Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 09-30062

54. **TÍTULO** COMPUESTOS QUE MODULAN EL RECEPTOR CB2

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** BOEHRINGER INGELGEIM INTERNATIONAL GMBH

DOMICILIO INGELHEIM AM RHEIN, ALEMANIA

74. **APODERADO** EMILIO FERRERO

CC. 438.019 de Usaquén

22. **BOGOTÁ, D. C.,** 99/

(FORMA P-10)

Sin Pagotty
21-01-2011

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
sociedad constituida y existente bajo las leyes de Alemania.

Dirección: Binger Strasse 173,
55216 Ingelheim am Rhein,
Alemania

Domicilio: Ingelheim am Rhein,
Alemania

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

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Oxfordshire OX14 4RZ,
Reino Unido

13. Nigel BLUMIRE
111 Milton Park,
Abingdon,
Oxfordshire OX14 4RZ,
Reino Unido

(5) **PCT (86)**
Solicitud Internacional No. PCT/US2007/078341 Fecha: 13 de septiembre de 2007
Publicación Internacional No. WO 2008/039645 A1 Fecha: 3 de abril de 2008

(6) **Título (54)**

COMPUESTOS QUE MODULAN EL RECEPTOR CB2

(7) **Clasificación Internacional (51)** C07C 317/044

(8) **Prioridad** SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	25 de septiembre de 2006	60/826,819

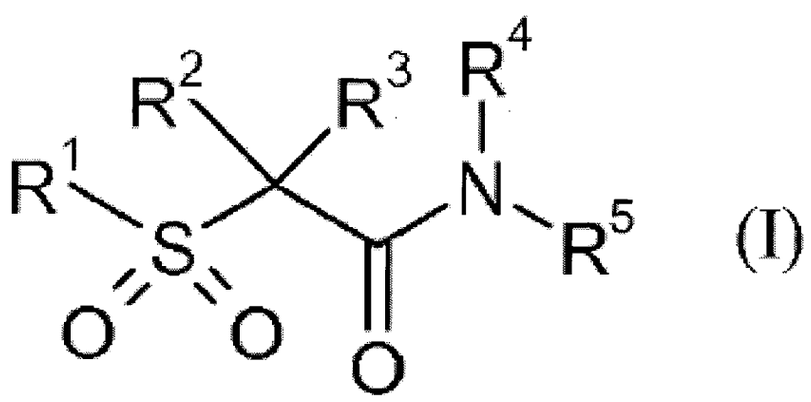
(9) **Comprobante de pago No.:** 09-18,933 y 09-18,934 **Fecha:** 9 de marzo de 2009

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 540.000.oo.
- ☐ Comprobante de pago por reivindicaciones adicionales después de la decimoquinta reivindicación por.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

JGG

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2008/039645 A1

   Descripción:

   Páginas 90 en el idioma original

   Páginas 116 en español

   Reivindicaciones: Número (s) 14

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

5

CONSULADO GENERAL DE COLOMBIA

MUNICH

Nr. 169

El Cónsul General de Colombia

C E R T I F I C A

Que el Dr. Hanns Paul Tüttenberg -----, quién autentica la firma del signatario en el presente documento, ejercía en la fecha alli indicada las funciones de Presidente del Tribunal Regional -en Mainz. ----------

Que la firma BOEHRINGER INGELHEIM INTERNATIONAL GmbH, domiciliada en 55216 Ingelheim am Rhein, Registro Mercantil Nr. HR B 1063 del Juzgado Municipal de Bingen ----------
está constituída y ejerce su objeto social de conformidad con las leyes de la República Federal de Alemania.

Que los señores Dr. DIETER LAUDIN Y Dr. GERHARD HUBER
quien (es) firman el presente documento tiene (n) facultad legal suficiente para representar a la mencionada firma y otorgar poderes en su nombre.

Que ha tenido a la vista la documentación que prueba lo anterior.

Munich, 18 de Diciembre de 1995

CONSULADO GENERAL DE COLOMBIA * MUNICH *

RICARDO MOSQUERA MESA
CONSUL GENERAL DE COLOMBIA

Derechos para la Nación US $ 6.-
Fondo Rotatorio US $ 100.-
Tasa consular US $ 1 x DM 1,60 = DM 169,60 PAGADO

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME HA SIDO TENIDO A LA VISTA
BOGOTA D.C., REPÚBLICA DE COLOMBIA
20 MAR. 2009
AMPARO QUINTERO ARTURO
NOTARIA

MINISTERIO DE RELACIONES EXTERIORES

05 ENE 09

LA FIRMA ... DOCUMENTO DE ... LAS FUNCIONES INDICA...

NO SE ASUME RESPONSABILIDAD DEL TEXTO

09 ENE -4 A 11:44

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C

LUZ AIRIVIA ... TRADUCTORA E INTÉR...

1-044513 3 f Cert

Resolución No. 59 ... Ministerio ...

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTÁ D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA BOGOTÁ D.C., REPÚBLICA DE COLOMBIA

20 MAR. 2009

AMPARO QUINTERO ARTURO
NOTARIA

...AL DE COLOMBIA ... CONSU...

EDIFICIO SIS...
CARRERA 4ª Nº 72-35
BOGOTA, D. - COLOMBIA

b

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseño industriales, marcas de fábrica, nombre comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

925
0569

I (we), the undersigned/Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

of/domiciliado (s) en D-55216 Ingelheim am Rhein, GERMANY

por el presente nombramos a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; y LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, renounce and ratify the acts done by representatives without authority.

Given and signed this/Dado y firmado hoy Ingelheim am Rhein, 12/12/1995

BOEHRINGER INGELHEIM
in/en INTERNATIONAL GMBH

ppa. ppa.

Dr. Dieter Laudien — Dr. Gerhard Huber
Signature — Firma

NOTARIA SEXTA DEL CIRCULO DE BOGOTA
HACE CONSTAR QUE LA FOTOCOPIA COINCIDE
EL ORIGINAL QUE SE TUVO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAR. 2009
AMPARO QUINTERO ARTURO
NOTARIA

LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular certificate*, on (1) the legal existence of the company which grants the Power-of-Attorney, (2) that it is in actual exercise of company purposes, and (3) that the persons who execute the Power of Attorney is autorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA

20 MAR. 2009

AMPARO QUINTERO ARTURO
NOTARIA

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

...ue a consular certificate on (1)
...t. It is in actual exercise of
...company which grants
...hat the persons who execute the
...o this so. To this effect, please
...rove the above facts (1), (2).

UR.Nr. 2659 / 95 V

Vorseitige, vor mir gefertigte Namensunterschriften der Herren:

1. Dr. Dieter L a u d i e n, Dipl.-Chemiker, wohnhaft in 55127 Mainz,.

2. Dr. Gerhard H u b e r, Rechtsanwalt, wohnhaft in 55411 Bingen,

- mir bekannt -

beglaubige ich hiermit.

Gleichzeitig bescheinige ich aufgrund heutiger Einsichtnahme in das Handelsregi-
ter des Amtsgerichts Bingen, daß die Firma Boehringer Ingelheim International
GmbH mit Sitz in Ingelheim am Rhein im Handelsregister des Amtsgerichts Bingen
unter HR B 1063 eingetragen ist und daß die Herren Dr. Laudien und Dr. Huber als
Prokuristen gemeinschaftlich zur Vertretung der Gesellschaft berechtigt sind.

Ingelheim am Rhein, den 12. Dezember 1995/hün

Notariatsverweser
anstelle des Notars
Prof. Dr. Weirich in Ingelheim

Landgericht Mainz

- 910 E 1 -

Die Echtheit vorstehender Unterschrift des Notarassessors Dr. Peter Wirth - Notariatsverweser anstelle des Notars Prof. Dr. Weirich in Ingelheim und die Echtheit des beigedrückten Dienst - ~~xxxxxxxx~~ - siegels werden hierdurch bestätigt. Zugleich wird bescheinigt, daß der Vorgenannte zur Vornahme der Amtshandlung gesetzlich befugt war.

Mainz, den dreizehnten Dezember neunzehnhundertneunzig
Der Präsident des Landgerichts
(Dr. Hans Paul Tittelberg)

Landgericht Mainz

Kostenberechnung:
Gebühr für Legalisation
(Wert: DM 5.000,-)
JVKostO. v. 26.7.1957
BGBl. I S. 861
DM 20,-
Mainz, den 13. DEZ. 1995
Amtsinspektor

REPUBLICA DE COLOMBIA
NOTARIA 35 TREINTA Y CINCO DEL CIRCULO DE BOGOTA
DOY FE: HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE
CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
ZU MAR. 2000
AMPARO QUINTERO ARTURO
NOTARIA

TRADUCCION OFICIAL No. 5133

de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente.-

---

(A continuación del poder conferido a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO tpa, 31929; y LUZ CLEMENCIA DE PAEZ, tpa 23555; domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia, por la BOEHRINGER INGELHEIM INTERNATIONAL GMBH, domiciliada en D-55216 Ingelheim am Rhein, RFA, a través de sus representantes los Srs. Dr. Dieter Laudien y Dr. Gerhard Huber:)

Legalización

Protocolo notarial No. 2659/95 V

Certifico la autenticidad de las firmas antecedentes puestas ante mí por los señores:

1. Dr. Dieter Laudien, Dipl. Chim., domiciliado en 55127 Mainz,

2. Dr. Gerhard Huber, abogado, domiciliado en 55411 Bingen

a quienes conozco en persona.

COPIA NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAR. 2009
AMPARO QUINTERO ARTURO
NOTARIA

Igualmente certifico, por haber examinado en la fecha el Registro de Comercio del Juzgado Municipal de Bingen, HR B 1063, que la firma Boehringen Ingelheim International GmbH, domiciliada en Ingelheim am Rhein, está inscrita bajo el No. HR B 1063 en el Registro de Comercio del Juzgado Municipal de Bingen y que los señores Dr. Laudien y Dr. Huber, en su calidad de apoderados, están facultados para representar conjuntamente a la sociedad.

Ingelheim am Rhein, 12 de diciembre de 1995/hün

Fdo.: firma ilegible
El notario suplente
del notario de Ingelheim
Prof. Dr. Weirich

(Hilo y oblea roja en relieve:)
El notario suplente - Ingelheim

(dos sellos redondos en tinta del Tribunal Regional de Mainz)

910 E 1

Se certifica la autenticidad de la firma antecedente del Dr. Peter Wirth, como notario suplente del Prof. Dr. Weirich, notario de Ingelheim, y la del sello oficial que la acompaña. Igualmente se certifica que el mencionado notario estaba facultado para realizar ese acto oficial.

Mainz, trece de diciembre de mil novecientos noventa y cinco

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAR. 2009
AMPARO QUINTERO ARTURO
NOTARIA

Resolución No. 599 Ministerio

El Presidente del Tribunal Regional

(E) Fdo.: firma ilegible

(Dr. Hanns Paul Tüttenberg)

Costas

Derechos de legalización
(Valor:DM 5.000,-)
JVKostO del 26 de julio 1957
Gacetas Oficial I Pag. 861
DM 20,--
Mainz, 13 de diciembre de 1995
Fdo.: firma ilegible
Inspector

EN ESPAÑOL: La legalización de las firmas antecedentes por el Consulado de Colombia en Munich bajo el No. 1 de 18 de diciembre de 1995, y por el Ministerio de Relaciones Exteriores de Colombia bajo el No. 051606 del 4 de enero de 1996. Pagados derechos y Fondo Rotatorio US$ 106,--

---

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas oficinas para su confrontación.

Santafé de Bogotá, 6 de enero de 1996.

LUZ ARRIAGA DE HERRERA
TRADUCTORA E INTERPRETE OFICIAL
Resolución 0599 Ministerio

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAR. 2009
AMPARO QUINTERO ARTURO
NOTARIA

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE

_____

_____

C. C. _____

COINCIDE CON LA REGISTRADA POR EL (ELLA) EN ESTA NOTARIA.

09 ENE 1996

SANTAFE DE BOGOTA D.C.

NOTARIA SEXTA
PABLO MENDEZ BARAJAS
Notario Sexto Encargado

NO SE ASUME RESPONSABILIDAD DEL VIDRIO

10 ENE 96 A 11:33

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

1007911

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTÁ D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTÁ D.C. REPÚBLICA DE COLOMBIA

20 MAR. 2009

AMPARO QUINTERO ARTURO
NOTARIA

TELEFAX: (57) (1) 3[illegible] 9850
TELEX: 45479 CAVE CO
(231)740 7375 CAVE UC

CAVELIER
ABOGADOS

EDIFICIO SISKI
CARRERA 4º, No. 72-35
BOGOTA 8, COLOMBIA

CORREO ELECTRONICO MUNDIAL: CAVE
TELEFONO (57) (1) 2120100
CABLES: CAVELEYES

21

Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Poderdante: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Poder conferido el: 12-12-95.

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil ya que los otros sustitutos faltan en este momento.

Señor Jefe,

GERMAN CAVELIER
T.P.A. No. 832
C.C. No. 2.877.924 de Bogotá

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
20 MAR. 2009
AMPARO QUINTERO ARTURO
NOTARIA

Acepto:

EMILIO FERRERO
T.P.A. Nº 31.929
C.C. No. 438.019 de Usaquén

2e-780-2

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá,,D. C. 11 ENE 1996

Ante M, PABLO MENDEZ BARAJAS S.

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quien(es) exhibió(eron) la(s) C. C. 2877927 y 438014

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NOTARIA SEXTA
PABLO MENDEZ BARAJAS
Notario Sexto Encargado

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2008 (03.04.2008)

PCT

(10) International Publication Number
WO 2008/039645 A1

(51) International Patent Classification:
C07C 317/44 (2006.01) *C07D 261/12* (2006.01)
A61K 31/16 (2006.01) *C07D 277/46* (2006.01)
A61P 29/00 (2006.01) *C07D 277/82* (2006.01)
A61P 37/00 (2006.01) *C07D 309/04* (2006.01)
C07D 213/75 (2006.01) *C07D 403/12* (2006.01)
C07D 215/38 (2006.01) *C07D 405/12* (2006.01)
C07D 217/22 (2006.01) *C07D 407/12* (2006.01)
C07D 231/40 (2006.01)

(21) International Application Number:
PCT/US2007/078341

(22) International Filing Date:
13 September 2007 (13.09.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/826,819 25 September 2006 (25.09.2006) US

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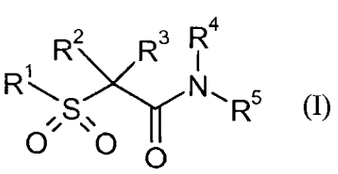
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) Title: COMPOUNDS WHICH MODULATE THE CB2 RECEPTOR



(I)

(57) Abstract: Compounds of formula (I) are disclosed. Compounds according to the invention bind to and are agonists, antagonists or inverse agonists of the CB2 receptor, and are useful for treating inflammation. Those compounds which are agonists are additionally useful for treating pain.

WO 2008/039645 A1

Compounds Which Modulate The CB2 Receptor

APPLICATION DATA

This application claims benefit to US provisional application serial no. 60/826,819 filed September 25, 2006.

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The present invention relates to novel compounds which modulate the CB2 receptor and their use as medicaments.

2. BACKGROUND INFORMATION

Cannabinoids are a group of about 60 distinct compounds found in *Cannabis sativa* (also know as marijuana) with cannabinol, cannabidiol and Δ^9-tetrahydrocannabinol (THC) being the most representative molecules. The therapeutic usage of *Cannabis* can be dated back to ancient dynasties of China and includes applications for various illnesses ranging from lack of appetite, emesis, cramps, menstrual pain, spasticity to rheumatism. The long history of *Cannabis* use has led to the development of several pharmaceutical drugs. For example, Marinol and Cesamet which are based on THC and its analogous nabilone, respectively, are used as anti-emetic and appetite stimulant. Despite of the clinical benefits, the therapeutic usage of cannabis is limited by its psychoactive effects including hallucination, addiction and dependence. Mechoulam R, ed. *Cannabinoids as Therapeutic Agents*, Boca Raton, FL; CRC Press, 1986 provides a review of the medicinal use of cannabis.

The physiological effects of cannabinoids are mediated by at least two G-protein coupled receptors, CB1 and CB2. Autoradiographic studies have demonstrated that CB1 receptors are expressed primarily in the central nervous system, specifically in the cerebral cortex, hippocampus, basal ganglia and cerebellum. They are also found to a lesser degree in the reproductive system and other peripheral tissues including that of the immune system. CB1 receptors regulate the release of neurotransmitters from the pre-synaptic neurons and are believed to mediate most of the euphoric and other central nervous system effects of cannabis, such as THC-induced ring-catalepsy, hypomobility, and hypothermia, which were found to be completely absent in mice with a deletion of the CB1 gene (Zimmer et al., Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci U S A. (1999) 96:5780-5785.)

CB2 receptors are almost exclusively found in the immune system, with the greatest density in the spleen. It is estimated that the expression level of CB2 in the immune cells is about 10 to 100 times higher than CB1. Within the immune system, CB2 is found in various cell types, includung B cells, NK cells, monocytes, microglial cells, neutrophils, T cells, dentritic cells and mast cells, suggesting that a wide range of immune functions can be regulated through CB2 modulators (Klein et al., The cannabinoid system and immune system. J Leukoc Biol (2003) 74:.486-496). This is supported by the finding that the immunomodulatory effect of THC is absent in CB2 deficient mice mice (Bicklet et al., Immunomodulation by cannabinoid is absent in mice deficient for the cannabinoid CB2 receptor. Eur J Pharmacol (2000) 396:141-149). CB2 selective ligands have been developed and tested for their effects in various imflammatory settings. For example, in animal models of inflammation, CB2 selective agonists, inverse agonists and antagonists have been shown to be effective in suppressing inflammation (Hanus et al., HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor. Proc Natl Acad Sci U S A. (1999) 96:14228-14233, Ueda et al., Involvement of cannabinoid CB(2) receptor-mediated response and efficacy of cannabinoid CB(2) receptor inverse agonist, JTE-907, in cutaneous inflammation in mice. Eur J Pharmacol. (2005) 520:164-171 and Smith et al., The anti-inflammatory activities of cannabinoid receptor ligands in mouse peritonitis models Eur J Pharmacol. (2001) 432:107-119.). Furthermore, CB2 selective agonists inhibit disease severity and spasticity in animal models for multiple sclerosis (Baker et al., Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature (2000) 404:84-87.Arevalo-Martin et al., Therapeutic action of cannabinoids in a murine model of multiple sclerosis J Neurosci. (2003) 23:2511-2516.). Taken together, these results support the notion that CB2 receptor modulators can be employed for the treatment of medical conditions having an inflammatory component.

In addition to inflammation, CB2 agonists have been shown to inhibit pain and emesis. For instance, CB2 selective agonists blunt the pain response induced by thermal or other stimuli (Malan et al., CB2 cannabinoid receptor-mediated peripheral antinociception. Pain. (2001) 93:239-45 and Nackley et al., Selective activation of cannabinoid CB(2) receptors suppresses spinal fos protein expression and pain behavior in a rat model of inflammation. Neuroscience (2003) 119:747-57.) CB2 activation has also been demonstrated to inhibit neuropathic pain response (Ibrahim et al., Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. Proc Natl Acad Sci U S A. (2003) 100:10529-33.) Finally, in contrast to the earlier data which did not find CB2 in the brain, a recent article demonstrated the expression of CB2 in the brain, at about 1.5 % of the level in the spleen. CB2 activation is shown by this article to be responsible for the anti-emetic effect of endocannabinoid (Van Sickle et al., Identification and

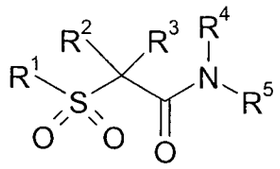
functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005 310:329-332.) The foregoing results confirm that CB2 agonists can be used for the treatment of inflammatory and neuropathic pain as well as emesis.

BRIEF SUMMARY OF THE INVENTION

The present invention provides novel compounds which bind to and modulate the CB2 receptor. The invention also provides a method and pharmaceutical compositions for treating inflammation by way of the administration of therapeutic amounts of these compounds. Lastly, the invention provides a method and pharmaceutical compositions for treating pain by way of the administration of therapeutic amounts of the new compounds which are CB2 agonists.

