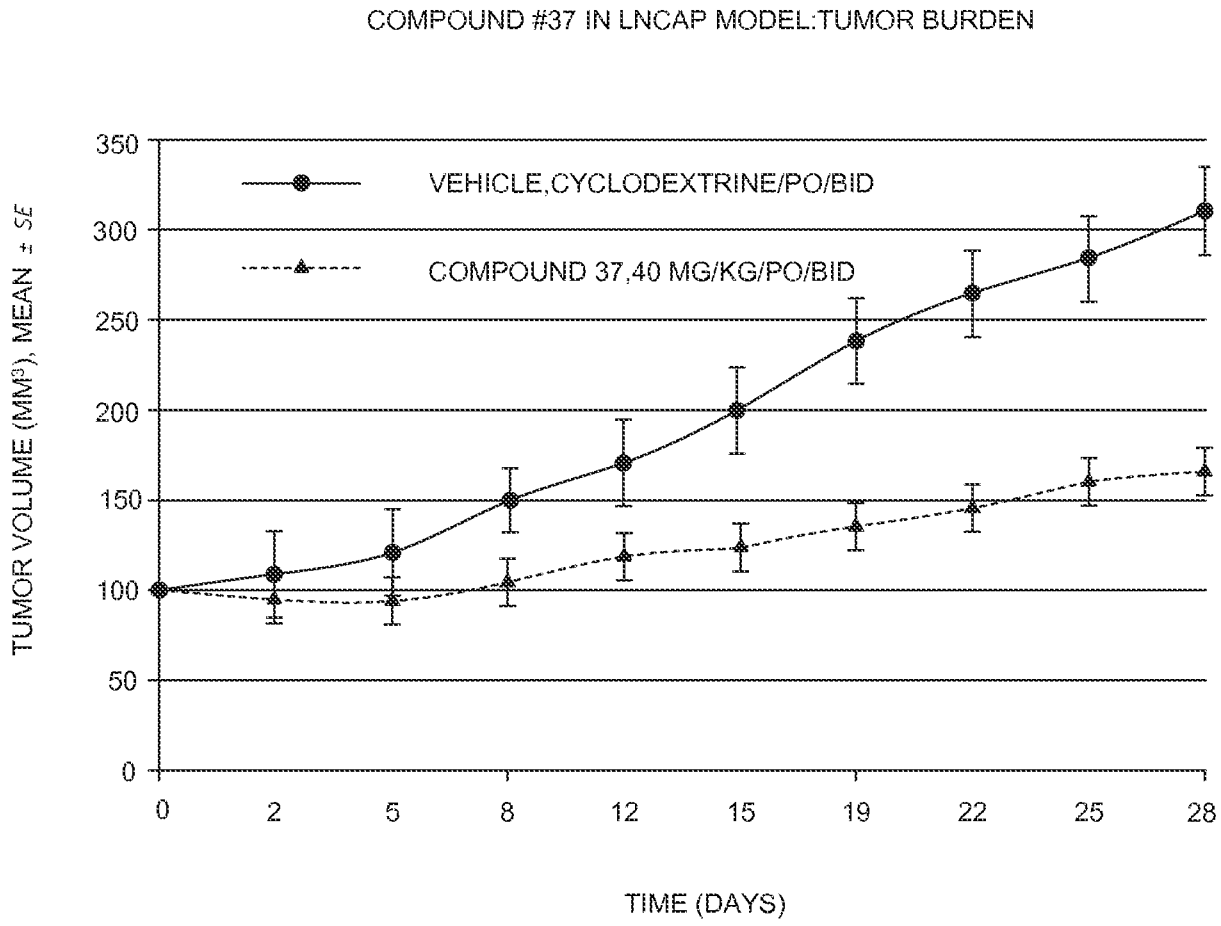

COMPOUND #37 IN LNCAP MODEL:TUMOR BURDEN
VEHICLE,CYCLODEXTRINE/PO/BID
COMPOUND 37,40 MG/KG/PO/BID
TUMOR VOLUME (MM3), MEAN ± SE
350
300
250
200
150
100
50
0
0
2
5
8
12
15
19
22
25
28
TIME (DAYS)