DETAILED DESCRIPTION OF THE INVENTION

In its broadest generic aspect the invention provides compounds of the formula



(I)

wherein:

R^1 is C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, 3-10 membered saturated heterocyclic ring, benzyl or phenethyl each optionally independently substituted with 1-3 substituents chosen from C_{1-10} alkyl optionally substituted with 1 to 3 halogen atoms, C_{3-10} cycloalkyl, 3-10 membered saturated heterocyclic ring optionally substituted with acyl, oxo or methyl sulfone, acyl, cyano, phenyl, oxo, hydroxyl and halogen;

R^2 and **R^3** are independently hydrogen or C_1-C_6 alkyl; or R^2 and R^3 together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or heterocyclic ring;

R^4 is hydrogen or methyl;

$\mathbf{R^5}$ is aryl or heteroaryl each optionally independently substituted with 1 to 3 substituents chosen from C_1-C_6 alkyl optionally substituted with 1 to 3 halogen atoms or with a heterocyclyl group, C_1-C_6 alkoxy optionally substituted with 1 to 3 halogen atoms, C_3-C_6 cycloalkyl, phenoxy, halogen, cyano, dimethylaminoC_1-C_4alkyl, phenyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen, thienyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen and pyridinyl optionally substituted with 1 to 2 C_1-C_4 alkyl optionally substituted with halogen;

or a tautomer or pharmaceutically acceptable salt thereof.

In a first subgeneric aspect, the invention provides compounds of the formula I wherein,

$\mathbf{R^1}$ is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyranyl, bicylco(3.3.0)octanyl, bicyclo[4.3.0]nonyl, benzyl or phenethyl each optionally independently substituted with 1 to 3 substituents chosen from methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl (optionally substituted with acyl, oxo or methylsulfonyl), piperidinyl (optionally substituted with acyl, oxo or methylsulfone, acyl, cyano, phenyl, oxo, fluoro, chloro, bromo and hydroxyl, ;

$\mathbf{R^2}$ and $\mathbf{R^3}$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl, or R^2 and R^3 together with the carbon to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or tetrahydropyranyl ring;

$\mathbf{R^4}$ is hydrogen;

$\mathbf{R^5}$ is phenyl, naphthyl, pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, indolyl, benzoxazolyl, benzopyrazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzimidazolyl, tetrahydrobenzoxazolyl, tetrahydrobenzothiazolyl or tetrahydrobenzimidazolyl each optionally independently substituted with 1 to 3 substituents chosen from C_1-C_6 alkyl optionally substituted with 1 to 3 halogen atoms, C_1-C_6 alkoxy optionally substituted with 1 to 3 halogen atoms, C_3-C_6 cycloalkyl, phenoxy, halogen, cyano, dimethylaminoC_1-C_4alkyl, phenyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen, thienyl optionally substituted with 1 to 2 halogen

atoms or C_1-C_4 alkyl optionally substituted with halogen and pyridinyl optionally substituted with 1 to 2 C_1-C_4 alkyl optionally substituted with halogen.

In a further subgeneric aspect, the invention provides compounds of the formula I wherein,

R^1 is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyranyl, , bicylco(3.3.0)octanyl, or bicyclo[4.3.0]nonyl each optionally independently substituted with 1 to 3 substituents chosen from methyl, ethyl, pivaloyl, cyclopropyl, cyclobutyl, cyclohexyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl optionally substituted with methylsulfone, fluoro, chloro, bromo, oxo and hydroxy;

R^2 and **R^3** are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl, or R^2 and R^3 together with the carbon to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or tetrahydropyranyl ring;

R^4 is hydrogen;

R^5 is phenyl, naphthyl, pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, indolyl, benzoxazolyl, benzopyrazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzimidazolyl, tetrahydrobenzoxazolyl, tetrahydrobenzothiazolyl, or tetrahydrobenzimidazolyl each optionally independently substituted with 1 to 3 substituents chosen from C_1-C_6 alkyl optionally substituted with 1 to 3 halogen atoms, C_1-C_6 alkoxy optionally substituted with 1 to 3 halogen atoms, C_3-C_6 cycloalkyl, phenoxy, halogen, cyano, dimethylaminoC_1-C_4alkyl, phenyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen, thienyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen and pyridinyl optionally substituted with 1 to 2 C_1-C_4 alkyl optionally substituted with halogen.

In another subgeneric aspect, the invention provides compounds of the formula I wherein,

R^1 is benzyl or phenethyl each optionally independently substituted with 1 to 3 substituents chosen from methyl, fluoro, chloro and bromo.

In another subgeneric aspect, the invention provides compounds of the formula I wherein,

R^1 is methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl or benzyl each optionally substituted with methyl, pivaloyl, cyclopropyl, cyclobutyl, cyclohexyl tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl optionally substituted with methylsulfonyl or chloro;

R^2 and **R^3** are independently hydrogen, methyl, isopropyl, tert-butyl, or R^2 and R^3 together with the carbon to which they are attached form a cyclopropyl or cyclobutyl, ring;

R^4 is hydrogen;

R^5 is phenyl, pyridinyl, quinolinyl, isoquinolinyl, pyrazolyl, isoxazolyl, benzothiazolyl, thiadiazolyl, or thiazolyl each optionally independently substituted with 1 to 2 substituents chosen from, methyl, ethyl, tert-butyl, neopentyl, cyclohexyl, trifluoromethyl or phenyl optionally substituted with a chlorine atom.

The term "alkyl", or any substituent containing an alkyl group such as alkoxy or acylamino, shall be understood to be branched or unbranched alkyl groups, preferably C_1-C_6 and shall be understood to be optionally partially or fully halogenated.

The compounds of formula I may be made using the general synthetic methods described below, which also constitute part of the invention.

GENERAL SYNTHETIC METHODS

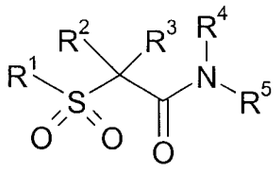
The invention also provides processes for making compounds of Formula (I). In all methods, unless specified otherwise, R^1, R^2, R^3, R^4 and R^5 in the formulas below shall have the meaning of R^1, R^2, R^3, R^4 and R^5 in Formula (I) of the invention described herein above.

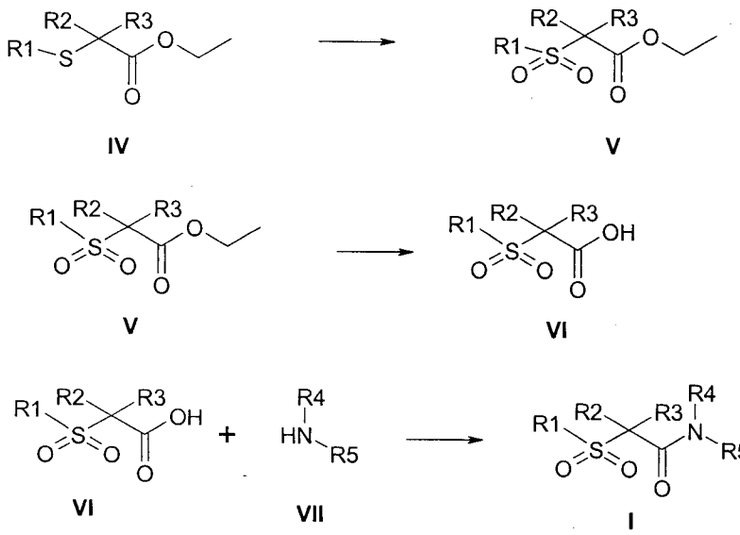
Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may

be monitored by thin layer chromatography (TLC), if desired, and intermediates and products may be purified by chromatography on silica gel and/or by recrystallization.

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials and intermediates used, in the methods below, are either commercially available or easily prepared from commercially available materials by those skilled in the art.

Compounds of Formula (I) may be synthesized by the method illustrated in Method A



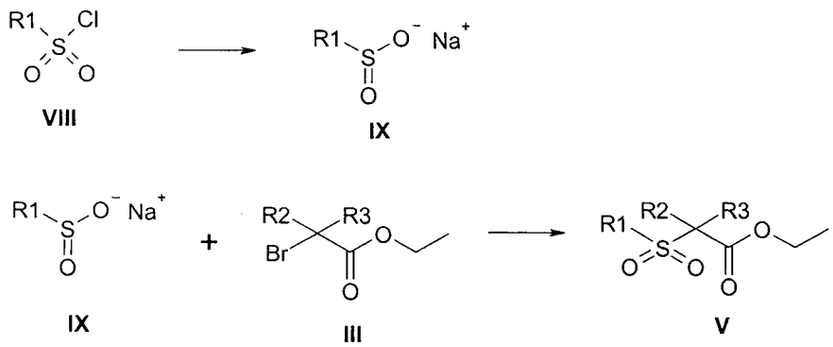


Method A

As illustrated in Method A, reaction of a thiol of formula II with a bromo ethyl ester of formula III, in a suitable solvent in the presence of a suitable base, provides a thioether of formula IV. Reacting the thioether of formula IV with a suitable oxidizing agent provides the corresponding sulfone of formula V. Hydrolysis of the ester group of sulfone of formula V in a suitable solvent in the presence of a suitable base such as lithium hydroxide, provides the corresponding acid of formula VI. Reacting the acid of formula VI with a reagent such as thionyl chloride or oxalyl chloride, provides the acid chloride which is then reacted with an amine of formula VII in a suitable solvent in the presence of a suitable base, to provide a compound of formula (I). Alternatively, the acid of formula VI may also be coupled with an amine of formula VII under standard coupling conditions, to provide a compound of formula

(I). Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses. An example of suitable coupling conditions is treatment of a solution of the carboxylic acid in a suitable solvent such as DMF with EDC, HOBT, and a base such as diisopropylethylamine, followed by the desired amine. Further modification of the initial product of formula (I) by methods known in the art and illustrated in the Examples below, may be used to prepare additional compounds of this invention.

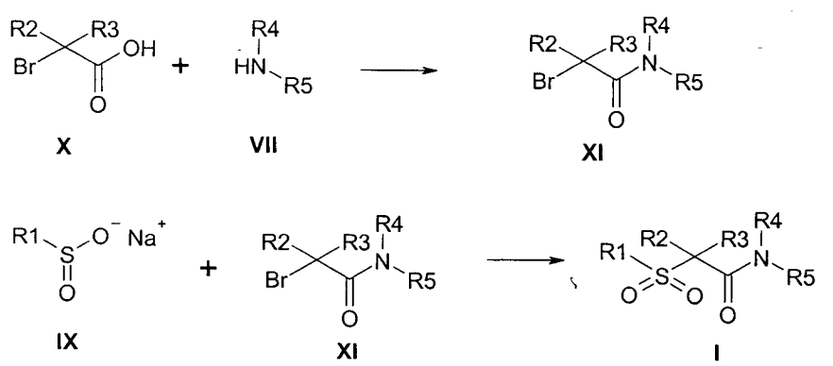
Compounds of Formula (I) may also be synthesized by the method illustrated in Method B



Method B

As shown in Method B, sulfonyl chloride of formula VIII is converted to the corresponding sulfinic acid sodium salt of formula IX, using procedures reported in the literature. Reaction of the sulfone of formula IX with a bromo ethyl ester of formula III in a suitable solvent, provides a sulfone of formula V. The sulfone of formula V is subjected to the sequence of reactions as shown in Method A, to provide a compound of formula (I).

Compounds of Formula (I) may be synthesized by the method illustrated in Method C



Method C

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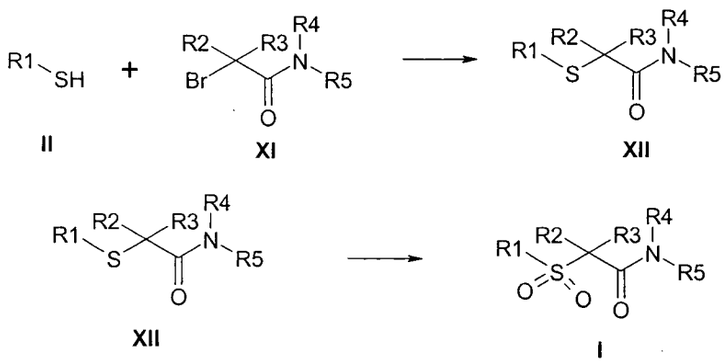
As illustrated in Method C, reacting the acid of formula X with a reagent such as thionyl chloride or oxalyl chloride, provides the acid chloride which is then reacted with an amine of formula VII in a suitable solvent in the presence of a suitable base, to provide a compound of formula (XI). Alternatively, the acid of formula X may also be coupled with an amine of formula VII under standard coupling conditions, to provide a compound of formula (XI). Reaction of the amide of formula XI with a sulfinic acid sodium salt of formula IX, in a suitable solvent in the presence of a suitable base, provides a compound of formula (I).

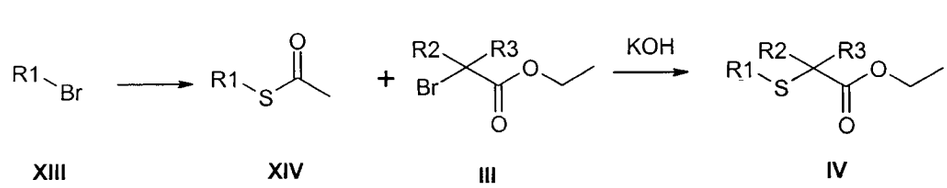
Compounds of Formula (I) may be synthesized by the method illustrated in Method D



Method D

As illustrated in Method A, reaction of a thiol of formula II with a bromo amide of formula XI, in a suitable solvent in the presence of a suitable base, provides a thioether of formula XII. Reacting the thioether of formula XII with a suitable oxidizing agent in a suitable solvent, provides a compound of formula (I).

Compounds of Formula (I) may be synthesized by the method illustrated in Method E

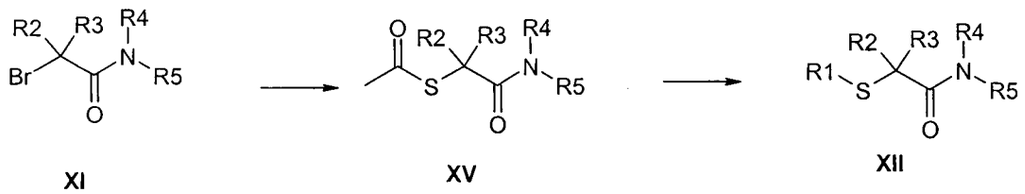


Method E

Reaction of the starting bromide of formula XIII with a reagent such as potassium thioacetate, in a suitable solvent, provides a thioacetic acid ester of formula XIV. Reaction of the thioacetic acid ester XIV with the bromo ethyl ester of formula III, in a suitable solvent in the presence of a suitable base, provides the corresponding sulfanyl acid ethyl ester of formula IV

which may be converted to a compound of formula (I) by the sequence of steps shown in Method A.

Compounds of Formula (I) may be synthesized by the method illustrated in Method F

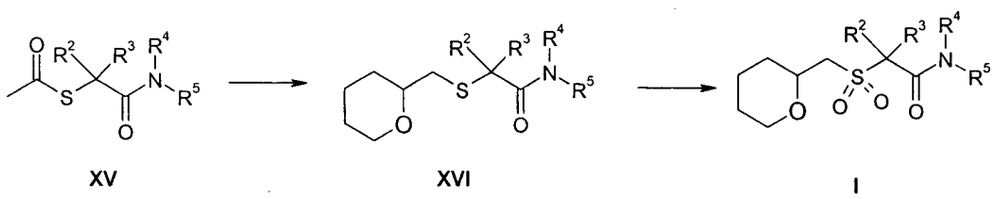


XI XV XII

Method F

Reaction of a bromoamide of formula XI with a reagent such as potassium thioacetate, in a suitable solvent provides a thio compound of formula XV. Reaction of the thio compound of formula XV with the appropriate bromo compound, in a suitable solvent, in the presence of a suitable base provides the thio amide of formula XII which may be converted to a compound of formula (I) as in Method D.

Compounds of Formula (I) may be synthesized by the method outlined in Method G.

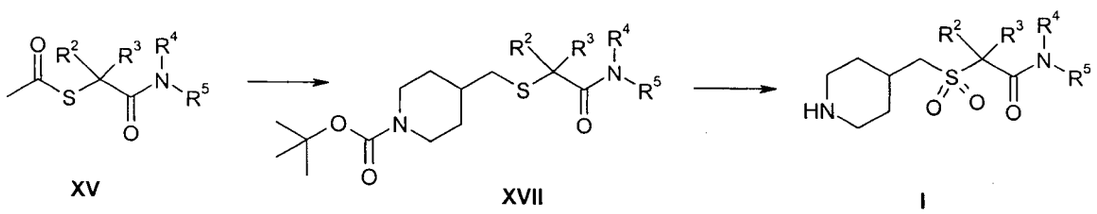


XV XVI I

Method G

Reaction of an acylated thio-compound of formula XV with bromomethyltetra- hydropyran, in the presence of a suitable base, such as sodium methoxide, in a suitable solvent, provides an intermediate of formula XVI. Reaction of the intermediate of formula XVI with a suitable oxidizing agent such as hydrogen peroxide provides a compound of formula I.

Compounds of Formula (I) may be synthesized by the method shown in Method H.



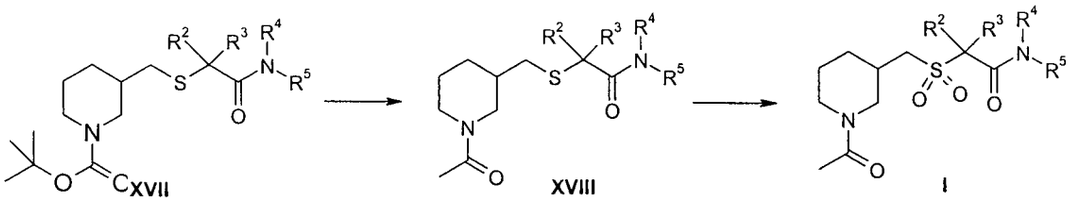
XV XVII I

23

Method H

As illustrated above, reaction of an acylated thio-compound of formula XV with N-Boc-bromomethylpiperdine, in the presence of a suitable base, such as sodium methoxide, in a suitable solvent, provides an intermediate of formula XVII. Removal of the protecting group in the presence of an acid, and oxidation under standard reaction conditions, provides a compound of formula I.

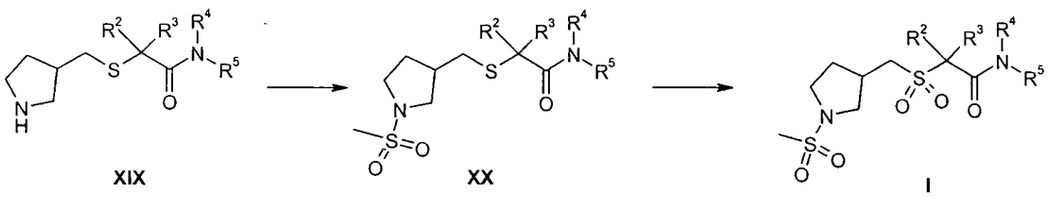
Compounds of Formula (I) may be synthesized by the method shown in Method I.



Method I

As outlined above, deprotection of a N-Boc protected piperidine of formula XVII, with a suitable acid followed by acylation with a reagent such as acetic anhydride, in the presence of a suitable base, provides a compound of formula XVIII. Reaction of the intermediate of formula XVIII with a suitable oxidizing agent such as m-chloroperbenzoic acid, provides a compound of formula I.

Compounds of Formula (I) may be synthesized by the method illustrated in Method J.



Method J

As outlined in the above method J, reaction of a compound of formula XIX with methane sulfonyl chloride, in the presence of a suitable base, in a suitable solvent, provides an intermediate of formula XX. Reaction of the intermediate of formula XX with a suitable oxidizing agent such as m-chloroperbenzoic acid, provides a compound of formula I.

Compounds of Formula (I) may be synthesized by the method illustrated in Method K.

I I

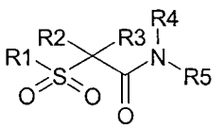
Method K

A compound of formula I may be converted to another compound of formula I as shown in method K. Alkylation of a compound of formula 1 with a reagent such as methyl iodide, in the presence of a suitable base such as lithium diisopropylamide, provides a methylated compound of formula 1.

EXAMPLES

The manner in which the compounds of the invention can be made will be further understood by way of the following Examples.