FIG. 2

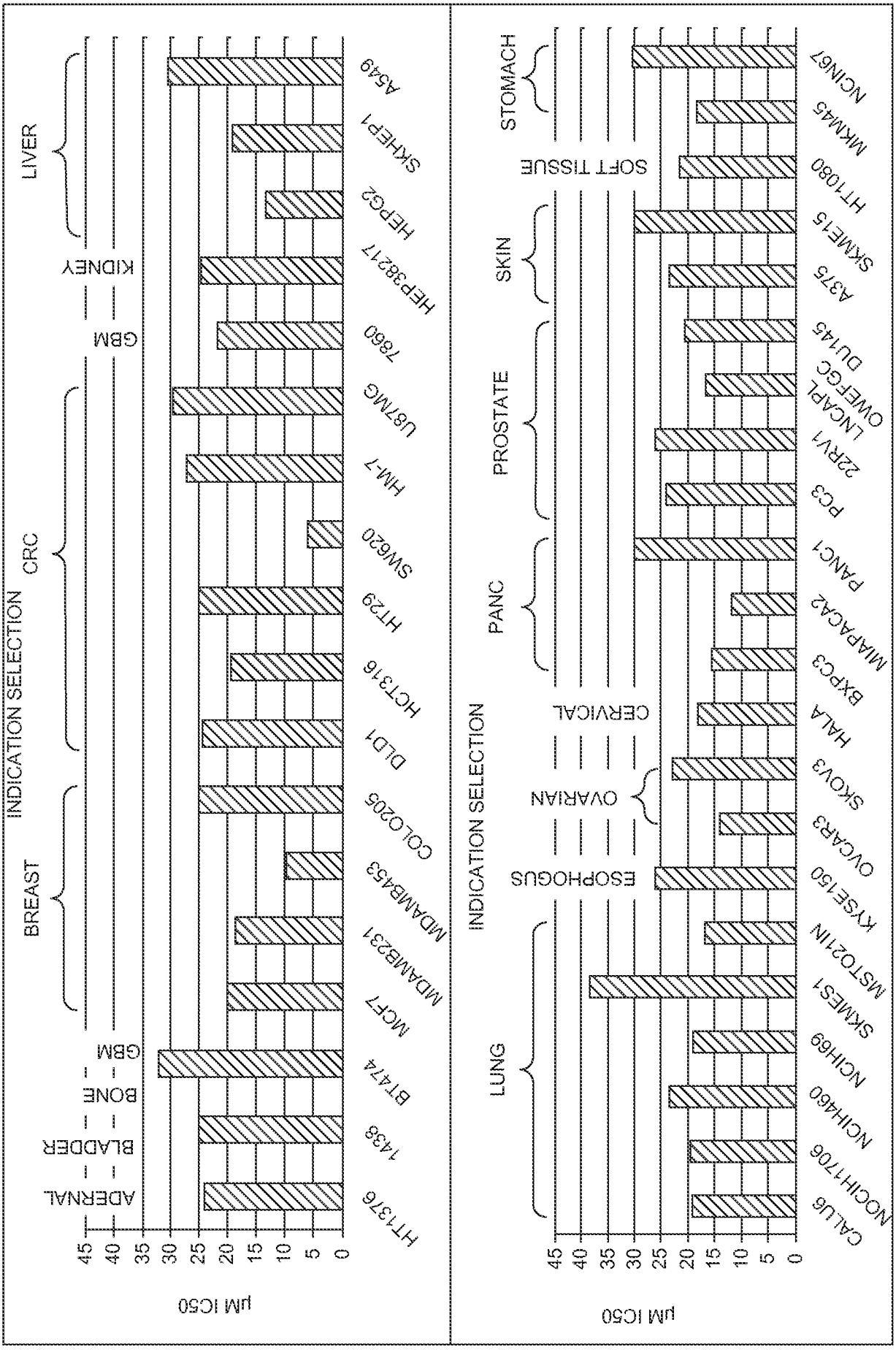

INDICATION SELECTION
BREAST
CRC
GBM
KIDNEY
LIVER
ADERNAL
BLADDER
BONE
GBM
HT1376
1438
BT474
MCF7
MDAMB231
MDAMB453
COLO205
DLD1
HCT116
HT29
SW620
HM-7
U87MG
7860
HEP3B217
HEPG2
SKHEP1
A549
µM IC50
INDICATION SELECTION
LUNG
PANC
OVARIAN
CERVICAL
ESOPHOGUS
SKIN
PROSTATE
SOFT TISSUE
STOMACH
CALU6
NCIH1706
NCIH460
NCIH69
SKMES1
MSTO211N
KYSE150
OVCAR3
SKOV3
HALA
BXPC3
MIAPACA2
PANC1
PC3
22RV1
LNCAPCLONEFGC
DU145
A375
SKMEL5
HT1080
MKN45
NCIN87
µM IC50

FIG. 3

COMPOUND #37
MOUSE PK

PO(10MG/KG)	
PK PARAMETERS	MEAN
C_{MAX} (μM)	32.4
T_{MAX} (h)	1
AUC_{FAST} (μM*h)	294
TERMINAL $t_{1/2}$ (h)	4.23
BIOAVAILABILITY(%)	151%

FIG. 4A

COMPOUND #37
DOG ORAL PK

PO DOSE LEVEL (MG/KG)	2(N=3)		10(N=1)	
PK PARAMETERS	MEAN	SD	DOG2002	SD
C_{MAX} (μm)	27.0	1.21	182	-
T_{MAX} (h)	1.5	0	1.5	-
AUC_{FAST} (μM*h)	449	17.3	4200	-
TERMINAL $t_{1/2}$ (h)	10.7	2.05	11.3	-
BIOAVAILABILITY	99.3%	20.1%	62.9%	-