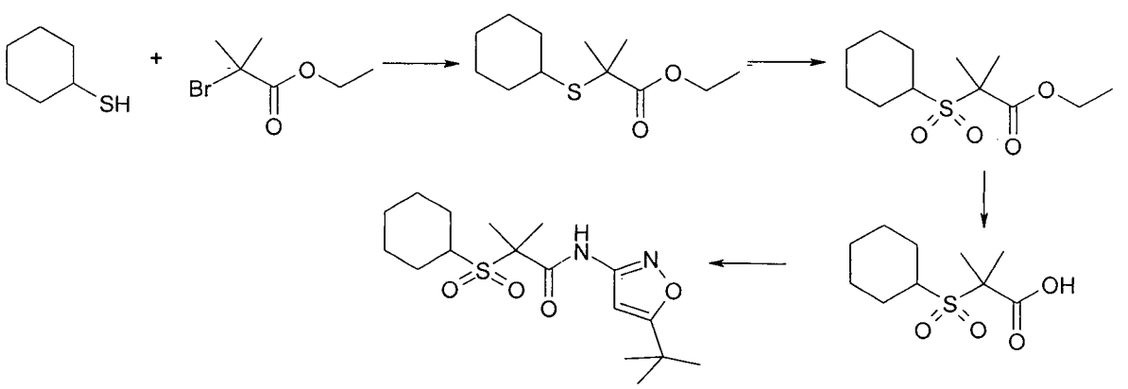
Experimental Procedures for Compounds of Formula I



I

Method A

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide (Example 1 in Table 17)



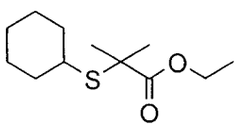
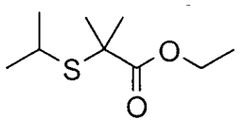
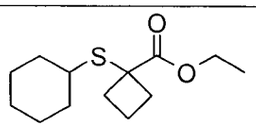
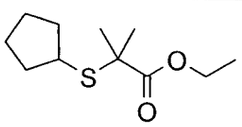
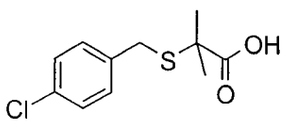
Step 1: Synthesis of 2-Cyclohexylsulfanyl-2-methyl-propionic acid ethyl ester

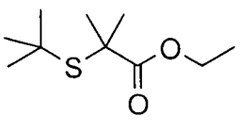
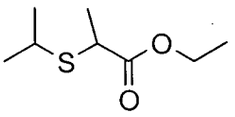
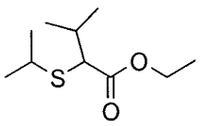
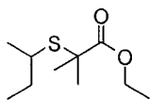
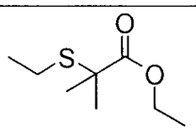
Prepared as described by adaptation of the following reference: Brown *et al. J. Med. Chem.* **1999**, *42*, 3785-3788

To a solution of 2.5 g (21.5 mmol) of cyclohexyl thiol in ethanol (75 mL) were added 1.2 g (21.5 mmol) of KOH pellets, followed by 4.2 g (21.5 mmol) of ethyl α-bromoisobutyrate. The reaction was heated to reflux for 18 h and then cooled to room temperature. The solid (KBr) was separated by filtration and rinsed with ethanol (20 mL). The filtrate was concentrated under reduced pressure and the residue dissolved in DCM (50 mL). The organic layer was washed with water (2 x 20 mL). The aqueous washes were back-extracted with DCM (10 mL). The combined organics were washed with brine, dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded 4.15 g of 2-cyclohexylsulfanyl-2-methyl-propionic acid ethyl ester.

According to this procedure the following thioethers were synthesized:

Table 1

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-Cyclohexylsulfanyl-2-methyl-propionic acid ethyl ester	84	231
	2-Isopropylsulfanyl-2-methyl-propionic acid ethyl ester	83	191
	1-Cyclohexylsulfanyl-cyclobutanecarboxylic acid ethyl ester	68	243
	2-Cyclopentylsulfanyl-2-methyl-propionic acid ethyl ester	77	217
	2-(4-Chloro-benzylsulfanyl)-2-methyl-propionic acid	40*	245/247

	2-tert-Butylsulfanyl-2-methyl-propionic acid ethyl ester	88	205
	2-Isopropylsulfanyl-propionic acid ethyl ester	50	177
	2-Isopropylsulfanyl-3-methyl-butyric acid ethyl ester	45	structure confirmed by 1H NMR
	2-sec-Butylsulfanyl-2-methyl-propionic acid ethyl ester	55	205
	2-Ethylsulfanyl-2-methyl-propionic acid ethyl ester	44	177

*hydrolysis of the ethyl ester occurred during reaction conditions

Step 2: Synthesis of 2-Cyclohexanesulfonyl-2-methyl-propionic acid ethyl ester

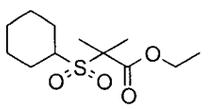
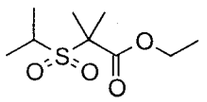
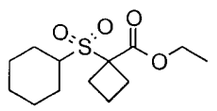
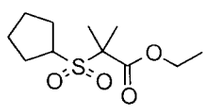
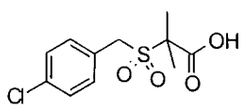
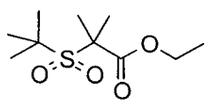
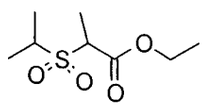
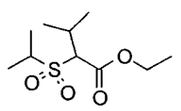
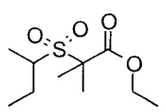
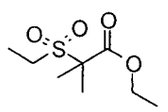
Prepared as described by adaptation of the following reference:

Aranapakam, V. *et al. J. Med. Chem.*, **2004**, *47*, 6255-6269.

To a solution of 4.15 g (18 mmol) of 2-cyclohexylsulfanyl-2-methyl-propionic acid ethyl ester in dioxane/water (5/1, 40 mL) were added in one portion 33.2 g (54 mmol) of potassium monopersulfate triple salt (OXONE®). The white suspension was stirred at room temperature for 18 h. The white solid was separated by filtration and washed with dioxane (10 mL). The filtrate was concentrated under reduced pressure to remove the organic solvent. The resulting aqueous solution was extracted with DCM (3 x 40 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 3.47 g of 2-cyclohexanesulfonyl-2-methyl-propionic acid ethyl ester.

According to this procedure the following sulfones were synthesized:

Table 2

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-Cyclohexanesulfonyl-2-methyl-propionic acid ethyl ester	50	263
	2-Methyl-2-(propane-2-sulfonyl)-propionic acid ethyl ester	75	223
	1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid ethyl ester	76	275
	2-Cyclopentanesulfonyl-2-methyl-propionic acid ethyl ester	78	249
	2-(4-Chloro-phenylmethanesulfonyl)-2-methyl-propionic acid	81*	277/279, 294/296 [M+H_2O^+]
	2-Methyl-2-(2-methyl-propane-2-sulfonyl)-propionic acid ethyl ester	86	237
	2-(Propane-2-sulfonyl)-propionic acid ethyl ester	99	209
	3-Methyl-2-(propane-2-sulfonyl)-butyric acid ethyl ester	100	237
	2-(Butane-2-sulfonyl)-2-methyl-propionic acid ethyl ester	77	237
	2-Ethanesulfonyl-2-methyl-propionic acid ethyl ester	85	209

*2-(4-Chloro-benzylsulfanyl)-2-methyl-propionic acid used for oxidation step

Step 3: Synthesis of 2-Cyclohexanesulfonyl-2-methyl-propionic acid

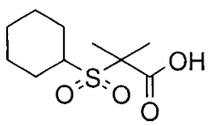
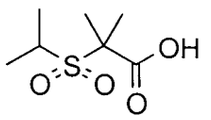
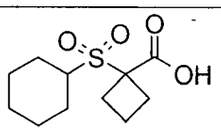
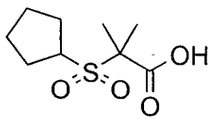
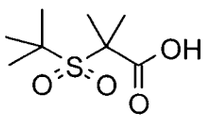
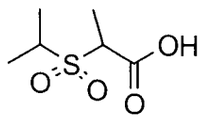
Prepared as described by adaptation of the following reference:

Troeger, Uhde., *J. Prakt. Chem.* **1899**, *59*, 320- 349

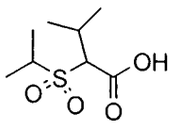
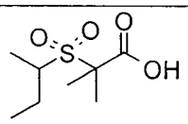
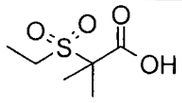
To a solution of 3.47g (13.2 mmol) of 2-cyclohexanesulfonyl-2-methyl-propionic acid ethyl ester in THF/water (4/1, 50 mL) were added 1.11 g (26.4 mmol) of lithium hydroxide monohydrate. The reaction was stirred at room temperature for 18 h. The reaction was further diluted with water (20 mL) and then washed with DCM (2 x 15 mL). The basic aqueous layer was cooled in an ice bath and then acidified with 1M aqueous HCl solution to pH 2. The acidic aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. Concentration of the filtrate under reduced pressure afforded 2.96 g of 2-cyclohexanesulfonyl-2-methyl-propionic acid.

According to this procedure the following acids were synthesized:

Table 3

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-Cyclohexanesulfonyl-2-methyl-propionic acid	64	258 [M+Na$^+$+H$^+$]
	2-Methyl-2-(propane-2-sulfonyl)-propionic acid	92	195, 212 [M+H$_2$O$^+$]
	1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid	89	247
	2-Cyclopentanesulfonyl-2-methyl-propionic acid	92	221
	2-Methyl-2-(2-methyl-propane-2-sulfonyl)-propionic acid	69	209, 226 [M+H$_2$O$^+$]
	2-(Propane-2-sulfonyl)-propionic acid	29	181

29

	3-Methyl-2-(propane-2-sulfonyl)-butyric acid	32	209
	2-(Butane-2-sulfonyl)-2-methyl-propionic acid	78	209, 226 $[M+H_2O^+]$
	2-Ethanesulfonyl-2-methyl-propionic acid	89	198 $[M+H_2O^+]$

Step 4: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

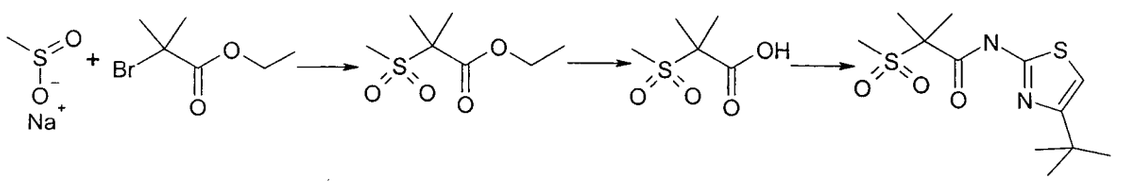
Activation of 100 mg (0.4 mmol) of 2-cyclohexanesulfonyl-2-methyl-propionic acid as the corresponding acid chloride was achieved by treatment with thionyl chloride (1 mL) at 80 °C for 2 h. The reaction was cooled to room temperature and excess thionyl chloride was removed under reduced pressure.

The crude acid chloride was dissolved in DCM (0.5 mL) and added to a solution of 67 mg (0.48 mmol) of 3-amino-5-tert-butylisoxazole and N,N-diisopropylethylamine (83 mL, 0.48 mmol) in DCM (1 mL). The reaction was stirred at room temperature for 18 h, before it was evaporated to dryness. The reaction mixture was diluted with DCM (4 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 mL). The organic layers was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, eluent: DCM, 0-5% ethyl acetate) to afford 14 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide.

Examples listed in Table 17, Method A were made according to this procedure.

Method B

Synthesis of N-(4-tert-Butyl-thiazol-2-yl)-2-methanesulfonyl-2-methyl-propionamide (Example 51 in Table 17)



Step 1: Synthesis of 2-Methanesulfonyl-2-methyl-propionic acid ethyl ester

30

Prepared as described by adaptation of the following references:

Faucher, A.-M. *et al. J. Med. Chem.* **2004**, *47*, 19-21.

Binsiti, C. *Eur. J. Med. Chem. Chim. Ther.* **2001**, *36*, 809-828.

Field, L.; Clark, R.D. *Org. Synth.* **1958**, *38*, 62-64.

Troeger; U., *J. Prakt. Chem.* **1899**, *59*, 320-349.

To a suspension of 5 g (49 mmol) of sodium methane sulfite in DMF (50 mL) were added pyridine (6.3 mL) and ethyl α-bromoisobutyrate (2.9 mL). The reaction was stirred for 18 h at 50 °C under nitrogen. The reaction mixture was diluted with ethyl acetate (250 mL), washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), 2M aqueous HCl solution (50 mL), brine (1 x 50 mL) and dried over Na_2SO_4. Filtration, concentration under reduced pressure afforded 3.04 g of 2-methanesulfonyl-2-methyl-propionic acid ethyl ester.

The compound did not ionise under LCMS conditions, thus the structure was confirmed by ^{1}H-NMR spectroscopy: ^{1}H NMR (360 MHz, *CHLOROFORM-d*) δ ppm 1.33 (3 H, t, *J*=7.1 Hz), 1.66 (6 H, s), 3.06 (3 H, s), 4.28 (2 H, q, *J*=7.1 Hz).

Step 2: Synthesis of 2-Methanesulfonyl-2-methyl-propionic acid

2-Methanesulfonyl-2-methyl-propionic acid was generally prepared as described in step 3, method A:

To a solution of 500 mg (2.6 mmol) of 2-methanesulfonyl-2-methyl-propionic acid ethyl ester in THF/water (4/1, 5 mL) were added 270 mg (6.6 mmol) of lithium hydroxide monohydrate. The reaction was stirred at room temperature for 18 h. The reaction was further diluted with water (20 mL) and then washed with DCM (2 x 15 mL). The basic aqueous layer was cooled in an ice bath and acidified with 1M aqueous HCl solution to pH 2. The acidic aqueous layer was extracted with isopropanol/chloroform (1/1, 3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. Concentration of the filtrate under reduced pressure afforded 413 mg of 2-methanesulfonyl-2-methyl-propionic acid. The compound did not ionise under LCMS conditions, thus the structure was confirmed by ^{1}H-NMR spectroscopy:

^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 1.49 (6 H, s), 3.08 (3 H, s).

Step 3: Synthesis of N-(4-tert-butyl-thiazol-2-yl)-2-methanesulfonyl-2-methyl-propionamide

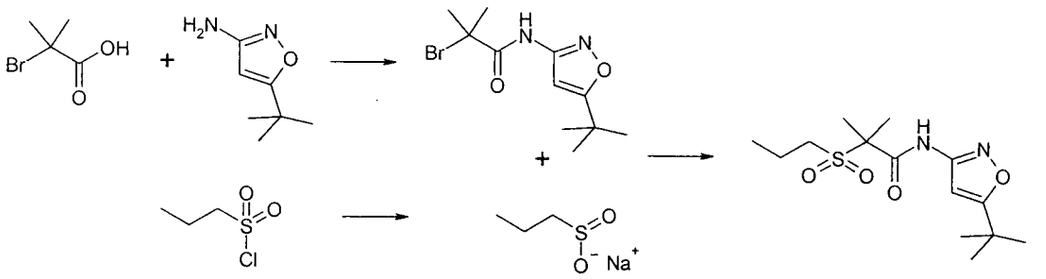
Activation of 97 mg (0.6 mmol) of 2-methanesulfonyl-2-methyl-propionic acid as the corresponding acid chloride was achieved by treatment with thionyl chloride (2 mL) at 80 °C for 2 h. The reaction was cooled to room temperature and excess thionyl chloride was removed under reduced pressure.

The crude acid chloride was dissolved in DCM (2 mL) and added to a solution of 91 mg (0.6 mmol) of 2-amino-4-tert-butylthiazole and N, N-diisopropylethylamine (0.13 mL) in DCM (1 mL). The reaction was stirred at room temperature for 18 h. The reaction mixture was diluted with DCM, washed with saturated aqueous $NaHCO_3$ solution (2 mL), brine (2 mL) and dried over Na_2SO_4. Filtration and concentration of the filtrate afforded the crude product. Further purification by column chromatography (silica, eluent: heptanes, 0-20% ethyl acetate) yielded 116 mg of N-(4-tert-butyl-thiazol-2-yl)-2-methanesulfonyl-2-methyl-propionamide.

Examples listed in Table 17, Method B were made according to this procedure.

Method C

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide (Example 10 in Table 17)



Step 1: Synthesis of 1-propanesulfinic acid sodium salt

Prepared as described by adaptation of the following references:

Faucher, A.-M. *et al. J. Med. Chem.* **2004**, *47*, 19-21.

Binsiti, C. *Eur. J. Med. Chem. Chim. Ther.* **2001**, *36*, 809-828.

Field, L.; Clark, R.D. *Org. Synth.* **1958**, *38*, 62-64.

To a solution of 0.26g (3.2 mmol) of $NaHCO_3$ and 0.4 g (3.2 mmol) of Na_2SO_3 in water (1.5 mL) were added 0.23 g (1.6 mmol) of 1-propanesulfonyl chloride. The reaction was heated at 80 °C for 3 h. The solvent was removed under reduced pressure. The crude material was suspended in boiling ethanol (20 mL) and the inorganic solids were removed by filtration. The filtrate was concentrated under reduced pressure to afford 0.18 g of 1-propanesulfinic acid sodium salt.

Step 2: Synthesis of 2-Bromo-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

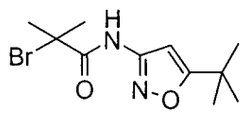
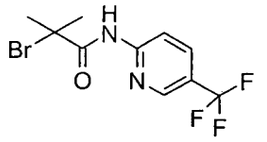
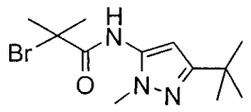
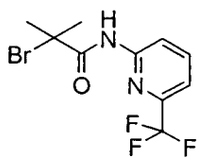
Prepared as described by adaptation of the following references: Katoh A. *et al. Heterocycles* **1999**, *50*, 299-308

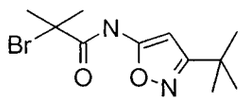
Activation of 5 g (30 mmol) of 2-bromo-2-methylpropionic acid as the corresponding acid chloride was achieved by treatment with thionyl chloride (10 mL) at 60 °C for 2 h. The reaction was cooled and excess thionyl chloride was removed under reduced pressure to afford the corresponding acid chloride.

To a solution of 4.2 g (30 mmol) of 3-amino-5-tert-butylisoxazole and 5.2 mL (30 mmol) of N,N-diisopropylethylamine in DCM (20 mL) was added dropwise the acid chloride, as solution in DCM (15 mL). The reaction was stirred at room temperature for 18 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 x 15 mL) and the layers were separated. The organic layer was further washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by dry flash column chromatography (silica, eluent DCM, 0-20% ethyl acetate) to yield 8.5 g of 2-bromo-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide.

According to this procedure the following amides were synthesized:

Table 4

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-Bromo-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide	97	289/291
	2-Bromo-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	55	311/313
	2-Bromo-N-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-propionamide	51	302/304
	2-Bromo-2-methyl-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide	72	311/313

	2-Bromo-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide	68	289/291

Step 3: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

Prepared as described by adaptation of the following references:

Faucher, A.-M. *et al. J. Med. Chem.* **2004**, *47*, 19-21.

Troeger; Uhde; *J. Prakt. Chem.* **1899**, *59*, 320-349.

Binsiti, C. *Eur. J. Med. Chem. Chim. Ther.* **2001**, *36*, 809-828.

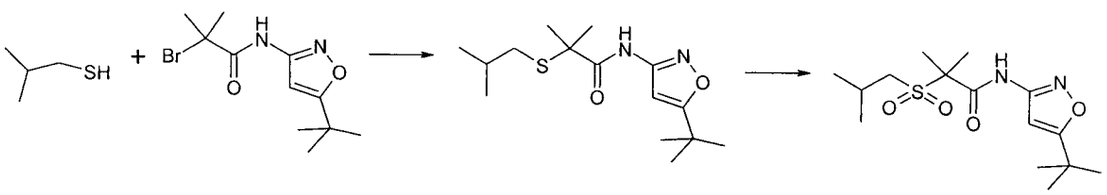
Field, L.; Clark, R.D. *Org. Synth.* **1958**, *38*, 62-64.

To a solution of 160 mg (0.55 mmol) of 2-bromo-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide in DMF (3 mL) were added 87 mg (0.71 mmol) of 1-propanesulfinic acid sodium salt in one portion. Pyridine (48 µL) was added and the reaction was stirred at 50 °C for 18 h. The mixture was acidified with 1M aqueous HCl solution (1 mL) and extracted with diethyl ether (3 x 3 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The crude material was purified by column chromatography (silica, eluent heptanes, 0-20% ethyl acetate) to afford 86 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide.