FIG. 4B

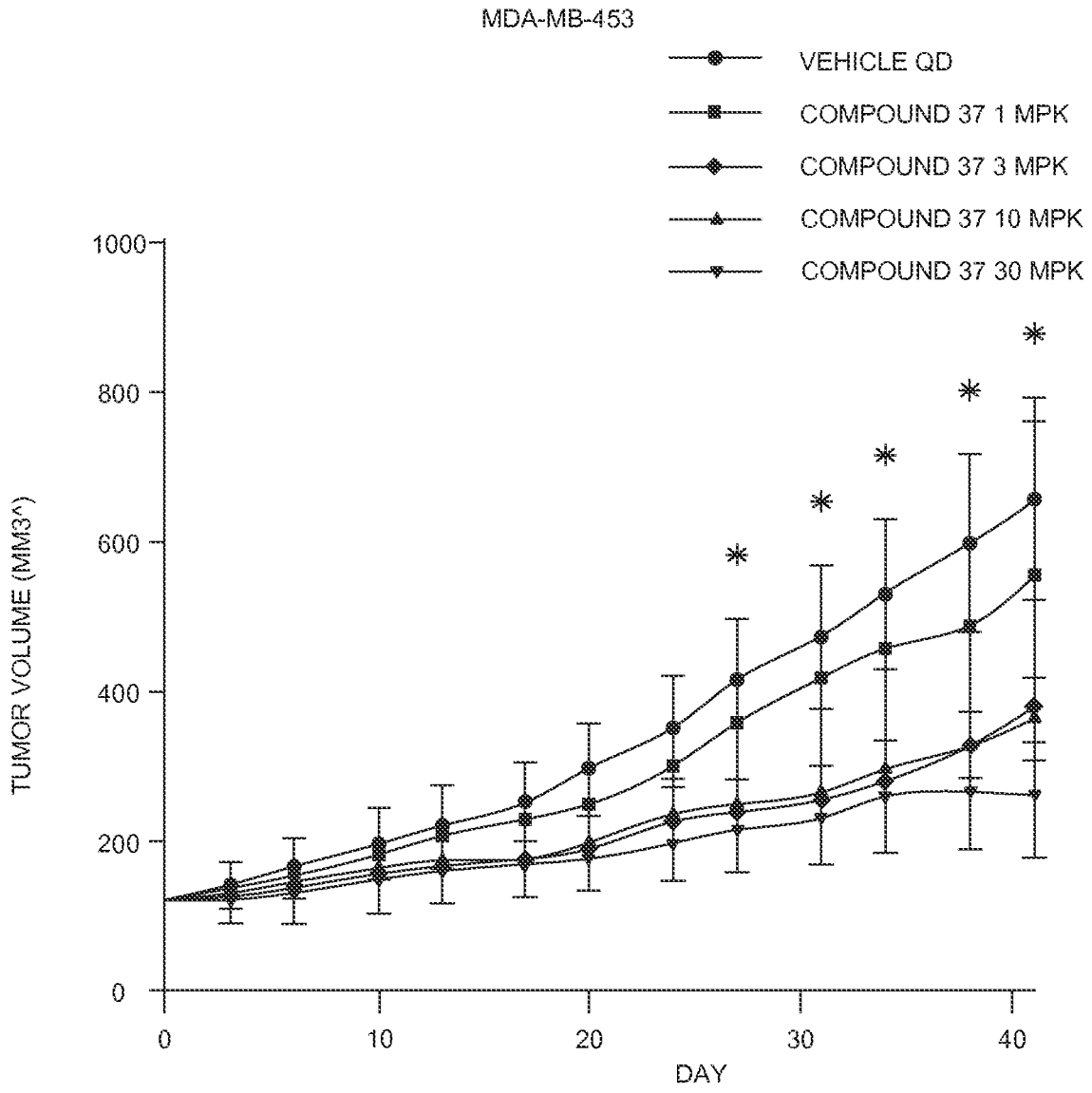

MDA-MB-453
VEHICLE QD
COMPOUND 37 1 MPK
COMPOUND 37 3 MPK
COMPOUND 37 10 MPK
COMPOUND 37 30 MPK
TUMOR VOLUME (MM3^)
1000
800
600
400
200
0
0
10
20
30
40
DAY

FIG. 5

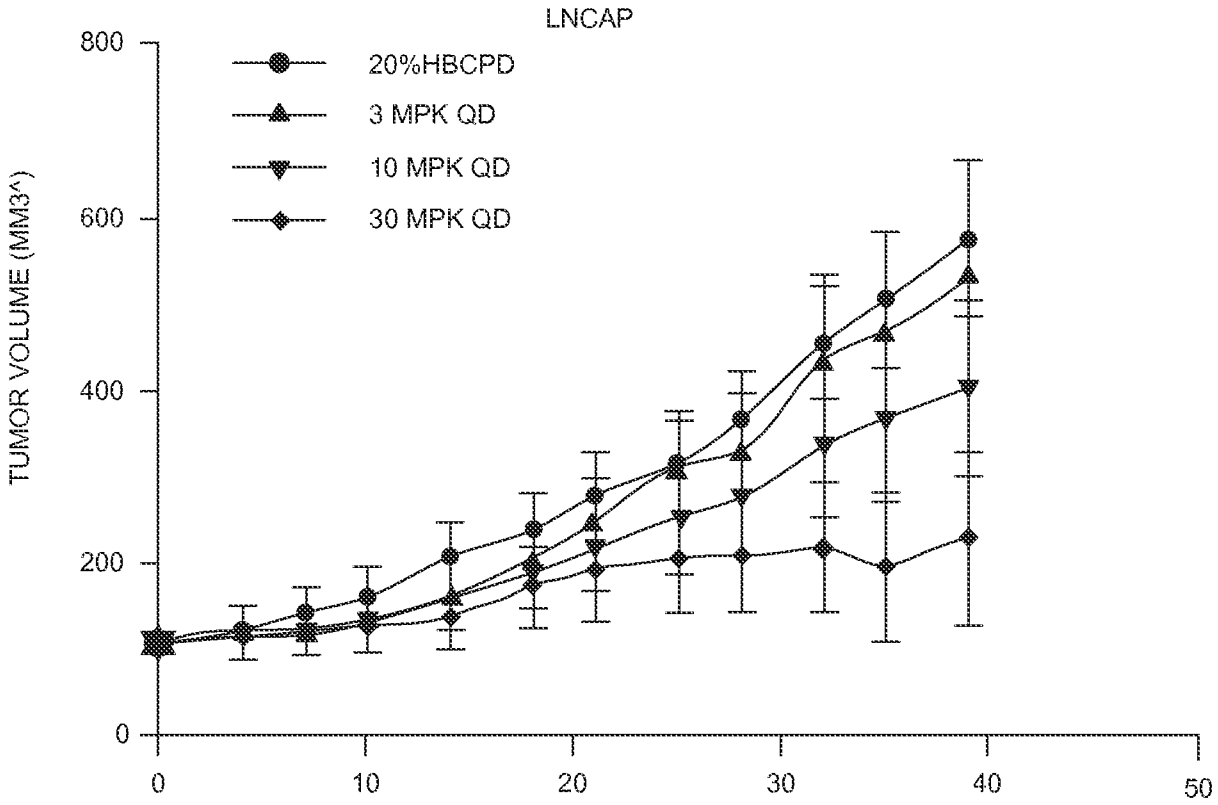

LNCAP
20%HBCPD
3 MPK QD
10 MPK QD
30 MPK QD
TUMOR VOLUME (MM3^)
800
600
400
200
0
0
10
20
30
40
50

FIG. 6A

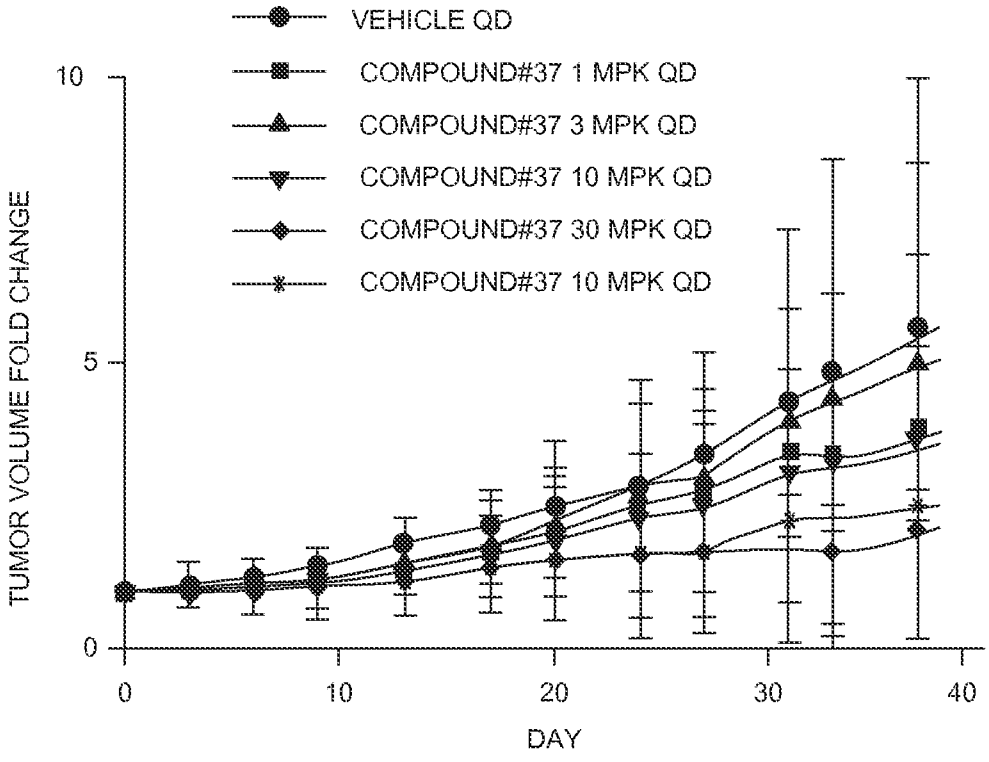

VEHICLE QD
COMPOUND#37 1 MPK QD
COMPOUND#37 3 MPK QD
COMPOUND#37 10 MPK QD
COMPOUND#37 30 MPK QD
COMPOUND#37 10 MPK QD
TUMOR VOLUME FOLD CHANGE
10
5
0
0
10
20
30
40
DAY

FIG. 6B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/053215

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/425 (2015.01)
CPC - A61K 31/425 (2014.11)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/425, 31/427, 31/4439, 31/454 (2015.01)
CPC - A61K 31/425; C07D 401/04, 413/04, 417/04 (2014.11) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/341, 365, 426, 438, 447 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, STN, Google Patents, Google Scholar, PubChem
Search terms used: thiazol-4-yl phenyl-1,1,1-trifluoromethane sulfonamide sulfonamide trifluoro perfluro

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/085269 A1 (SELEXAGEN THERAPEUTICS INC) 14 July 2011 (14.07.2011) entire document	1-6, 28-31
A	US 2001/0031781 A1 (ILLIG et al) 18 October 2001 (18.10.2001) entire document	1-6, 28-31
A	US 6,444,687 B1 (STAMFORD et al) 03 September 2002 (03.09.2002) entire document	1-6, 28-31
A	WO 99/40088 A1 (3-DIMENSIONAL PHARMACEUTICALS INC) 12 August 1999 (12.08.1999) entire document	1-6, 28-31

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 January 2015	29 JAN 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/053215

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 10-27, 32-38
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Claims 1 and 6 have been analyzed subject to the restriction that the claims read on the formula (Ia) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a compound of formula (Ia): a pharmaceutically acceptable salt thereof, wherein: A is an aryl, having only one ring, substituted with 1 substituent selected from halogen; RC4, RC5, and RC6, is independently hydrogen; RC7 is hydrogen; RC8 is a linear C1-C6 perhaloalkyl; X is a heteroatom selected from S.