Examples listed in Table 17, Method C were made according to this procedure.

<u>Method D</u>

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide (Example 52 in Table 17)

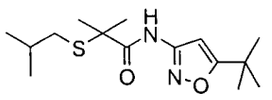
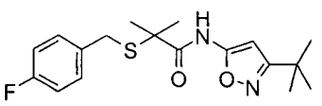


Step 1: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-isobutylsulfanyl-2-methyl-propionamide

To a stirred solution of 82 µL (1.31 mmol) of 2-methyl-1-propanethiol in ethanol (2 mL) were added 37 mg (0.65 mmol) of KOH pellets, followed by 190 mg (0.65 mmol) 2-bromo-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide (prepared as described in step 2, method B). The reaction mixture was heated to reflux for 18 h. The reaction was cooled to room temperature. The solid (KBr) was separated by filtration and rinsed with ethanol (15 mL). The filtrate was concentrated under reduced pressure to yield 160 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-isobutylsulfanyl-2-methyl-propionamide.

According to this procedure the following amides were synthesized:

Table 5

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	N-(5-tert-Butyl-isoxazol-3-yl)-2-isobutylsulfanyl-2-methyl-propionamide	83	299
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-(4-fluoro-benzylsulfanyl)-2-methyl-propionamide	63	351

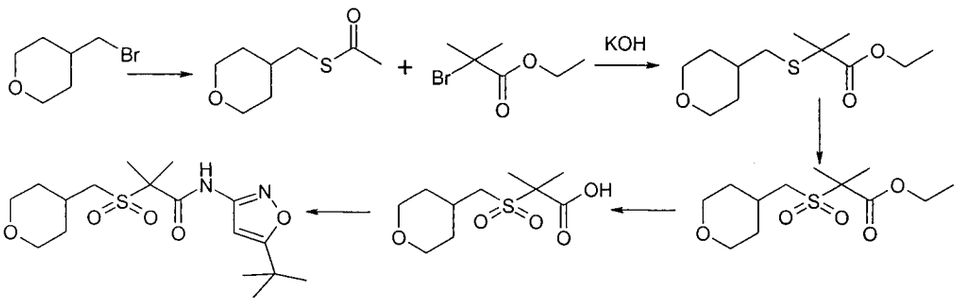
Step 2: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-isobutylsulfonyl-2-methyl-propionamide

To a solution of 160 mg (0.54 mmol) of N-(5-tert-butyl-isoxazol-3-yl)-2-isobutylsulfanyl-2-methyl-propionamide in dioxane/water (5/1, 2.5 mL) were added in one portion 0.99 g (1.61 mmol) of potassium monopersulfate triple salt (OXONE®). The white suspension was stirred at room temperature for 18 h. The white solid was separated by filtration and washed with dioxane (5 mL). The filtrate was concentrated under reduced pressure to remove the organic solvent. The resulting aqueous solution was extracted with DCM (2 x 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica, eluent DCM, 0-10 % ethyl acetate) to afford 98 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-isobutylsulfonyl-2-methyl-propionamide.

Examples listed in Table 17, Method D were made according to this procedure.

Method E

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide (Example 56, Table 17)



Step 1: Synthesis of Thioacetic acid S-(tetrahydro-pyran-4-ylmethyl) ester

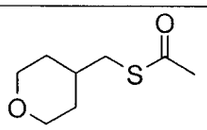
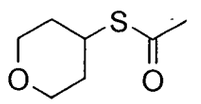
Prepared as described by adaptation of the following literature reference:

Watson, R.J. *et al. Tetrahedron Lett.* **2002**, *43*, 683-685.

To a solution of 0.97 g (5.4 mmol) of 4-bromomethyl tetrahydropyran in DMF (9.7 mL) were added 1.27 g (11.2 mmol) of potassium thioacetate. The reaction was stirred at room temperature for 3 h. Diethyl ether (100 mL) was added and the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 x 25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica, eluent: heptanes, 10 % ethyl acetate) to afford 0.81 g of thioacetic acid S-(tetrahydro-pyran-4-ylmethyl) ester.

According to this procedure the following thioacetates were synthesized:

Table 6

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	Thioacetic acid S-(tetrahydro-pyran-4-ylmethyl) ester	86	175
	Thioacetic acid S-(tetrahydro-pyran-4-yl) ester	68	161

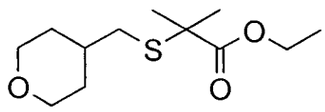
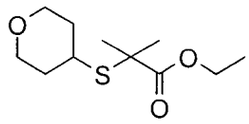
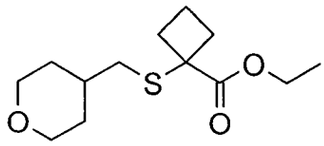
Step 2: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-ylmethylsulfanyl)-propionic acid ethyl ester

A solution of 0.86 g (15.2 mmol) of potassium hydroxide in ethanol (78 mL, degassed and under nitrogen) was added to 0.81 g (4.66 mmol) of thioacetic acid S-(tetrahydro-pyran-4-ylmethyl) ester. The reaction was stirred at room temperature under nitrogen for 0.5 h. Then 2.1 mL (14.1

mmol) of ethyl α-bromoisobutyrate were added and the reaction stirred for 4 h. The resulting precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The residue was dissolved in DCM (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL) and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure, followed by column chromatography of the residue (silica, eluent: heptanes, 0-20 % ethyl acetate) afforded 0.76 g of 2-methyl-2-(tetrahydro-pyran-4-ylmethylsulfanyl)-propionic acid ethyl ester.

According to this procedure the following ethyl esters were synthesized:

Table 7

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-Methyl-2-(tetrahydro-pyran-4-ylmethylsulfanyl)-propionic acid ethyl ester	66	247
	2-Methyl-2-(tetrahydro-pyran-4-ylsulfanyl)-propionic acid ethyl ester	75	233
	1-(Tetrahydro-pyran-4-ylmethylsulfanyl)-cyclobutanecarboxylic acid ethyl ester	77	259

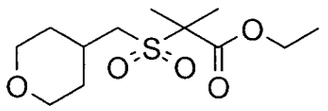
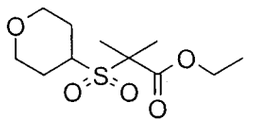
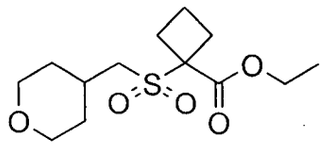
Step 3: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid ethyl ester

Prepared as described by adaptation of Method A, step 2.

To a solution of 0.76 g (3.1 mmol) of 2-methyl-2-(tetrahydro-pyran-4-ylmethylsulfanyl)-propionic acid ethyl ester in dioxane/water (1/1, 10 mL) was added in one portion 4.1 g (6.6 mmol) of potassium monopersulfate triple salt (OXONE®). The white suspension was stirred at room temperature for 1 h. The white solid was separated by filtration and washed with dioxane (5 mL). The filtrate was concentrated under reduced pressure to remove the organic solvent. The resulting mixture was diluted with DCM (50 mL) and water (5 mL). The organic layer was separated and washed with a saturated aqueous $NaHCO_3$/brine (1/1) mixture (20 mL) and dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded 0.77 g of 2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid ethyl ester.

According to this procedure the following sulfones were synthesized:

Table 8

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid ethyl ester	90	279
	2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid ethyl ester	84	265
	1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid ethyl ester	60	291

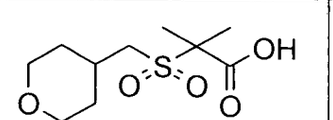
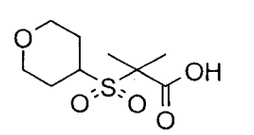
Step 4: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid

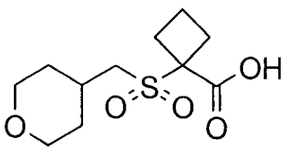
Prepared as described by adaptation of Method A, step 3.

To a solution of 769 mg (2.77 mmol) of 2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid ethyl ester in THF/water (1/1, 10 mL) were added 228 mg (5.43 mmol) of lithium hydroxide monohydrate. The reaction was stirred at room temperature for 18 h. The reaction was concentrated under reduced pressure. The residue was dissolved in water (10 mL) and washed with diethyl ether (2 x 25 mL). The aqueous layer was cooled in an ice bath and then acidified with 1M aqueous HCl solution to pH 2. The acidic aqueous layer was extracted with ethyl acetate (2 x 50 mL) and with isopropanol/chloroform (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. Concentration of the filtrate under reduced pressure afforded 734 mg of 2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid.

According to this procedure the following acids were synthesized:

Table 9

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid	100	251
	2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid	93	237

	1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid	80	263

Step 5: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

Prepared as described by adaptation of Method A, step 4.

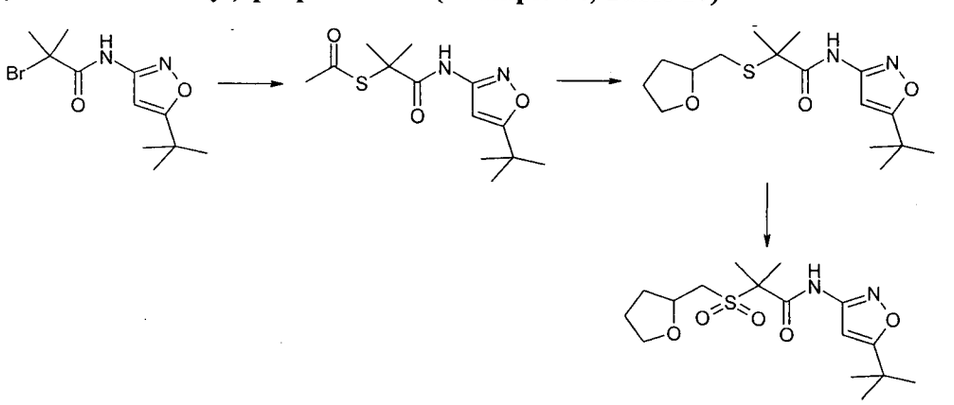
Activation of 122 mg (0.49 mmol) of 2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid as the corresponding acid chloride was achieved by treatment with thionyl chloride (0.4 mL) at 50 °C for 1 h. The reaction was cooled to room temperature and excess thionyl chloride was removed under reduced pressure.

The crude acid chloride was dissolved in DCM (2 mL) and added to a solution of 63 mg (0.49 mmol) of 3-amino-5-tert-butylisoxazole and N,N-diisopropylethylamine (145 mL, 0.88 mmol) in DCM (2 mL). The reaction was stirred at room temperature for 18 h. The reaction mixture was diluted with DCM (2 mL) and washed with a saturated aqueous $NaHCO_3$ solution/brine mixture (1/1, 2 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, eluent: heptanes, 0-20 % ethyl acetate, then DCM, 0-20 % ethyl acetate) to afford 41 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide.

Examples listed in Table 17, Method E were made according to this procedure.

Method F

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-4-ylmethanesulfonyl)-propionamide (Example 74, Table 17)

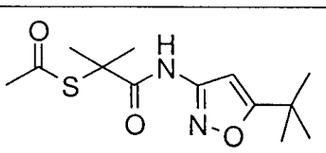
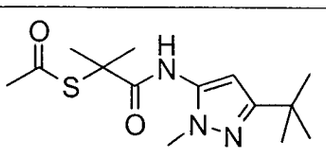
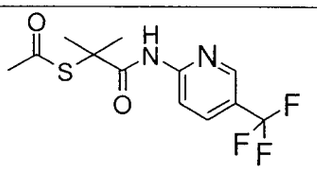
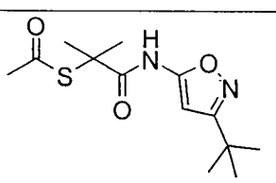


Step 1: Synthesis of Thioacetic acid S-[1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethyl] ester

To a solution of 200 mg (0.69 mmol) of 2-bromo-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide (prepared as described in Method B, step 2) in DMF (3 mL) were added 157 mg (1.4 mmol) of potassium thioacetate. The reaction was stirred at room temperature for 3 h. The reaction mixture was diluted with diethyl ether (5 mL) and washed with 2M aqueous HCl solution (5 mL). The organic layer was dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded 151 mg of thioacetic acid S-[1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethyl] ester.

According to this procedure the following thioacetates were synthesized:

Table 10

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	Thioacetic acid S-[1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethyl] ester	76	285
	Thioacetic acid S-[1-(5-tert-butyl-2-methyl-2H-pyrazol-3-ylcarbamoyl)-1-methyl-ethyl] ester	73	298
	Thioacetic acid S-[1-methyl-1-(5-trifluoromethyl-pyridin-2-ylcarbamoyl)-ethyl] ester	62	307
	Thioacetic acid S-[1-(3-tert-butyl-isoxazol-5-ylcarbamoyl)-1-methyl-ethyl] ester	62	285

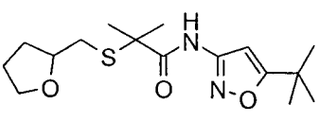
Step 2: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethylsulfanyl)-propionamide

To a solution of 100 mg (0.35 mmol) of thioacetic acid S-[1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethyl] ester in ethanol (2 mL) were added 70 mg (0.42 mmol) of 2-(bromomethyl)tetrahydrofuran and 340 µL (1.05 mmol) of sodium ethoxide solution (21% in ethanol) at room temperature. The reaction was heated to 50 °C for 18 h. The reaction mixture was concentrated under reduced pressure and the crude purified by column chromatography (silica, eluent: heptanes, 0-20% ethyl acetate) to afford 82 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethylsulfanyl)-propionamide.

39
40

According to this procedure the following thioethers were synthesized:

Table 11

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethylsulfanyl)-propionamide	71	327

Step 3: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

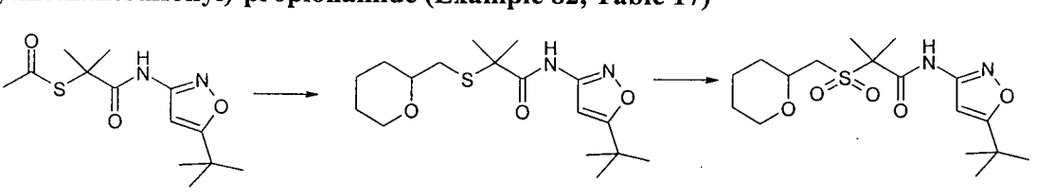
Prepared as described by adaptation of Method D, step 2.

To a solution of 82 mg (0.25 mmol) of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethylsulfanyl)-propionamide in dioxane/water (5/1, 4 mL) were added in one portion 460 mg (0.75 mmol) of potassium monopersulfate triple salt (OXONE®). The white suspension was stirred at room temperature for 3 h. The white solid was separated by filtration and washed with dioxane (5 mL). The filtrate was concentrated under reduced pressure to remove the organic solvent. The resulting aqueous solution was extracted with DCM (2 x 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica, eluent: DCM, 0-10 % ethyl acetate) to afford 5 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide.

Examples listed in Table 17, Method F were made according to this procedure.

Method G

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide (Example 82, Table 17)

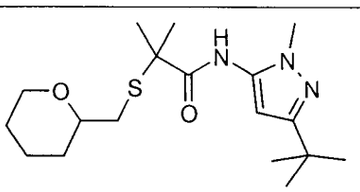
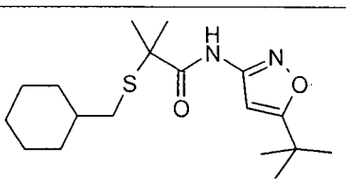
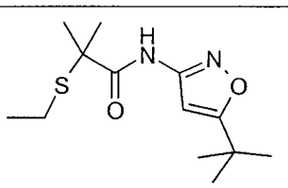
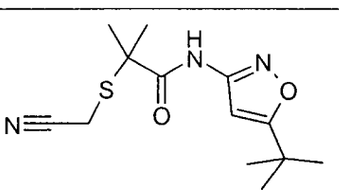
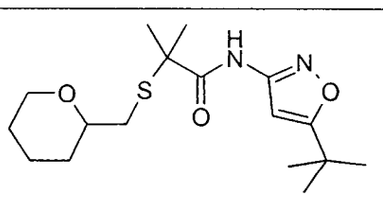


Step 1: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethylsulfanyl)-propionamide

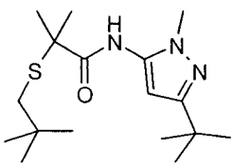
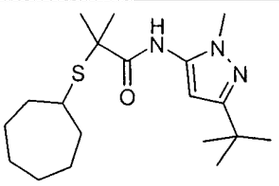
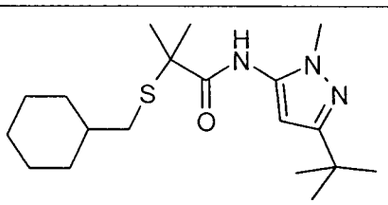
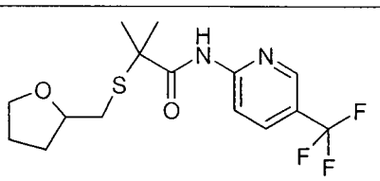
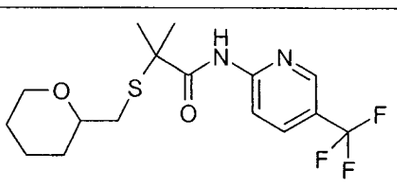
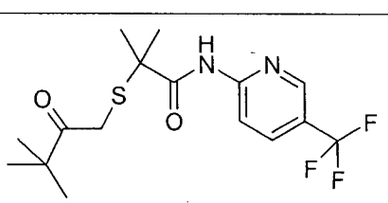
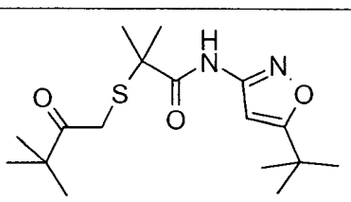
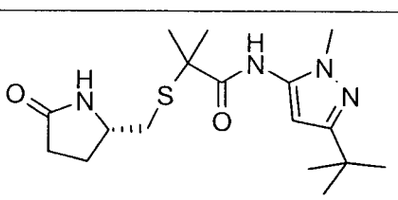
To a solution of 100 mg (0.352 mmol) of thioacetic acid S-[1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethyl] ester (synthesized according to Method F, step 1) in ethanol (2 mL) were added 126 mg (0.704 mmol) of 2-(bromomethyl)tetrahydropyran and 76 mg (1.41 mmol) of sodium methoxide at room temperature. The reaction was heated to 130 °C for 0.5 h within a microwave (CEM Discover). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5ml) and washed with saturated aqueous $NaHCO_3$ solution (5ml). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield 119 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethylsulfanyl)-propionamide.

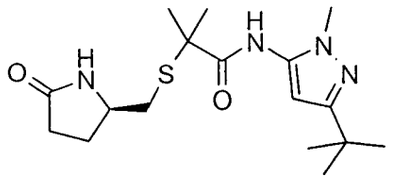
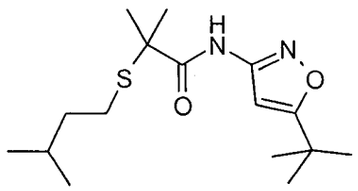
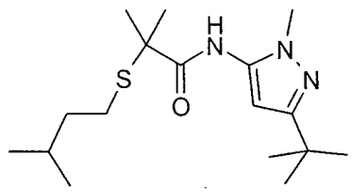
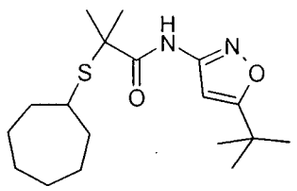
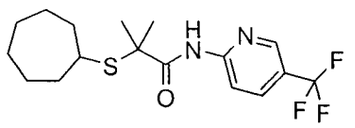
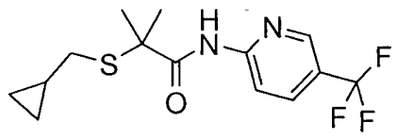
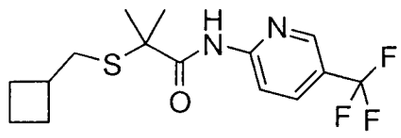
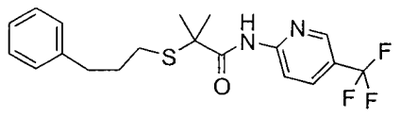
According to this procedure the following thioethers were synthesized:

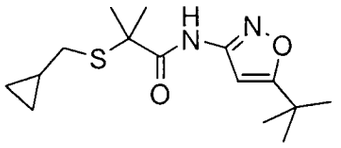
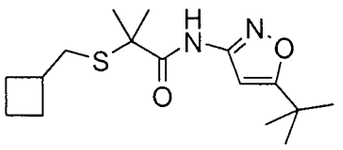
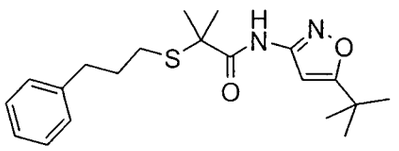
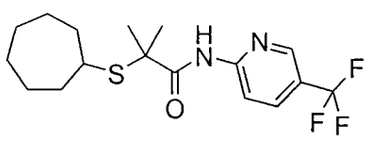
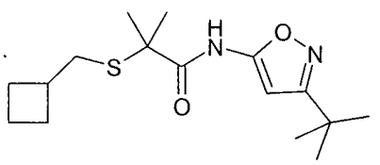
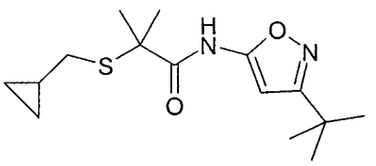
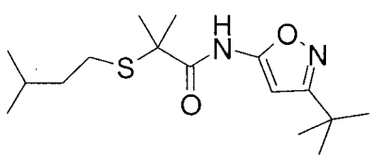
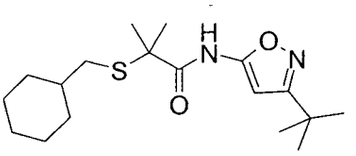
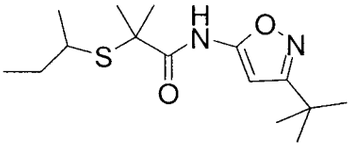
Table 12

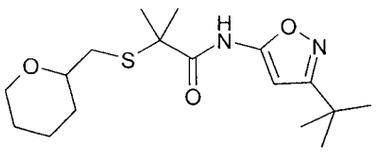
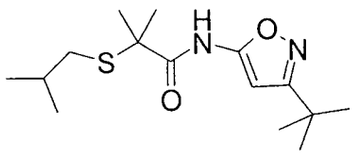
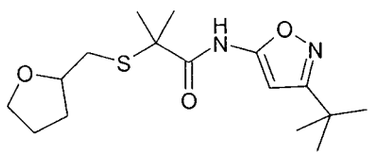
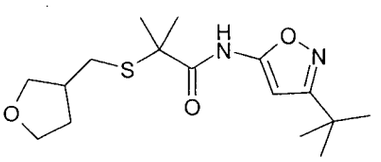
MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethylsulfanyl)-propionamide	100	354
	N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethylsulfanyl-2-methyl-propionamide	100	339
	N-(5-tert-Butyl-isoxazol-3-yl)-2-ethylsulfanyl-2-methyl-propionamide	90	271
	N-(5-tert-Butyl-isoxazol-3-yl)-2-cyanomethylsulfanyl-2-methyl-propionamide	96	282
	N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethylsulfanyl)-propionamide	100	341

42

	N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(2,2-dimethyl-propylsulfanyl)-2-methyl-propionamide	63	326
	N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptylsulfanyl-2-methyl-propionamide	68	352
	N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethylsulfanyl-2-methyl-propionamide	95	352
	2-Methyl-2-(tetrahydro-furan-2-ylmethylsulfanyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	53	349
	2-Methyl-2-(tetrahydro-pyran-2-ylmethylsulfanyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	54	363
	2-(3,3-Dimethyl-2-oxo-butylsulfanyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	45	363
	N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butylsulfanyl)-2-methyl-propionamide	75	341
	N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((S)-5-oxo-pyrrolidin-2-ylmethylsulfanyl)-propionamide	85	353

	N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((R)-5-oxo-pyrrolidin-2-ylmethylsulfanyl)-propionamide	97	353
	N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butylsulfanyl)-propionamide	70	313
	N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butylsulfanyl)-propionamide	90	326
	N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptylsulfanyl-2-methyl-propionamide	89	339
	2-Cycloheptylsulfanyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	83	361
	2-Cyclopropylmethylsulfanyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	100	319
	2-Cyclobutylmethylsulfanyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	97	333
	2-Methyl-2-(3-phenyl-propylsulfanyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	82	383

	N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethylsulfanyl-2-methyl-propionamide	74	297
	N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethylsulfanyl-2-methyl-propionamide	77	311
	N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-phenyl-propylsulfanyl)-propionamide	86	361
	2-Cycloheptylsulfanyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	83	361
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-cyclobutylmethylsulfanyl-2-methyl-propionamide	55	311
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-cyclopropylmethylsulfanyl-2-methyl-propionamide	70	297
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butylsulfanyl)-propionamide	50	313
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-cyclohexylmethylsulfanyl-2-methyl-propionamide	50	339
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-*sec*-butylsulfanyl-2-methyl-propionamide	73	299

	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethylsulfanyl)-propionamide	75	341
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-isobutylsulfanyl-2-methyl-propionamide	73	299
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethylsulfanyl)-propionamide	100	327
	*N*-(3-*tert*-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethylsulfanyl)-propionamide	100	327

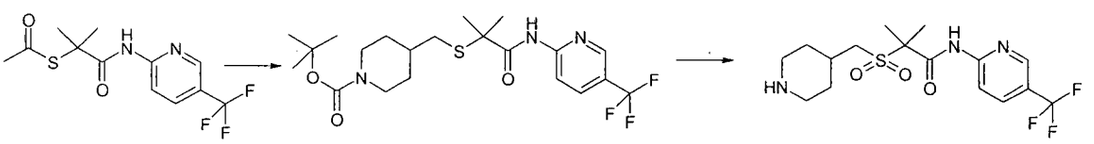
Step 3: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

To a solution of 119 mg (0.365 mmol) of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethylsulfanyl)-propionamide in acetic acid (1 mL) were added 103 μL (1.83 mmol) of hydrogen peroxide (50% solution, stabilized in water) and heated to 80 °C for 50 minutes. The colorless solution was quenched with ethanol (2 mL) and concentrated under reduced pressure. The crude material was purified by mass-triggered preparative LCMS and residual TFA was removed by filtration through a small plug of Ambersep 900-OH resin to yield 27 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide.

Examples listed in Table 17, Method G were made according to this procedure.

Method H

Synthesis of 2-Methyl-2-(piperidin-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide (Example 98, Table 17)



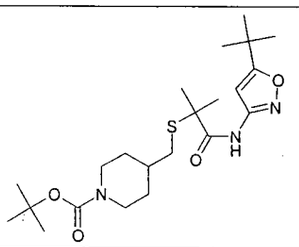
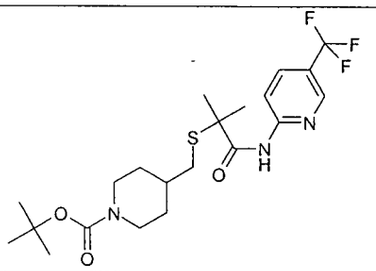
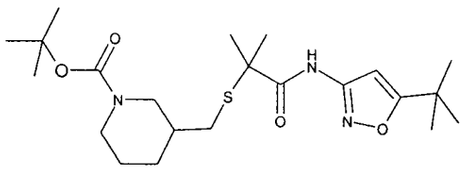
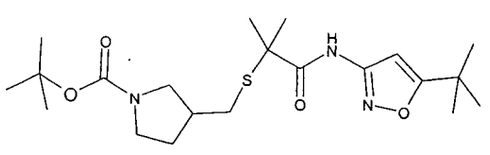
46

Step 1: Synthesis of 4-[1-Methyl-1-(5-trifluoromethyl-pyridin-2-ylcarbamoyl)-ethylsulfanylmethyl]-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 200 mg (0.654 mmol) of thioacetic acid S-[1-methyl-1-(5-trifluoromethyl-pyridin-2-ylcarbamoyl)-ethyl] ester (synthesized according to Method F, step 1) in ethanol (2 mL) were added 363 mg (1.31 mmol) of 4-bromomethyl-piperidine-1-carboxylic acid tert-butyl ester and 141mg (2.61 mmol) of sodium methoxide at room temperature. The reaction was heated to 130 °C for 0.5 h within a microwave (CEM Discover). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (4 mL) and washed with saturated aqueous $NaHCO_3$ solution (5mL). The organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to yield 375 mg of 4-[1-methyl-1-(5-trifluoromethyl-pyridin-2-ylcarbamoyl)-ethylsulfanylmethyl]-piperidine-1-carboxylic acid tert-butyl ester.

According to this procedure the following thioethers were synthesized:

Table 13

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	4-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethylsulfanylmethyl]-piperidine-1-carboxylic acid tert-butyl ester	89	462 [M+Na$^+$], 340 [M+H$^+$-$C_5H_8O_2$]
	4-[1-Methyl-1-(5-trifluoromethyl-pyridin-2-ylcarbamoyl)-ethylsulfanylmethyl]-piperidine-1-carboxylic acid tert-butyl ester	100	462 [M+H$^+$], 485 [M+Na$^+$]
	3-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethylsulfanylmethyl]-piperidine-1-carboxylic acid tert-butyl ester	88	462 [M+Na$^+$], 340 [M+H$^+$-$C_5H_8O_2$]
	3-[1-(5-tert-Butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethylsulfanylmethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester	30	426 [M+H$^+$], 448 [M+Na$^+$], 326 [M+H$^+$-$C_5H_8O_2$]

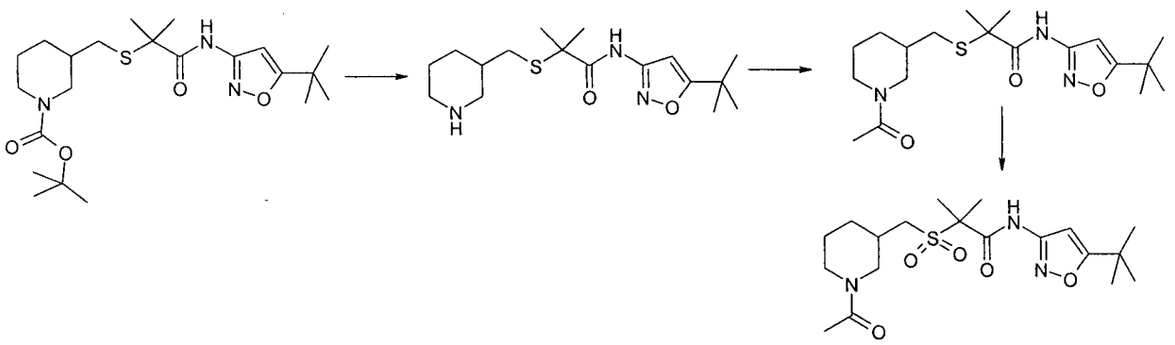
Step 2: Synthesis of 2-Methyl-2-(piperidin-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

To a solution of 375 mg (0.81 mmol) of 4-[1-methyl-1-(5-trifluoromethyl-pyridin-2-ylcarbamoyl)-ethylsulfanylmethyl]-piperidine-1-carboxylic acid tert-butyl ester in acetic acid (1ml) were added 241 µL (4.26 mmol) of hydrogen peroxide (50% solution, stabilized in water) and heated to 80 °C for 50 minutes. The colorless solution was quenched with ethanol (2 mL) and concentrated under reduced pressure. The crude material was treated with a solution of 10% TFA in DCM (5 mL) for 16 h. The solvents were removed under reduced pressure. The residue was purified by mass triggered preparative LC and residual TFA was removed by filtration through a small plug of Ambersep 900-OH resin to yield 24.8 mg of 2-methyl-2-(piperidin-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide.

Examples listed in Table 17, Method H were made according to this procedure.

Method I

Synthesis of 2-(1-Acetyl-piperidin-3-ylmethanesulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide (Example 39, Table 17)

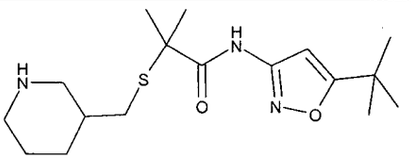
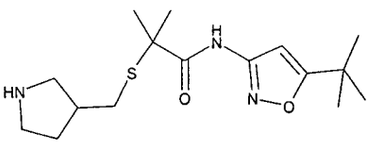


Step 1: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(piperidin-3-ylmethylsulfanyl)-propionamide

To a solution of 288 mg (0.65 mmol) of 3-[1-(5-tert-butyl-isoxazol-3-ylcarbamoyl)-1-methyl-ethylsulfanylmethyl]-piperidine-1-carboxylic acid tert-butyl ester (synthesized according to Method H, step 1) in DCM (5 mL) were added 1.1 mL of HCl (2M solution in dioxane). The reaction was stirred at room temperature for 16 h. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (5 mL), the organic layer was separated and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure afforded 175 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(piperidin-3-ylmethylsulfanyl)-propionamide.

According to this procedure the following thioethers were synthesized

Table 14

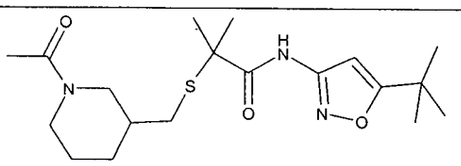
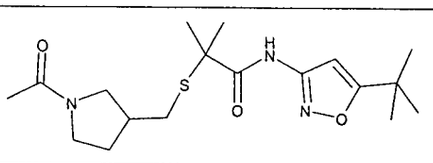
MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(piperidin-3-ylmethylsulfanyl)-propionamide	79	340
	N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(pyrrolidin-3-ylmethylsulfanyl)-propionamide	89	326

Step 2: Synthesis of 2-(1-Acetyl-piperidin-3-ylmethylsulfanyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

A solution of 175 mg (0.52 mmol) of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(piperidin-3-ylmethylsulfanyl)-propionamide 0.18 mL (1.04 mmol) of N,N-diisopropylethylamine and acetic anhydride (1.5 mL) were heated for 0.5 h to 100 °C within a microwave (CEM discover). The solvent was removed under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (5 mL). The organic phase was dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford 183 mg of 2-(1-acetyl-piperidin-3-ylmethylsulfanyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide, which was used in the next step without further purification.

According to this method the following amides were synthesized.

Table 15

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]
	2-(1-Acetyl-piperidin-3-ylmethylsulfanyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide	92	382
	2-(1-Acetyl-pyrrolidin-3-ylmethylsulfanyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide	80	368

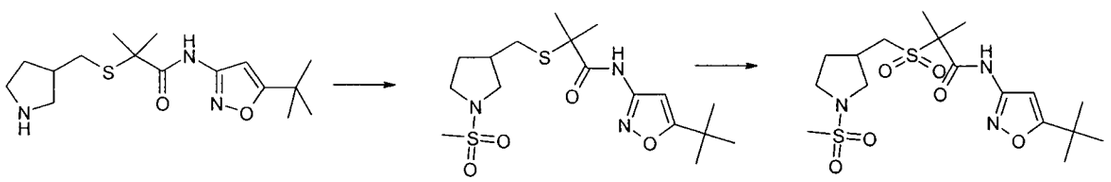
Step 3: Synthesis of 2-(1-Acetyl-piperidin-3-ylmethanesulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

To a solution of 183 mg (0.48 mmol) of 2-(1-acetyl-piperidin-3-ylmethylsulfanyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide in DCM (5 mL) were added 123 mg (0.72 mmol) of *m*-chloroperoxybenzoic acid. The reaction was stirred at room temperature until completion. Then 774 mg (2.4 mmol) of aminomethylene polystyrene were added to the reaction and the mixture was shaken for 18h. The resins were separated by filtration and rinsed with DCM. The filtrate was concentrated under reduced pressure and purified by mass triggered preparative LCMS (at neutral pH) to afford 34 mg of 2-(1-acetyl-piperidin-3-ylmethanesulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide.

Examples listed in Table 17, Method I were made according to this procedure.

Method J

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide (Example 127, Table 17)



Step 1: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethylsulfanyl)-2-methyl-propionamide

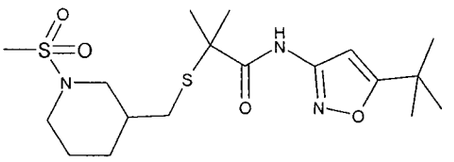
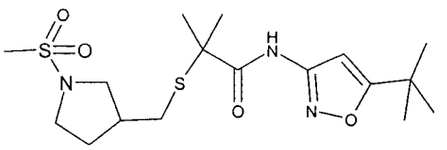
To a solution of 172 mg (0.52 mmol) of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(pyrrolidin-3-ylmethylsulfanyl)-propionamide (prepared according to Method I, step 1) and 0.18 mL (1.04 mmol) of N,N-diisopropylethylamine in THF were added 0.16 mL (2.11 mmol) of methanesulfonyl chloride. The reaction was heated within a microwave to 90 °C for 0.5 h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford 168 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethylsulfanyl)-2-methyl-propionamide, which was used in the next step without further purification.

According to this method, the following sulfonamides were synthesized.

Table 16

MOLSTRUCTURE	NAME	YIELD [%]	m/z [M+H$^+$]

50

	N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-piperidin-3-ylmethylsulfanyl)-2-methyl-propionamide	73	418
	N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethylsulfanyl)-2-methyl-propionamide	78	404

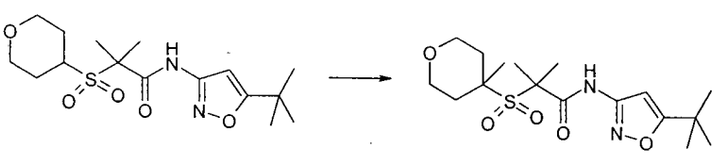
Step 2: Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide

To a solution of 168 mg (0.41 mmol) of N-(5-tert-butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethylsulfanyl)-2-methyl-propionamide in DCM (5 mL) were added 107 mg (0.63 mmol) of *m*-chloroperoxybenzoic acid. The reaction was stirred at room temperature until completion. Then 672 mg (2.08 mmol) of aminomethylene polystyrene were added to the reaction and the mixture was shaken for 18 h. The resins were separated by filtration and rinsed with DCM. The filtrate was concentrated under reduced pressure and the residue was purified by mass triggered preparative LCMS (at neutral pH) to afford 37 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide.

Examples listed in Table 17, Method J were made according to this procedure.

Method K

Synthesis of N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(4-methyl-tetrahydro-pyran-4-sulfonyl)-propionamide (Example 100, Table 17)

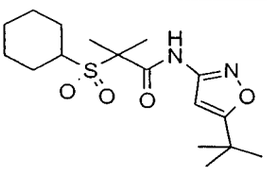
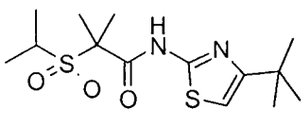
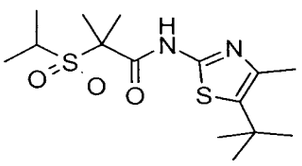
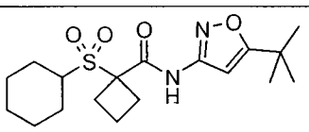
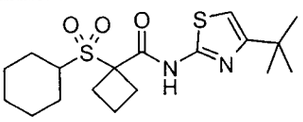
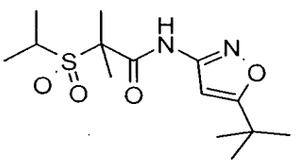
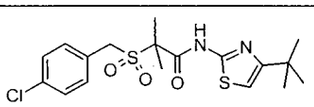


To a solution of 202 mg (0.56 mmol) of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (prepared according to Method E) in anhydrous THF (10 mL) at -78 °C under nitrogen atmosphere were added 0.8 mL (1.4 mmol) of lithium diisopropylamide (1.8 M solution in THF/heptane/ethylbenzene) and the reaction was stirred at -78 °C for 0.5 h. Then 0.1 mL (1.6 mmol) of methyl iodide were added in one portion and stirring was continued for further 0.5 h at -78 °C, before the reaction was warmed to room temperature. After 18 h at room temperature the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (25

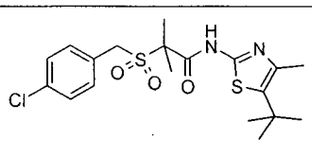
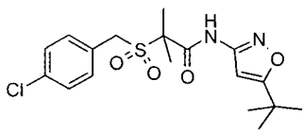
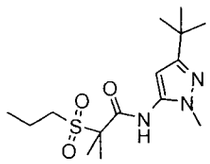
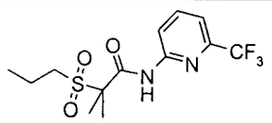
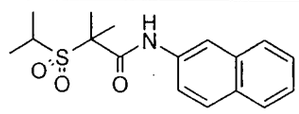
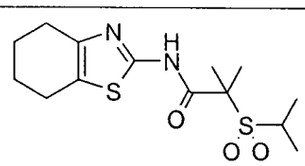
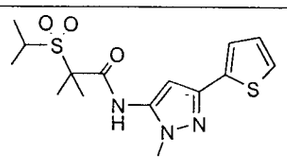
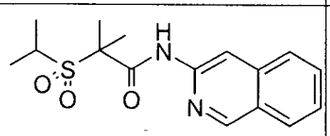
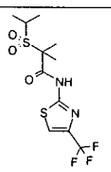
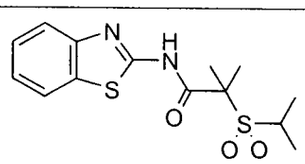
mL). The mixture was extracted with ethyl acetate (3 x 25 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue purified by mass-triggered preparative LCMS to afford 31 mg of N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-2-(4-methyl-tetrahydro-pyran-4-sulfonyl)-propionamide.