Claims 1-6 and 28-31 have been analyzed subject to the restriction that the claims read on the formula (Ia) as described in the Response to the Invitation to Pay Additional Fees in the International Application dated 09 December 2014. The claims are restricted to a compound of formula (Ia): A is heteroaryl, with one substitutent which is C1-C6 linear or branched alkyl; RC4 is H; RC5 is halogen; RC6 is H; RC7 is H; RC8 is linear or branched C1-C6 perhaloalkyl; and X is S.

<See Extra Sheet>

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-6, 28-31

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/053215

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: Claims 1-9 and 28-31 are drawn to a compound of Formulae (Ia) or (Ib): or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound of formula (Ia): a pharmaceutically acceptable salt thereof, wherein: A is an aryl, having only one ring, substituted with 1 substituent selected from halogen; RC4, RC5, and RC6, is independently hydrogen; RC7 is hydrogen; RC8 is a linear C1-C6 perhaloalkyl; X is a heteroatom selected from S. It is believed that claims 1 and 6 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound of formula (Ia): a pharmaceutically acceptable salt thereof, wherein: A is an heteroaryl, having only one ring, substituted with 1 substituent selected from halogen; RC4, RC5, and RC6, is independently hydrogen; RC7 is hydrogen; RC8 is a linear C1-C6 perhaloalkyl; X is a heteroatom selected from S. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the Formulae (Ia) and (Ib) and compound variables A, RC4, RC5, RC6, RC7, RC8, and X.

The Groups I+ share the technical features of a compound having the core structure of formula (Ia) or (Ib): or a pharmaceutically acceptable salt thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 6,444,687 B1 to Stamford et al. teach a compound having the core structure of formula (Ib), wherein A is aryl, having only one ring, substituted with 1 substituent consisting of CF3; each of RC4, RC5, and RC6 is independently hydrogen; RC7 is hydrogen; and X is NRB wherein RB is hydrogen (Col. 35, Lines 55-67; Example 5...see shown structure...).

Further, WO 2011/085269 A1 to Vernier et al. teach a compound having the core structure of formula (Ia) of the instant invention: or a pharmaceutically acceptable salt thereof, wherein A is aryl; Each of RC4, RC5, and RC6 is independently hydrogen; and RC7 is hydrogen (Para. [0045], Table 1, Example 2, N-(3-(2-phenyl-4-(pyridin-4-yl)-1H-imidazol-5-yl)phenyl)methanesulfonamide;...see shown structure...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

SPEHLMANN, Benjamin
BANNER & WITCOFF, LTD.
1100 13th Street NW
Suite 1200
Washington, District of Columbia 20005-4051
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
09 March 2016 (09.03.2016)

Applicant's or agent's file reference
006810.00170

IMPORTANT NOTIFICATION

International application No.
PCT/US2014/053215

International filing date *(day/month/year)*
28 August 2014 (28.08.2014)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
CHAKRAVARTY, Sarvajit
RAI, Roopa
PHAM, Son Minh
PUJALA, Brahmam
JANGIR, Ramniwas
GUGULOTH, Rambabu
SHARMA, Vijay Kumar

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
See Box 3.

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The persons identified in Box 1 are now inventors only.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Martin Jean-Luc
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Telephone No. +41 22 338 74 03

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

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SPEHLMANN, Benjamin
BANNER & WITCOFF, LTD.
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Suite 1200
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ÉTATS-UNIS D'AMÉRIQUE

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International filing date *(day/month/year)*
28 August 2014 (28.08.2014)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
MEDIVATION TECHNOLOGIES, INC. 525 Market Street, 36th Floor San Francisco, CA 94105 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 has been added as applicant for all designated States.

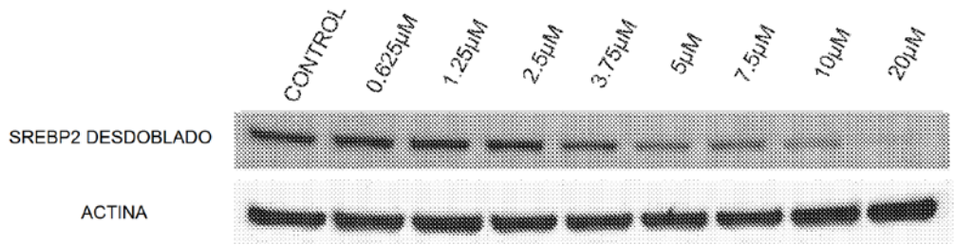
4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Martin Jean-Luc
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Telephone No. +41 22 338 74 03