Examples listed in Table 17, Method K were made according to this procedure.

Table 17: Examples

#	MOLSTRUCTURE	NAME	m/z [M+H$^+$]	Method
1		N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide	357	A
2		N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	333	A
3		N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	347	A
4		1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	369	A
5		1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (4-tert-butyl-thiazol-2-yl)-amide	385	A
6		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	317	A
7		N-(4-tert-Butyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide	415/417	A

52

8		N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide	429/431	A
9		N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide	399/401	A
10		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	317	C
11		2-Methyl-2-(propane-1-sulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide	339	A
12		2-Methyl-N-naphthalen-2-yl-2-(propane-2-sulfonyl)-propionamide	320.25	A
13		2-Methyl-2-(propane-2-sulfonyl)-N-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-propionamide	331.35	A
14		2-Methyl-N-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-2-(propane-2-sulfonyl)-propionamide	356.21	A
15		N-Isoquinolin-3-yl-2-methyl-2-(propane-2-sulfonyl)-propionamide	321.27	A
16		2-Methyl-2-(propane-2-sulfonyl)-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide	345.13	A
17		N-Benzothiazol-2-yl-2-methyl-2-(propane-2-sulfonyl)-propionamide	327.23	A

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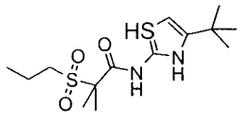
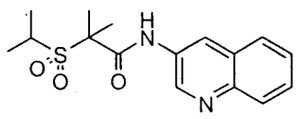
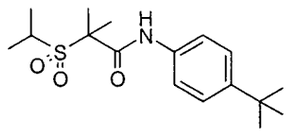
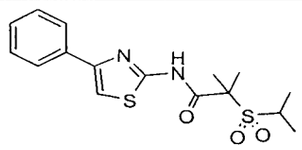
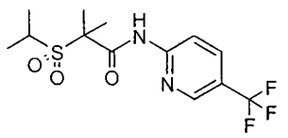
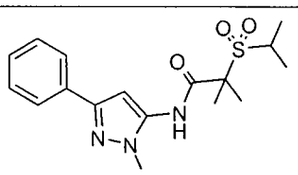
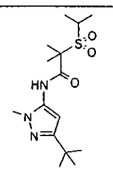
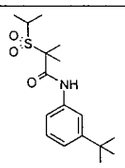
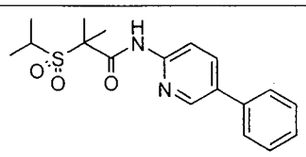
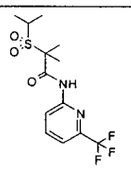
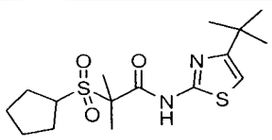
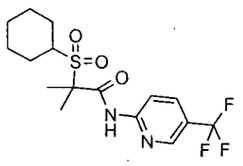
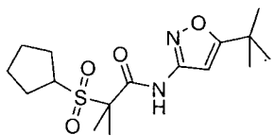
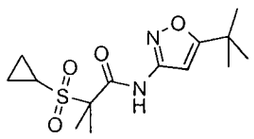
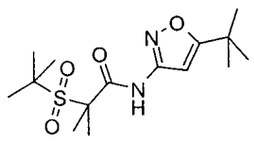
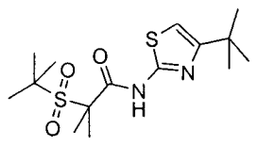
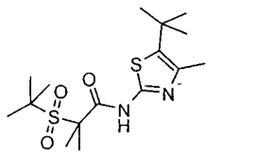
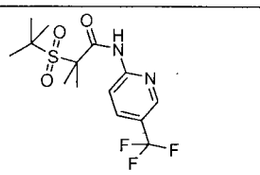
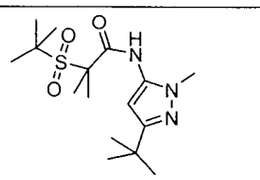
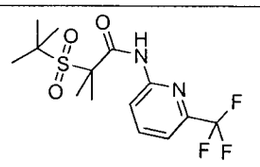
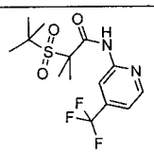
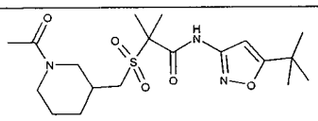
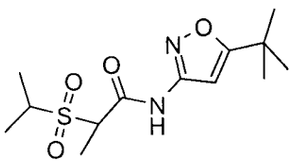
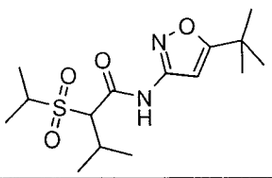
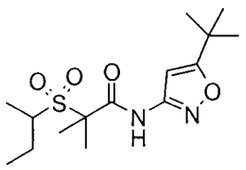
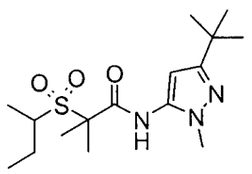
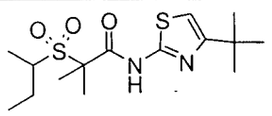
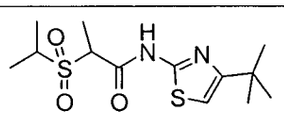
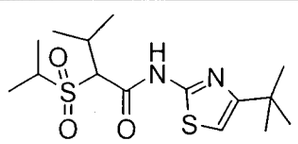
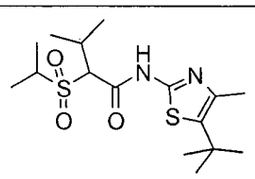
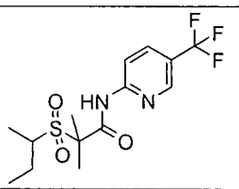
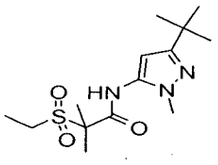
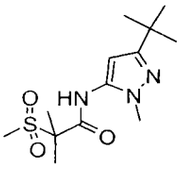
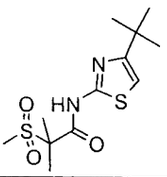
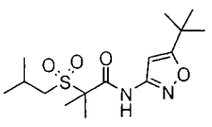
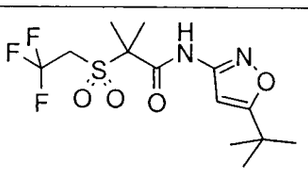
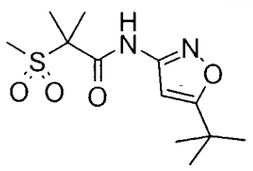
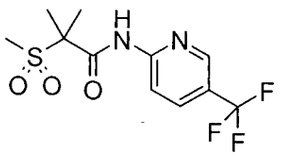
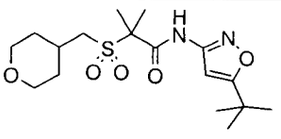
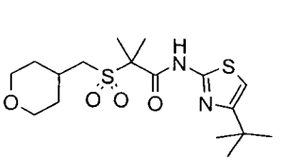
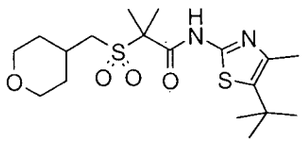
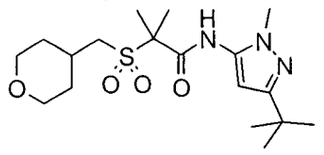
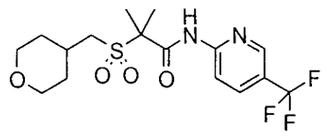
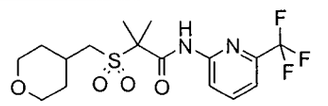
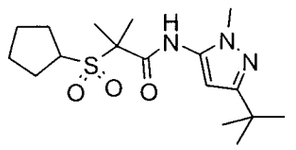
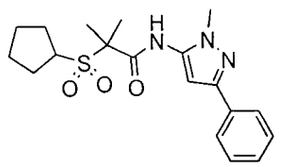
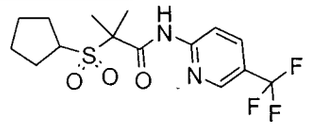
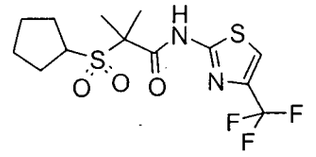
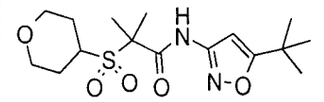
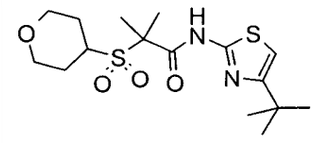
18		N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	333	A
19		2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-3-yl-propionamide	321.36	A
20		N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	326.27	A
21		2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(propane-2-sulfonyl)-propionamide	353.26	A
22		2-Methyl-2-(propane-2-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	339.23	A
23		2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(propane-2-sulfonyl)-propionamide	350.33	A
24		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	330.29	A
25		N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	326.27	A
26		2-Methyl-N-(5-phenyl-pyridin-2-yl)-2-(propane-2-sulfonyl)-propionamide	347.31	A
27		2-Methyl-2-(propane-2-sulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide	339.18	A

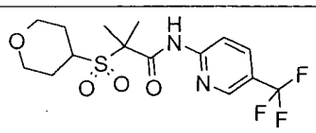
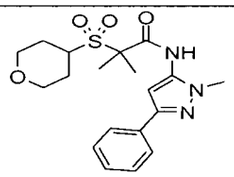
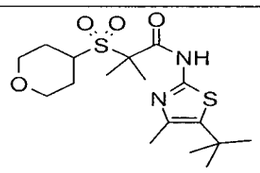
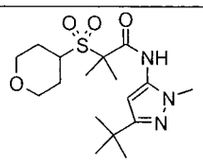
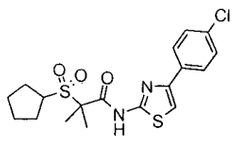
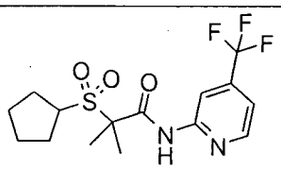
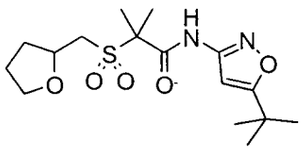
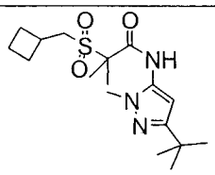
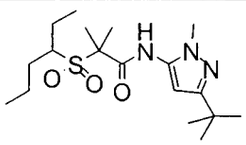
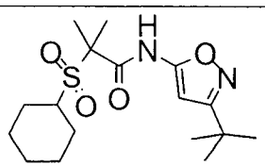
28		N-(4-tert-Butyl-thiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	359	A
29		2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	379	A
30		N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	343	A
31		N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropanesulfonyl-2-methyl-propionamide	315	C
32		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide	331	A
33		N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide	347	A
34		N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide	361	A
35		2-Methyl-2-(2-methyl-propane-2-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	353	A
36		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide	344	A
37		2-Methyl-2-(2-methyl-propane-2-sulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide	353	A

38		2-Methyl-2-(2-methyl-propane-2-sulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide	353	A
39		2-(1-Acetyl-piperidin-3-ylmethanesulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide	414	I
40		N-(5-tert-Butyl-isoxazol-3-yl)-2-(propane-2-sulfonyl)-propionamide	303	A
41		N-(5-tert-Butyl-isoxazol-3-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide	331	A
42		2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide	331	A
43		2-(Butane-2-sulfonyl)-N-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-propionamide	344	A
44		2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide	347	A
45		N-(4-tert-Butyl-thiazol-2-yl)-2-(propane-2-sulfonyl)-propionamide	319	A
46		N-(4-tert-Butyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide	347	A
47		N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide	361	A

48		2-(Butane-2-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	353	A
49		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-ethanesulfonyl-2-methyl-propionamide	316	A
50		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methanesulfonyl-2-methyl-propionamide	302	B
51		N-(4-tert-Butyl-thiazol-2-yl)-2-methanesulfonyl-2-methyl-propionamide	305	B
52		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide	331	D
53		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2,2,2-trifluoro-ethanesulfonyl)-propionamide	357	B
54		N-(5-tert-Butyl-isoxazol-3-yl)-2-methanesulfonyl-2-methyl-propionamide	289	B
55		2-Methanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	311	B
56		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	373	E
57		N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	389	E

58		N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	403	E
59		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	386	E
60		2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	395	E
61		2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide	395	E
62		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	356	A
63		2-Cyclopentanesulfonyl-2-methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-propionamide	376	A
64		2-Cyclopentanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	365	A
65		2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide	371	A
66		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	359	E
67		N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	375	E

58

68		2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	381	E
69		2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	392	E
70		N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	389	E
71		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	372	E
72		N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide	413/415	A
73		2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide	365	A
74		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide	359	F
75		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide	356	F
76		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(hexane-3-sulfonyl)-2-methyl-propionamide	372	F
77		N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide	357	A

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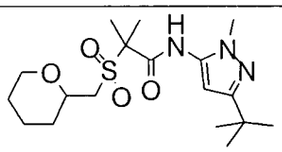
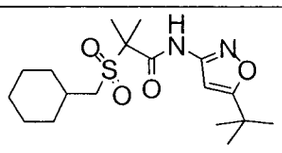
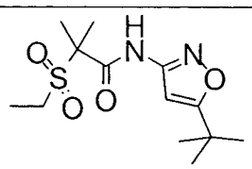
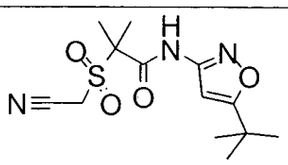
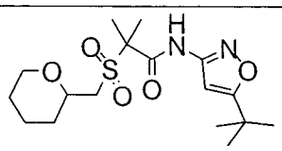
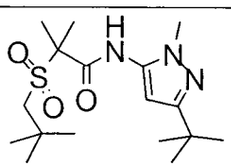
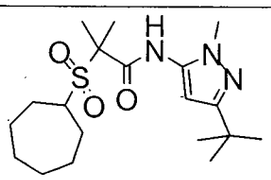
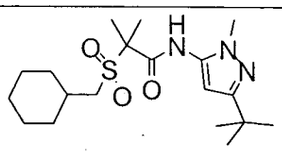
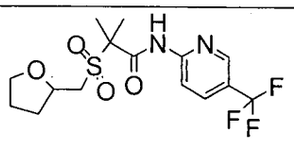
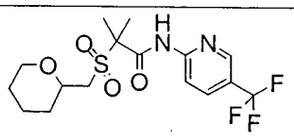
78		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide	386	G
79		N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide	371	G
80		N-(5-tert-Butyl-isoxazol-3-yl)-2-ethanesulfonyl-2-methyl-propionamide	303	G
81		N-(5-tert-Butyl-isoxazol-3-yl)-2-cyanomethanesulfonyl-2-methyl-propionamide	314	G
82		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide	373	G
83		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(2,2-dimethyl-propane-1-sulfonyl)-2-methyl-propionamide	358	G
84		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide	384	G
85		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide	384	G
86		2-Methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	381	G
87		2-Methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	395	G

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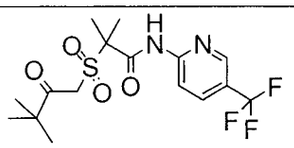
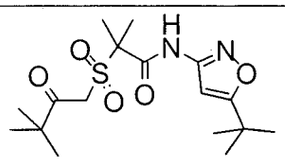
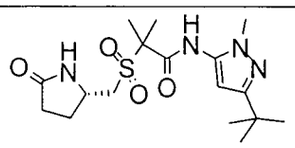
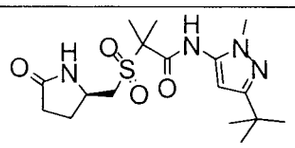
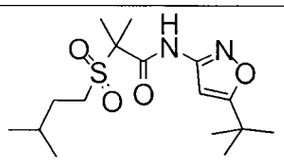
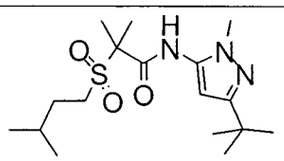
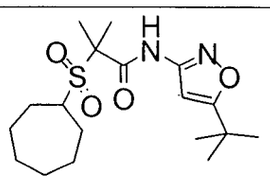
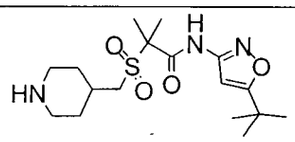
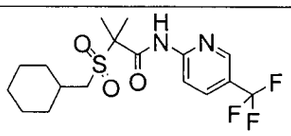
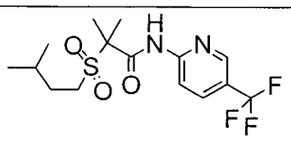
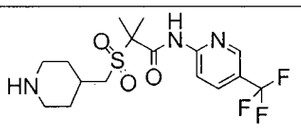
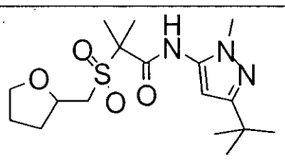
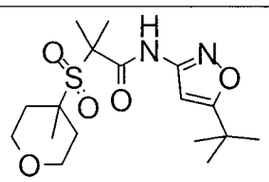
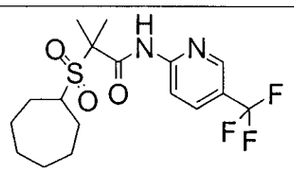
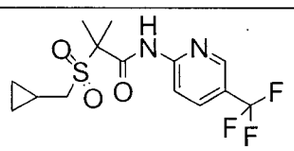
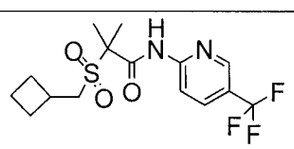
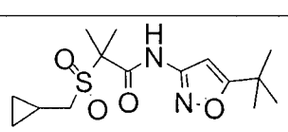
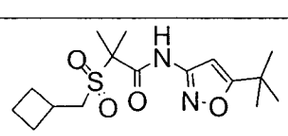
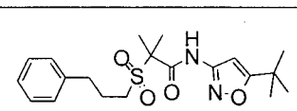
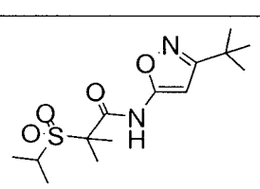
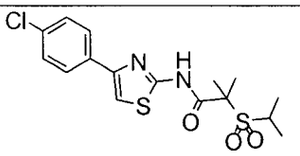
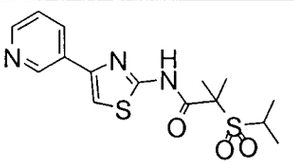
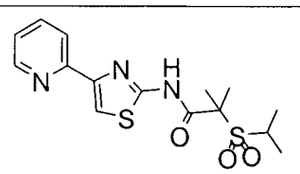
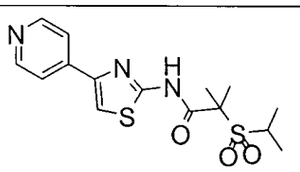
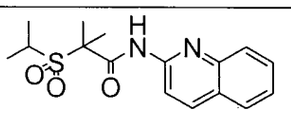
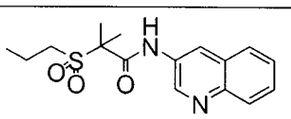
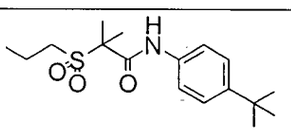
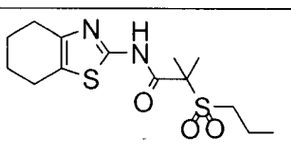
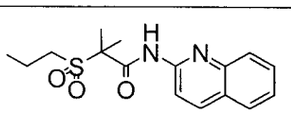
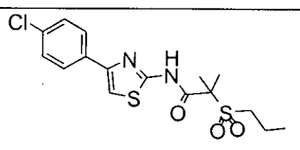
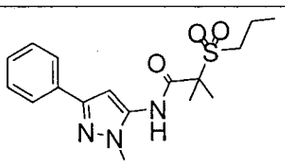
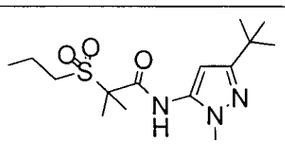
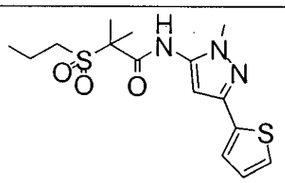
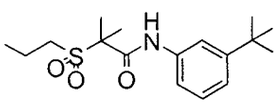
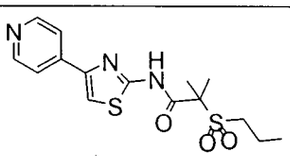
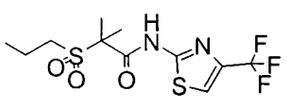
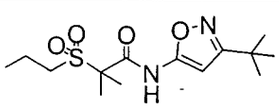
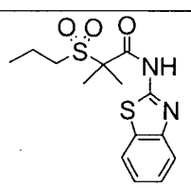
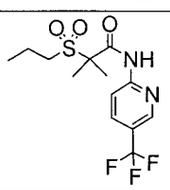
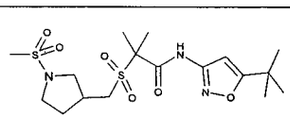
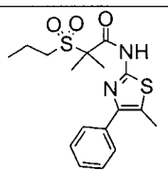
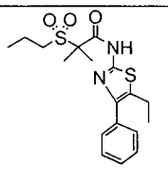
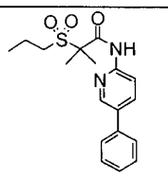
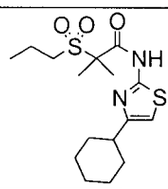
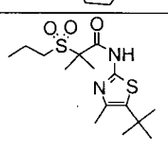
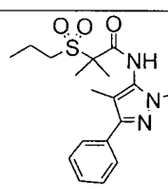
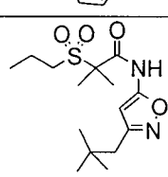
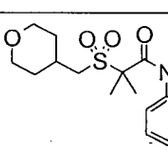
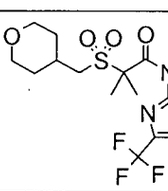
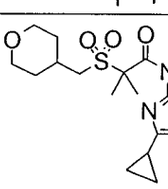
88		2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	395	G
89		N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide	373	G
90		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((S)-5-oxo-pyrrolidin-2-ylmethanesulfonyl)-propionamide	385	G
91		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((R)-5-oxo-pyrrolidin-2-ylmethanesulfonyl)-propionamide	385	G
92		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide	345	G
93		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide	358	G
94		N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide	371	G
95		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(piperidin-4-ylmethanesulfonyl)-propionamide	372	H
96		2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	393	G
97		2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	367	G