CONTROL
0.625μM
1.25μM
2.5μM
3.75μM
5μM
7.5μM
10μM
20μM
SREBP2 DESDOBLADO
ACTINA

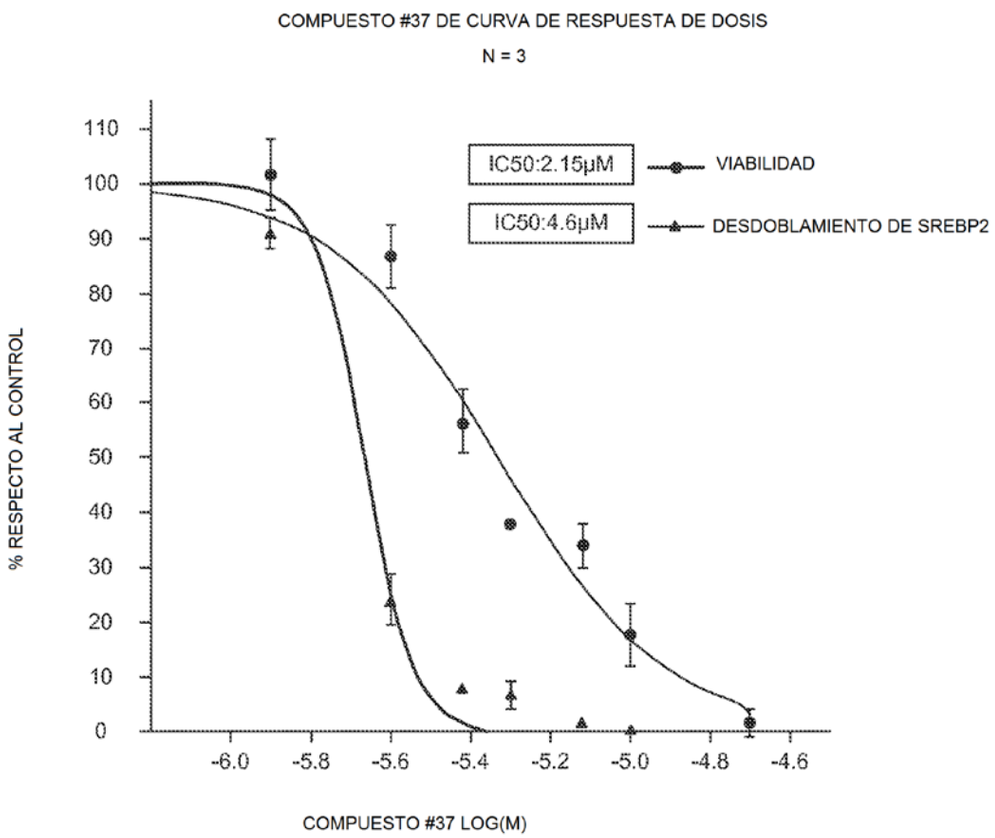

COMPUESTO #37 DE CURVA DE RESPUESTA DE DOSIS
N = 3
IC50:2.15μM
VIABILIDAD
IC50:4.6μM
DESDOBLAMIENTO DE SREBP2
% RESPECTO AL CONTROL
110
100
90
80
70
60
50
40
30
20
10
0
-6.0
-5.8
-5.6
-5.4
-5.2
-5.0
-4.8
-4.6
COMPUESTO #37 LOG(M)

FIG. 1

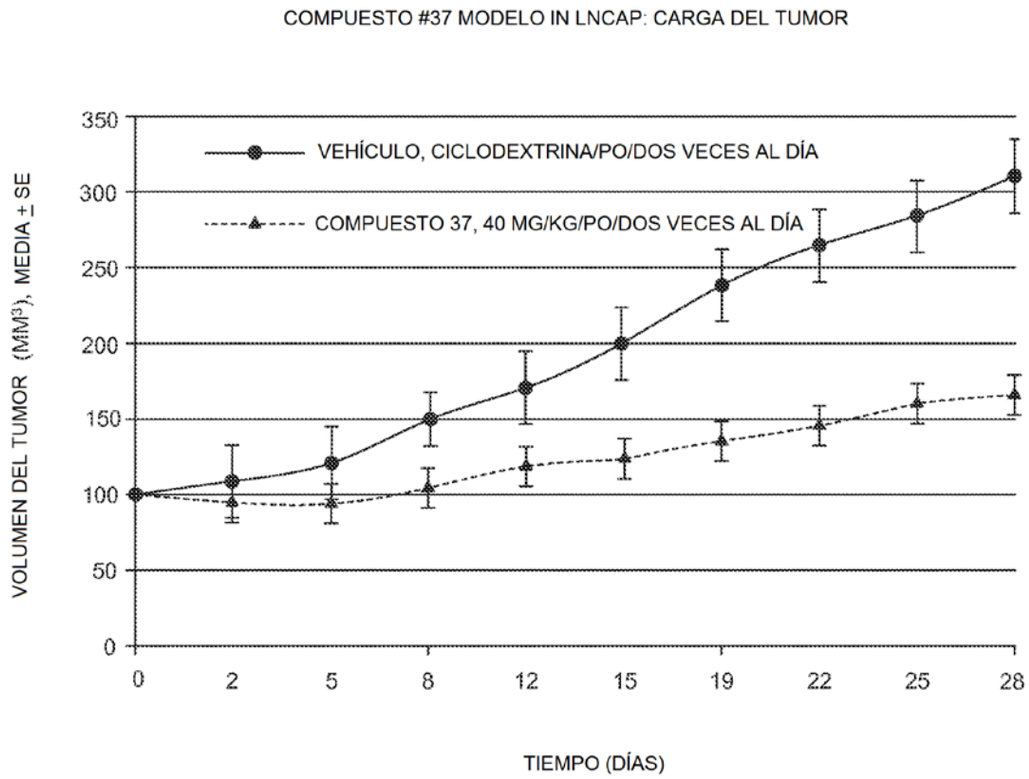

COMPUESTO #37 MODELO IN LNCAP: CARGA DEL TUMOR
VEHÍCULO, CICLODEXTRINA/PO/DOS VECES AL DÍA
COMPUESTO 37, 40 MG/KG/PO/DOS VECES AL DÍA
VOLUMEN DEL TUMOR (MM³), MEDIA ± SE
350
300
250
200
150
100
50
0
0
2
5
8
12
15
19
22
25
28
TIEMPO (DÍAS)

FIG. 2

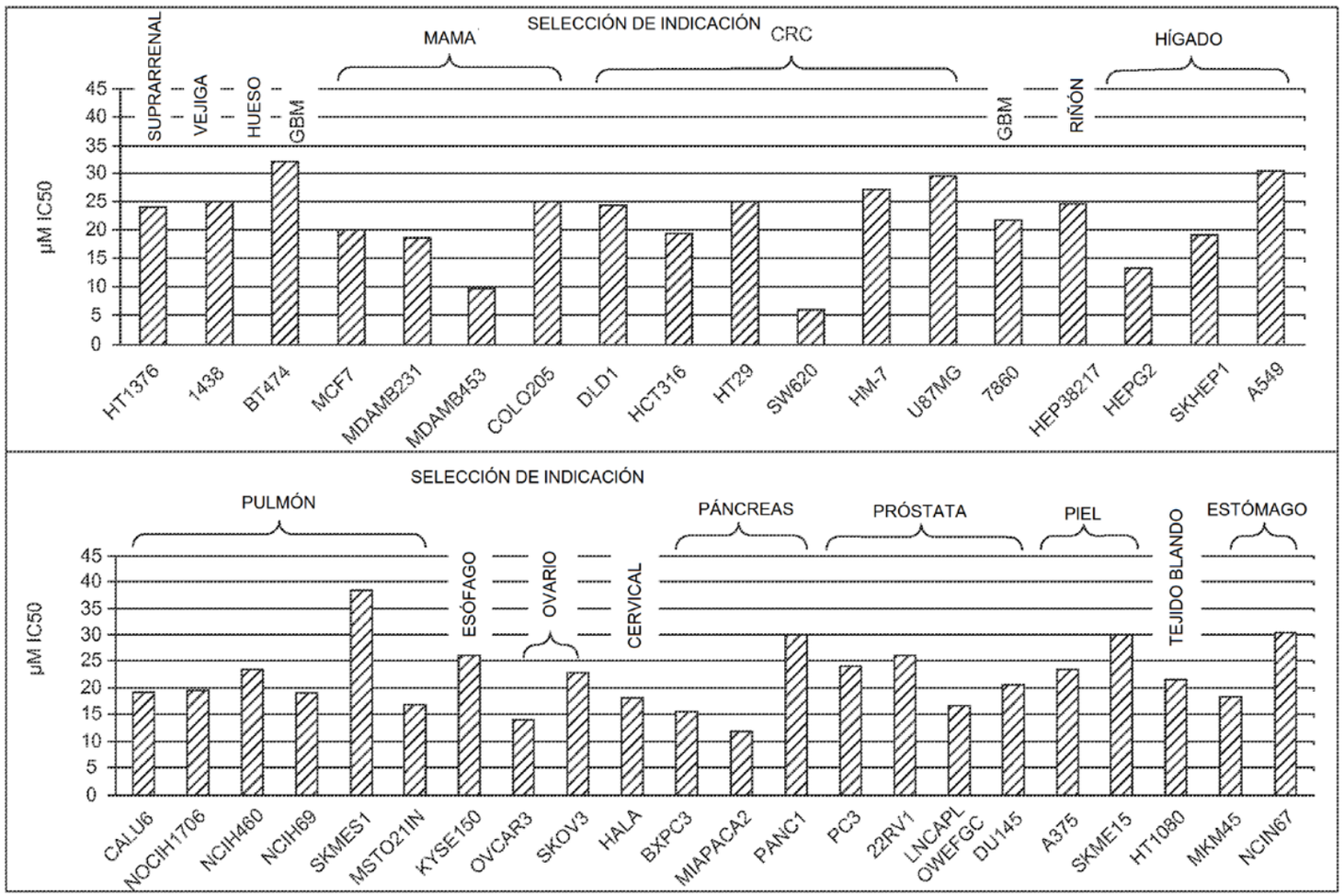

SELECCIÓN DE INDICACIÓN
SUPRARRENAL
VEJIGA
HUESO
GBM
MAMA
CRC
GBM
RIÑÓN
HÍGADO
µM IC50
45
40
35
30
25
20
15
10
5
0
HT1376
1438
BT474
MCF7
MDAMB231
MDAMB453
COLO205
DLD1
HCT316
HT29
SW620
HM-7
U87MG
7860
HEP38217
HEPG2
SKHEP1
A549
SELECCIÓN DE INDICACIÓN
PULMÓN
ESÓFAGO
OVARIO
CERVICAL
PÁNCREAS
PRÓSTATA
PIEL
TEJIDO BLANDO
ESTÓMAGO
µM IC50
CALU6
NOCIH1706
NCIH460
NCIH69
SKMES1
MSTO21IN
KYSE150
OVCAR3
SKOV3
HALA
BXPC3
MIAPACA2
PANC1
PC3
22RV1
LNCAPL
OWEFGC
DU145
A375
SKME15
HT1080
MKM45
NCIN67