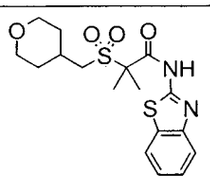
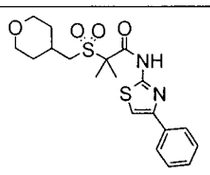
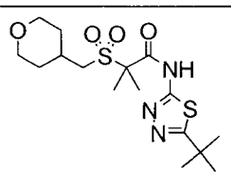
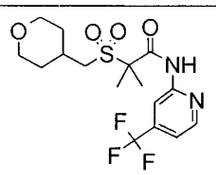
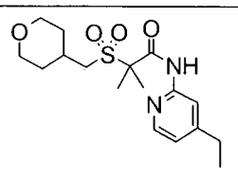
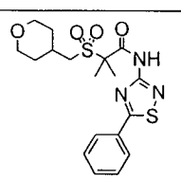
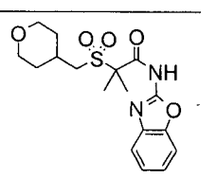
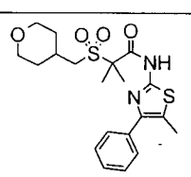
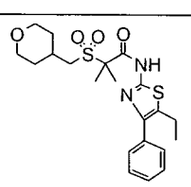
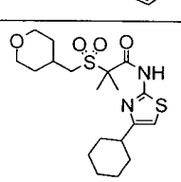
61

98		2-Methyl-2-(piperidin-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	394	H
99		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide	372	G
100		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(4-methyl-tetrahydro-pyran-4-sulfonyl)-propionamide	373	K
101		2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	393	G
102		2-Cyclopropylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	351	G
103		2-Cyclobutylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	365	G
104		N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide	329	G
105		N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide	343	G
106		N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-phenyl-propane-1-sulfonyl)-propionamide	393	G
107		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	317	A

108		N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide	387/389	A
109		2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-3-yl-thiazol-2-yl)-propionamide	354	A
110		2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-2-yl-thiazol-2-yl)-propionamide	354	A
111		2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-propionamide	354	A
112		2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-2-yl-propionamide	321	A
113		2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-3-yl-propionamide	321	A
114		N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	326	A
115		2-Methyl-2-(propane-1-sulfonyl)-N-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-propionamide	331	A
116		2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-2-yl-propionamide	321	A
1117		N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide	387/389	A

118		2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(propane-1-sulfonyl)-propionamide	350	A
119		N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	330	A
120		2-Methyl-N-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-2-(propane-1-sulfonyl)-propionamide	356	A
121		N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	326	A
122		2-Methyl-2-(propane-1-sulfonyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-propionamide	354	A
123		2-Methyl-2-(propane-1-sulfonyl)-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide	345	A
124		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	317	A
125		N-Benzothiazol-2-yl-2-methyl-2-(propane-1-sulfonyl)-propionamide	327	A
126		2-Methyl-2-(propane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	339	A
127		N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide	436	J

128		2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide	367	A
129		N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	381	A
130		2-Methyl-N-(5-phenyl-pyridin-2-yl)-2-(propane-1-sulfonyl)-propionamide	347	A
131		N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	359	A
132		N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	347	A
133		N-(2,4-Dimethyl-5-phenyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	364	A
134		N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide	331	A
135		N-(3-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	382	E
136		2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide	401	E
137		N-(4-Cyclopropyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	373	E

138		N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	383	E
139		2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	409	E
140		N-(5-tert-Butyl-[1,3,4]thiadiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	390	E
141		2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide	395	E
142		N-(4-Ethyl-pyridin-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	355	E
143		2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	410	E
144		N-Benzooxazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	367	E
145		2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	423	E
146		N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	437	E
147		N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	415	E

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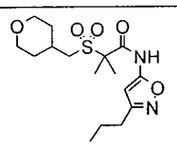
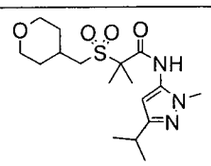
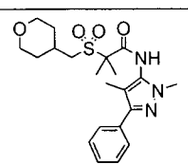
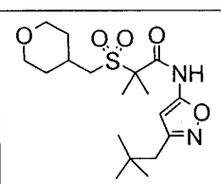
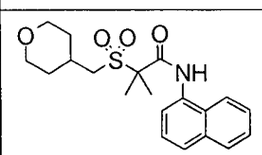
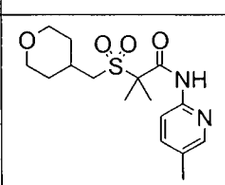
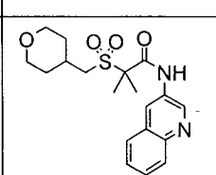
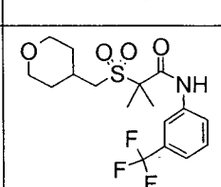
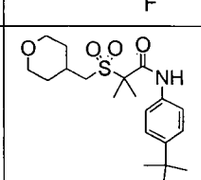
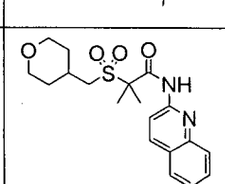
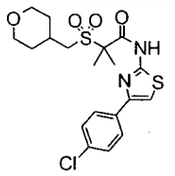
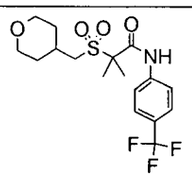
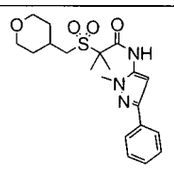
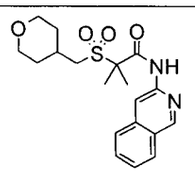
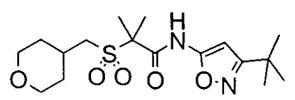
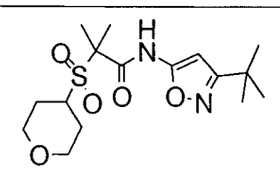
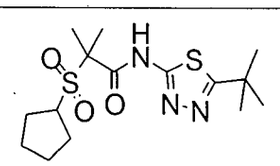
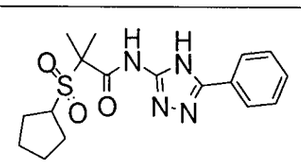
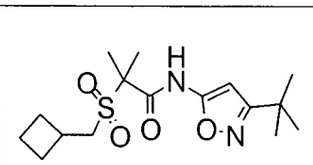
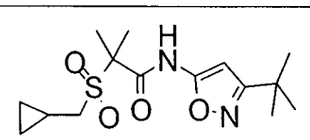
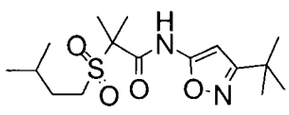
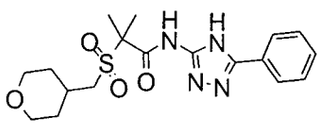
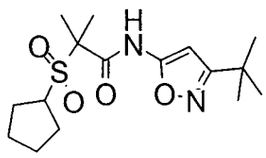
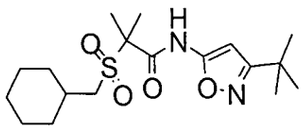
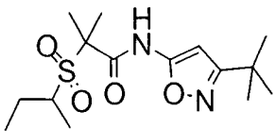
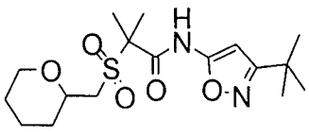
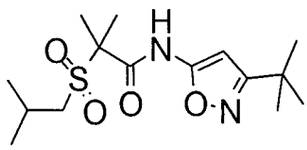
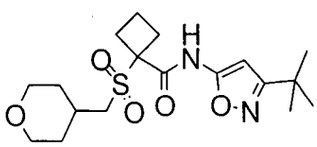
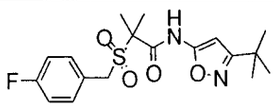
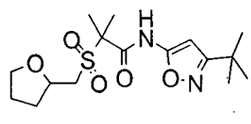
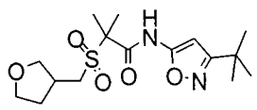
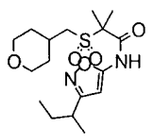
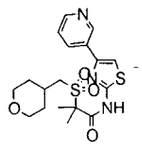
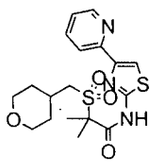
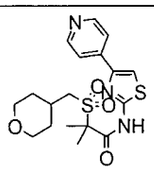
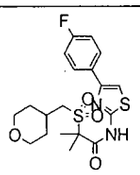
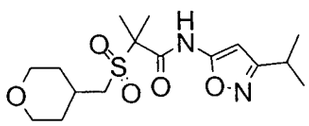
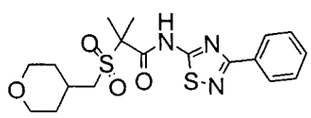
148		2-Methyl-N-(3-propyl-isoxazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	359	E
149		N-(5-Isopropyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	372	E
150		N-(2,4-Dimethyl-5-phenyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	420	E
151		N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	387	E
152		2-Methyl-N-naphthalen-1-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	376	E
153		2-Methyl-N-(5-methyl-pyridin-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	341	E
154		2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	377	E
155		2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(3-trifluoromethyl-phenyl)-propionamide	394	E
156		N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	382	E
157		2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	377	E

67

158		N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	443	E
159		2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-phenyl)-propionamide	394	E
160		2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	406	E
161		N-Isoquinolin-3-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	377	E
162		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	373	E
163		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	359	E
164		N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	360	A
165		2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide	363	A
166		N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide	343	G
167		N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide	329	G

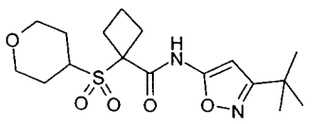
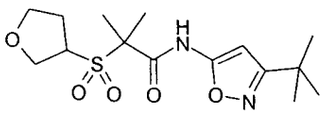
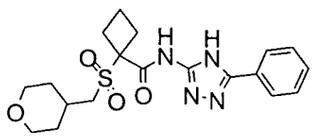
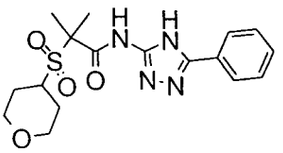
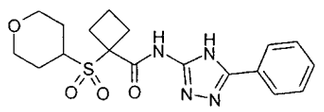
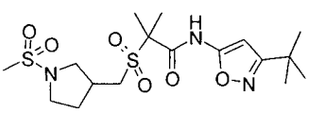
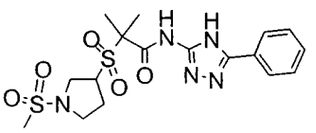
168		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide	345	G
169		2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	393	E
170		N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	343	A
171		N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide	371	G
172		2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide	331	G
173		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide	373	G
174		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide	331	G
175		1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	385	E
176		N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide	383	D
177		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide	359	G

178		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide	359	G
179		1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	373	E
180		2-Methyl-N-(4-pyridin-3-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	410	E
181		2-Methyl-N-(4-pyridin-2-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	410	E
182		2-Methyl-N-(4-pyridin-4-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	410	E
183		N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	427	E
184		N-(3-Isopropyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	359	E
185		2-Methyl-N-(3-phenyl-1,2,4-thiadiazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	410	E

The following compounds can also be made according the procedures described above:

Table 18: Examples

#	MOLSTRUCTURE	NAME

186		1-(Tetrahydro-pyran-4-sulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
187		N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-sulfonyl)-propionamide
188		1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (5-phenyl-4H-1,2,4-triazol-3-yl)-amide
189		2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-sulfonyl)-propionamide
190		1-(Tetrahydro-pyran-4-sulfonyl)-cyclobutanecarboxylic acid (5-phenyl-4H-1,2,4-triazol-3-yl)-amide
191		N-(3-tert-Butyl-isoxazol-5-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide
192		2-(1-Methanesulfonyl-pyrrolidine-3-sulfonyl)-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide

Assessment of Biological Properties

The biological properties of the compounds of the formula I were assessed using the assays described below.

A. Human CB1 and CB2 Receptor Binding:

Experimental Method:

CB2 membranes were purchased and made from HEK293 EBNA cells stably transfected with human CB2 receptor cDNA (Perkin Elmer Life and Analytical Sciences). CB1 membranes were isolated from HEK cells stably co-transfected with human CB1 receptor and Gα16

cDNA's. The membrane preparation was bound to scintillation beads (Ysi-Poly-L-lysine SPA beads, GE Healthcare) for 4 hours at room temperature in assay buffer containing 50mM Tris, pH 7.5, 2.5mM EDTA, 5mM $MgCl_2$, 0.8% fatty acid free Bovine Serum Albumin. Unbound membrane was removed by washing in assay buffer. Membrane–bead mixture was added to 96-well assay plates in the amounts of 15ug membrane per well (CB2) or 2.5ug per well (CB1) and 1mg SPA bead per well. Compounds were added to the membrane–bead mixture in dose-response concentrations ranging from 1x 10^{-5} M to 1x10^{-10} M with 0.25% DMSO, final. The competition reaction was initiated with the addition of ^{3}H-CP55940 (Perkin Elmer Life and Analytical Sciences) at a final concentration of 1.5nM (CB2) or 2.5nM (CB1). The reaction was incubated at room temperature for 18hours and read on TopCount NXT plate reader. Total and non-specific binding was determined in the absence and presence of 1.25uM Win 55212 (Sigma). IC50 values for each compound were calculated as the concentration of compound that inhibits the specific binding of the radioactively labeled ligand to the receptor by 50% using the XLFit 4.1 four parameter logistic model. IC50 values were converted to inhibition constant (Ki) values using Cheng-Prusoff equation.

B. CB2R mediated modulation of cAMP synthesis:

Compounds of the invention were evaluated for their CB2 agonist or inverse agonistic activity in accordance with the following experimental method. Compounds which were shown to bind to CB2 by the binding assay described above but which were not shown to exhibit CB2R-mediated modulation of cAMP synthesis by this assay were presumed to be CB2 antagonists.

Experimental Method:

CHO cells expressing human CB2R (Euroscreen) were plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells were treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay was incubated for 30 minutes at 37°C. Cells were lysed and the cAMP concentration was measured using DiscoverX –XS cAMP kit, following the manufacturer's protocol. In this setting, agonists will decrease forskolin induced production of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists were calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The EC50 value of each test compound was determined as the concentration at which 50% of the forskolin-stimulated cAMP synthesis was inhibited. Data was analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

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C. CB1R mediated modulation of cAMP synthesis:

Compounds of the invention were evaluated for their CB1 agonist or inverse agonistic activity in accordance with the following experimental method. Compounds which were shown to bind to CB1 by the binding assay described above but which were not shown to exhibit CB1R-mediated modulation of cAMP synthesis by this assay were presumed to be CB1 antagonists.

Experimental Method:

CHO cells expressing human CB1R (Euroscreen) were plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells were treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay was incubated for 30 minutes at 37°C. Cells were lysed and the cAMP concentration was measured using DiscoverX –XS cAMP kit, following the manufacturer's protocol. In this setting, agonists will decrease forskolin induced production of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists were calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The EC50 value of each test compound was determined as the concentration at which 50% of the forskolin-stimulated cAMP synthesis was inhibited. Data was analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

Compounds Having Agonist Activity

NAME	**CB2 EC_{50} [nM]**
N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide	0.2
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide	25.8
1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide	0.5
1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (4-tert-butyl-thiazol-2-yl)-amide	11.7
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide	12.1
N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide	16.6
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	61.9
N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	19.2

N-(4-tert-Butyl-thiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	19.0
2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	11.8
N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	2.4
N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide	61.1
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide	10.7
2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide	18.7
2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide	14.4
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide	44.6
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	4.5
N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	23.0
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	0.2
2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	72.3
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	0.7
N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	12.4
2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	62.4
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	0.3
N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide	1.5
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide	70.5
N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide	33.0
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide	0.0
N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide	0.6
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide	0.2
N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide	6.5
N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide	23.8
2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-	41.5

propionamide	
N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide	39.8
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide	0.2
N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide	15.4
N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide	0.1
2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	15.4
2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	19.9
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(4-methyl-tetrahydro-pyran-4-sulfonyl)-propionamide	9.4
2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide	7.1
N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide	34.3
N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide	3.4
N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide	44.9
N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	12.3
N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide	13.0
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	89.7
N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide	44.1
2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide	52.2
N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	10.8
N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	31.1
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide	7.2
N-(3-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	14.3
N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	27.9
2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	7.1
2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	17.6
2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	2.5
N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	2.0

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	8.3
N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	74.3
2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	86.0
N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	3.3
2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	5.8
N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	2.2
N-Isoquinolin-3-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	99.1
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	4.0
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide	0.1
N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	18.6
2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide	3.8
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide	3.7
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide	12.5
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide	0.04
2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	1.7
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide	0.9
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide	0.1
2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide	3.3
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide	0.2
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide	1.6
1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide	6.2
N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide	17.0
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide	31.5
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide	18.5
N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	20.0

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N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide	5.5

Through the use of the above described assays the following compounds were found to exhibit agonistic activity and thus to be particularly well suited for the treatment of pain as well as for the treatment of inflammation.