FIG. 3

PK DE RATÓN
COMPUESTO #37

PO(10MG/KG)	
PARÁMETROS DE PK	MEDIA
$C_{MÁX}$ (μM)	32.4
$T_{MÁX}$ (h)	1
$AUC_{RÁPIDA}$ (μM*h)	294
TERMINAL $t_{1/2}$ (h)	4.23
BIODISPONIBILIDAD(%)	151%

FIG. 4A

COMPUESTO #37
PK ORAL EN PERRO

NIVEL DE DOSIS PO (MG/KG)	2(N=3)		10(N=1)	
PARÁMETROS DE PK	MEDIA	SD	DOG2002	SD
$C_{MÁX}$ (μm)	27.0	1.21	182	-
$T_{MÁX}$ (h)	1.5	0	1.5	-
$AUC_{RÁPIDA}$ (μM*h)	449	17.3	4200	-
TERMINAL $t_{1/2}$ (h)	10.7	2.05	11.3	-
BIODISPONIBILIDAD	99.3%	20.1%	62.9%	-

FIG. 4B

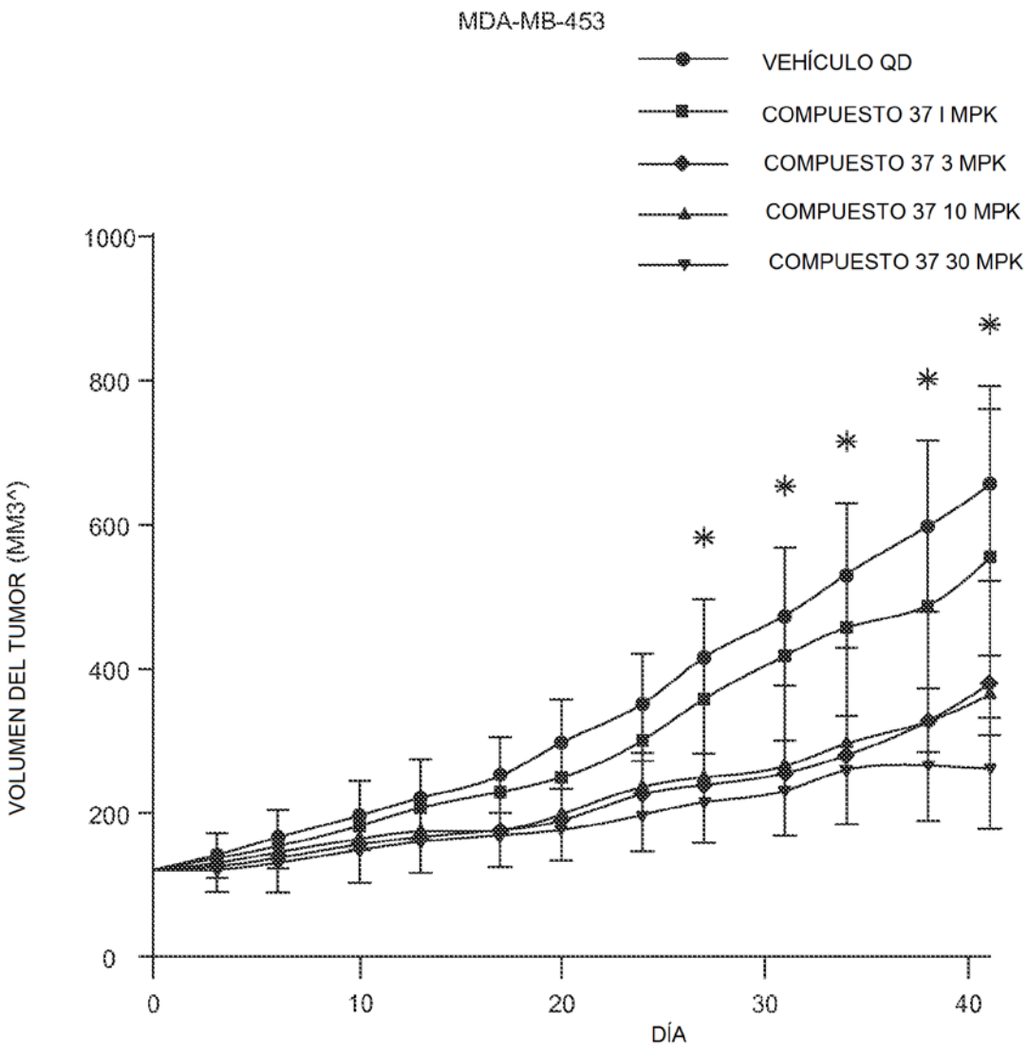

MDA-MB-453
VEHÍCULO QD
COMPUESTO 37 I MPK
COMPUESTO 37 3 MPK
COMPUESTO 37 10 MPK
COMPUESTO 37 30 MPK
VOLUMEN DEL TUMOR (MM3^)
1000
800
600
400
200
0
0
10
20
30
40
DÍA

FIG. 5

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos y métodos para usar estos compuestos para tratar trastornos metabólicos y trastornos hiperproliferativos, que incluye la administración de los compuestos en conjunto con antagonistas del receptor hormonal.