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide
N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide
1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide
1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (4-tert-butyl-thiazol-2-yl)-amide
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide
N-(4-tert-Butyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide
N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide
N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide
2-Methyl-2-(propane-1-sulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide
2-Methyl-N-naphthalen-2-yl-2-(propane-2-sulfonyl)-propionamide
2-Methyl-2-(propane-2-sulfonyl)-N-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-propionamide
2-Methyl-N-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-2-(propane-2-sulfonyl)-propionamide
N-Isoquinolin-3-yl-2-methyl-2-(propane-2-sulfonyl)-propionamide
N-Benzothiazol-2-yl-2-methyl-2-(propane-2-sulfonyl)-propionamide
N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide
2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-3-yl-propionamide
N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide
2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(propane-2-sulfonyl)-propionamide
2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(propane-2-sulfonyl)-propionamide
N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide
N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide
2-Methyl-2-(propane-2-sulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide
N-(4-tert-Butyl-thiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide
2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

2-Methyl-2-(2-methyl-propane-2-sulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(2-methyl-propane-2-sulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

2-(1-Acetyl-piperidin-3-ylmethanesulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

2-(Butane-2-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-ethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methanesulfonyl-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2,2,2-trifluoro-ethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(hexane-3-sulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-ethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyanomethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(2,2-dimethyl-propane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-Methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((S)-5-oxo-pyrrolidin-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((R)-5-oxo-pyrrolidin-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(piperidin-4-ylmethanesulfonyl)-propionamide

2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(piperidin-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(4-methyl-tetrahydro-pyran-4-sulfonyl)-propionamide

2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopropylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclobutylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-phenyl-propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-3-yl-thiazol-2-yl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-2-yl-thiazol-2-yl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-2-yl-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-3-yl-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-2-yl-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-N-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-N-(5-phenyl-pyridin-2-yl)-2-(propane-1-sulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(2,4-Dimethyl-5-phenyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide

N-(4-Cyclopropyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-[1,3,4]thiadiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

N-(4-Ethyl-pyridin-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-Benzooxazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(3-propyl-isoxazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-Isopropyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(2,4-Dimethyl-5-phenyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-naphthalen-1-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-methyl-pyridin-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(3-trifluoromethyl-phenyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-phenyl)-propionamide

2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-Isoquinolin-3-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

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N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide

N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide

N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-3-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-2-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-4-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-Isopropyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(3-phenyl-1,2,4-thiadiazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

Of the above compounds, the following are preferred:

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(hexane-3-sulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-Methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopropylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclobutylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-2-yl-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-3-yl-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-2-yl-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-[1,3,4]thiadiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(3-propyl-isoxazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(3-trifluoromethyl-phenyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-phenyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide

N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide

N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

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2-Methyl-N-(4-pyridin-3-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-2-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-4-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

Of the above compounds, the following are most preferred:

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide

N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide

N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

Therapeutic Use

As can be demonstrated by the assays described above, the compounds of the invention are useful in modulating the CB2 receptor function. By virtue of this fact, these compounds have therapeutic use in treating disease-states and conditions mediated by the CB2 receptor function or that would benefit from modulation of the CB2 receptor function.

As the compounds of the invention modulate the CB2 receptor function, they have very useful anti-inflammatory and immune-suppressive activity and they can be used in patients as drugs, particularly in the form of pharmaceutical compositions as set forth below, for the treatment of disease-states and conditions.

As noted before, those compounds which are CB2 agonists can also be employed for the treatment of pain.

The agonist, antagonist and inverse agonist compounds according to the invention can be used in patients as drugs for the treatment of the following disease-states or indications that are accompanied by inflammatory processes:

(i) Lung diseases: e.g. asthma, bronchitis, allergic rhinitis, emphysema, adult respiratory distress syndrome (ARDS), pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease (COPD), asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced bronchoconstriction, occupational asthma, viral- or bacterial exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome", pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis;

(ii) Rheumatic diseases or autoimmune diseases or musculoskeletal diseases: all forms of rheumatic diseases, especially rheumatoid arthritis, acute rheumatic fever, and polymyalgia rheumatica; reactive arthritis; rheumatic soft tissue diseases; inflammatory soft tissue diseases of other genesis; arthritic symptoms in degenerative joint diseases

(arthroses); tendinitis, bursitis, osteoarthritis, traumatic arthritis; collagenoses of any genesis, e.g., systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, Sjögren syndrome, Still disease, Felty syndrome; and osteoporosis and other bone resorption diseases;

(iii) Allergic diseases: all forms of allergic reactions, e.g., angioneurotic edema, hay fever, insect bites, allergic reactions to drugs, blood derivatives, contrast agents, etc., anaphylactic shock (anaphylaxis), urticaria, angioneurotic edema, and contact dermatitis;

(iv) Vascular diseases: panarteritis nodosa, polyarteritis nodosa, periarteritis nodosa, arteritis temporalis, Wegner granulomatosis, giant cell arthritis, atherosclerosis, reperfusion injury and erythema nodosum;

(v) Dermatological diseases: e.g. dermatitis, psoriasis; sunburn, burns, eczema;

(vi) Renal diseases: e.g. nephrotic syndrome; and all types of nephritis, e.g., glomerulonephritis; pancreatits;

(vii) Hepatic diseases: e.g. acute liver cell disintegration; acute hepatitis of various genesis, e.g., viral, toxic, drug-induced; and chronically aggressive and/or chronically intermittent hepatitis;

(viii) Gastrointestinal diseases: e.g. inflammatory bowel diseases, irritable bowel syndrome, regional enteritis (Crohns disease), colitis ulcerosa; gastritis; aphthous ulcer, celiac disease, regional ileitis, gastroesophageal reflux disease;

(ix) Neuroprotection: e.g. in the treatment of neurodegeneration following stroke; cardiac arrest; pulmonary bypass; traumatic brain injury; spinal cord injury or the like;

(x) Eye diseases: allergic keratitis, uveitis, or iritis; conjunctivitis; blepharitis; neuritis nervi optici; choroiditis; glaucoma and sympathetic ophthalmia;

(xi) Diseases of the ear, nose, and throat (ENT) area: e.g. tinnitus; allergic rhinitis or hay fever; otitis externa; caused by contact eczema, infection, etc.; and otitis media;

(xii) Neurological diseases: e.g. brain edema, particularly tumor-related brain edema; multiple sclerosis; acute encephalomyelitis; meningitis; acute spinal cord injury; trauma; dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease; Parkinson's disease and Creutzfeldt-Jacob disease; Huntington's chorea, Pick's disease; motor neuron disease), vascular dementia (including multi-infarct dementia) as well as dementia associated with intracranial space occupying lesions; infections and related conditions (including HIV infection); Guillain-Barre syndrome; myasthenia gravis, stroke; and various forms of seizures, e.g., nodding spasms;

(xiii) Blood diseases: acquired hemolytic anemia; aplastic anemia, and idiopathic thrombocytopenia;

(xiv) Tumor diseases: acute lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases,;

(xv) Endocrine diseases: endocrine ophthalmopathy; endocrine orbitopathia; thyrotoxic crisis; Thyroiditis de Quervain; Hashimoto thyroiditis; Morbus Basedow; granulomatous thyroiditis; struma lymphomatosa; and Graves disease; type I diabetes (insulin-dependent diabetes);

(xvi) Organ and tissue transplantations and graft-versus-host diseases;

(xvii) Severe states of shock, e.g., septic shock, anaphylactic shock, and systemic inflammatory response syndrome (SIRS);

(xviii) Acute pain such as dental pain, perioperative, post-operative pain, traumatic pain, muscle pain, pain in burned skin, sun burn, trigeminal neuralgia, sun burn; spasm of the gastrointestinal tract or uterus, colics;

(xix) Visceral pain such as pain associated with chronic pelvic pain, pancreatitis, peptic ulcer, interstitial cystitis, renal colic, angina, dysmenorrhoea, menstruation, gynaecological pain, irritable bowel syndrome (IBS), non-ulcer dyspepsia, non-cardiac chest pain, myocardial ischemia;

(xx) Neuropathic pain such as low back pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve injury, acquired immune deficiency syndrome (AIDS) related neuropathic pain, head trauma, painful traumatic mononeuropathy, toxin and chemotherapy induced pain, phantom limb pain, painful polyneuropathy, thalamic pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, stump pain, repetitive motion pain, pain induced by post mastectomy syndrome, multiple sclerosis, root avulsions, postthoracotomy syndrome, neuropathic pain associated hyperalgesia and allodynia.

(xxi) Inflammatory/nociceptive pain induced by or associated with disorders such as osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis, gout, vulvodynia, myofascial pain (muscular injury, fibromyalgia), tendonitis, osteoarthritis, juvenile arthritis, spondylitis, gouty arthritis, psoriatic arthritis, muscoskeletal pain, fibromyalgia, sprains and strains, sympathetically maintained pain, myositis, pain associated with migraine, toothache, influenza and other viral infections such as the common cold, rheumatic fever, systemic lupus erythematosus;

(xxii) Cancer pain induced by or associated with tumors such as lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases;

(xxiii) Headache such as cluster headache, migraine with and without aura, tension type headache, headache with different origins, headache disorders including prophylactic and acute use;

(xxiv) various other disease-states or conditions including, restenosis following percutaneous transluminal coronary angioplasty, acute and chronic pain, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis, pyrexia. edema resulting from trauma associated with bums, sprains or fracture, cerebral oedema and angioedema, Diabetes such as diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hypergiycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion).

Other indications include: epilepsy, septic shock e.g. as antihypovolemic and/or antihypotensive agents, cancer, sepsis, osteoporosis, benign prostatic hyperplasia and hyperactive bladder, pruritis, vitiligo, general gastrointestinal disorders, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, tissue damage and postoperative fever, syndromes associated with Itching.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like.

For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

Combination Therapy

These compounds may also be employed in combination therapies with the following compounds:

non-steroidal antiinfiammatory drugs (NSAIDs) including COX-2 inhibitors such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenhufen, fenoprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (meclofenamic acid, mefe- namic acid, and tolfenamic acid), biphenyl- carboxylic acid derivatives, oxicams (isoxicam, meloxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone), and the coxibs (celecoxib, valecoXID, rofecoxib and etoricoxib);

opiate receptor agonists such as morphine, propoxyphene (Darvon), tramadol, buprenorphin;

sodium channel blockers such as carbamazepine, mexiletine, lamotrigine, pregabaline, tectin, NW-1029, CGX-1002;

N-type calcium channel blockers such as Ziconotide, NMED-160, SPI-860;
serotonergic and noradrenergic modulators such as SR-57746, paroxetine, duloxetine, clonidine, amitriptyline, citalopram;

corticosteroids such as betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone;

histamine H1 receptor antagonists such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdiazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, desloratadine, fexofenadine and levocetirizine;

histamine H2 receptor antagonists such as cimetidine, famotidine and ranitidine;

proton pump inhibitors such as omeprazole, pantoprazole and esomeprazole;

leukotriene antagonists and 5-lipoxygenase inhibitors such as zafirlukast, montelukast, pranlukast and zileuton;

local anesthetics such as ambroxol, lidocaine;

VR1 agonists and antagonists such as NGX-4010, WL-1002, ALGRX-4975, WL-10001, AMG-517;

nicotinic acetylcholine receptor agonists such as ABT-202, A-366833, ABT-594; BTG-102, A-85380, CGX1204;

P2X3 receptor antagonists such as A-317491, ISIS-13920, AZD-9056;

NGF agonists and antagonists such as RI-724, RI-1024, AMG-819, AMG-403, PPH 207;

NK1 and NK2 antagonists such as DA-5018, R-116301; CP-728663, ZD-2249;

NMDA antagonist such as NER-MD-11, CNS-5161, EAA-090, AZ-756, CNP-3381;

potassium channel modulators such as CL-888, ICA-69673, retigabine;

GABA modulators such as lacosamide;

serotonergic and noradrenergic modulators such as SR-57746, paroxetine, duloxetine, clonidine, amitriptyline, citalopram, flibanserin; and

combination with anti-migraine drugs like sumatriptan, zolmitriptan, naratriptan, eletriptan.

General Administration and Pharmaceutical Compositions

When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased inhibitory activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally,

or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by *Remington: The Science and Practice of Pharmacy*, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; *Handbook of Pharmaceutical Additives*, Michael & Irene Ash (eds.), Gower, 1995; *Handbook of Pharmaceutical Excipients*, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art.

As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that is required for the formulation to be efficacious.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Injectable pharmaceutical formulations are commonly based upon injectable sterile saline, phosphate-buffered saline, oleaginous suspensions, or other injectable carriers known in the art and are generally rendered sterile and isotonic with the blood. The injectable pharmaceutical formulations may therefore be provided as a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, including 1,3-butanediol, water, Ringer's solution, isotonic sodium chloride

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solution, fixed oils such as synthetic mono- or diglycerides, fatty acids such as oleic acid, and the like. Such injectable pharmaceutical formulations are formulated according to the known art using suitable dispersing or setting agents and suspending agents. Injectable compositions will generally contain from 0.1 to 5% w/w of a compound of the invention.

Solid dosage forms for oral administration of the compounds include capsules, tablets, pills, powders, and granules. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such solid pharmaceutical formulations may include formulations, as are well-known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms, which include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form.

Liquid dosage forms for oral administration of the compounds include emulsions, microemulsions, solutions, suspensions, syrups, and elixirs, optionally containing pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like. These compositions can also contain additional adjuvants such as wetting, emulsifying, suspending, sweetening, flavoring, and perfuming agents.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, eye ointments, eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. Topical application may be once or more than once per day depending upon the usual medical considerations. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation, more usually they will form up to about 80% of the formulation.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Such patches suitably contain a compound of the invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%.

For administration by inhalation, the compounds of the invention are conveniently delivered in the form of an aerosol spray from a pump spray device not requiring a propellant gas or from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide, or other suitable gas. In any case, the aerosol spray dosage unit may be determined by providing a valve to deliver a metered amount so that the resulting metered dose inhaler (MDI) is used to administer the compounds of the invention in a reproducible and controlled way. Such inhaler, nebulizer, or atomizer devices are known in the prior art, for example, in PCT International Publication Nos. WO 97/12687 (particularly Figure 6 thereof, which is the basis for the commercial RESPIMAT® nebulizer); WO 94/07607; WO 97/12683; and WO 97/20590, to which reference is hereby made and each of which is incorporated herein by reference in their entireties.

Rectal administration can be effected utilizing unit dose suppositories in which the compound is admixed with low-melting water-soluble or insoluble solids such as fats, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, or fatty acid esters of polyethylene glycols, or the like. The active compound is usually a minor component, often from about 0.05 to 10% by weight, with the remainder being the base component.

In all of the above pharmaceutical compositions, the compounds of the invention are formulated with an acceptable carrier or excipient. The carriers or excipients used must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the patient. The carrier or excipient can be a solid or a liquid, or both, and is preferably formulated with the compound of the invention as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of

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the active compound. Such carriers or excipients include inert fillers or diluents, binders, lubricants, disintegrating agents, solution retardants, resorption accelerators, absorption agents, and coloring agents. Suitable binders include starch, gelatin, natural sugars such as glucose or β-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Pharmaceutically acceptable carriers and excipients encompass all the foregoing additives and the like.

Examples of Pharmaceutical Formulations

A. TABLETS	
Component	**Amount per tablet (mg)**
active substance	100
lactose	140
corn starch	240
polyvinylpyrrolidone	15
magnesium stearate	5
TOTAL	500

The finely ground active substance, lactose, and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B. TABLETS	
Component	**Amount per tablet (mg)**
active substance	80
lactose	55
corn starch	190
polyvinylpyrrolidone	15

magnesium stearate	2
microcrystalline cellulose	35
sodium-carboxymethyl starch	23
TOTAL	400

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose, and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C. COATED TABLETS	
Component	**Amount per tablet (mg)**
active substance	5
lactose	30
corn starch	41.5
polyvinylpyrrolidone	3
magnesium stearate	0.5
TOTAL	90

The active substance, corn starch, lactose, and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

D. CAPSULES	
Component	**Amount per capsule (mg)**
active substance	50
corn starch	268.5
magnesium stearate	1.5
TOTAL	320

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The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

E. AMPOULE SOLUTION	
Component	**Amount per ampoule**
active substance	50 mg
sodium chloride	50 mg
water for inj.	5 mL

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilized and sealed by fusion. The ampoules contain 5 mg, 25 mg, and 50 mg of active substance.

F. SUPPOSITORIES	
Component	**Amount per suppository (mg)**
active substance	50
solid fat	1650
TOTAL	1700

The hard fat is melted. At 40°C, the ground active substance is homogeneously dispersed therein. The mixture is cooled to 38°C and poured into slightly chilled suppository molds.

G. METERING AEROSOL	
Component	**Amount**
active substance	0.005
sorbitan trioleate	0.1
Monofluorotrichloromethane and difluorodichloromethane (2:3)	To 100

The suspension is transferred into a conventional aerosol container with a metering valve. Preferably, 50 µL of suspension are delivered per spray. The active substance may also be metered in higher doses if desired (e.g., 0.02% by weight).

H. POWDER FOR INHALATION	
Component	**Amount**
active substance	1.0 mg
lactose monohydrate	to 25 mg

I. POWDER FOR INHALATION	
Component	**Amount**
active substance	2.0 mg
lactose monohydrate	to 25 mg

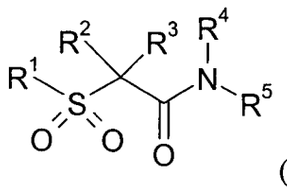
J. POWDER FOR INHALATION	
Component	**Amount**
active substance	1.0 mg
lactose monohydrate	to 5 mg

K. POWDER FOR INHALATION	
Component	**Amount**
active substance	2.0 mg
lactose monohydrate	to 5 mg

In Examples H, I, J, and K, the powder for inhalation is produced in the usual way by mixing the individual ingredients together.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



(I)

wherein:

R^1 is C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, 3-10 membered saturated heterocyclic ring, benzyl or phenethyl each optionally independently substituted with 1-3 substituents chosen from C_{1-10} alkyl optionally substituted with 1 to 3 halogen atoms, C_{3-10} cycloalkyl, 3-10 membered saturated heterocyclic ring optionally substituted with acyl, oxo or methyl sulfone, acyl, cyano, phenyl, oxo, hydroxyl and halogen;

R^2 and **R^3** are independently hydrogen or C_1-C_6 alkyl; or R^2 and R^3 together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or heterocyclic ring;

R^4 is hydrogen or methyl;

R^5 is aryl or heteroaryl each optionally independently substituted with 1 to 3 substituents chosen from C_1-C_6 alkyl optionally substituted with 1 to 3 halogen atoms or with a heterocyclyl group, C_1-C_6 alkoxy optionally substituted with 1 to 3 halogen atoms, C_3-C_6 cycloalkyl, phenoxy, halogen, cyano, dimethylaminoC_1-C_4alkyl, phenyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen, thienyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen and pyridinyl optionally substituted with 1 to 2 C_1-C_4 alkyl optionally substituted with halogen;

or a tautomer or pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein

$\mathbf{R^1}$ is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyranyl, bicylco(3.3.0)octanyl, bicyclo[4.3.0]nonyl, benzyl or phenethyl each optionally independently substituted with 1 to 3 substituents chosen from methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl (optionally substituted with acyl, oxo or methylsulfonyl), piperidinyl (optionally substituted with acyl, oxo or methylsulfone, acyl, cyano, phenyl, oxo, fluoro, chloro, bromo and hydroxyl, ;

$\mathbf{R^2}$ and $\mathbf{R^3}$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl, or R^2 and R^3 together with the carbon to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or tetrahydropyranyl ring;

$\mathbf{R^4}$ is hydrogen;

$\mathbf{R^5}$ is phenyl, naphthyl, pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, indolyl, benzoxazolyl, benzopyrazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzimidazolyl, tetrahydrobenzoxazolyl, tetrahydrobenzothiazolyl or tetrahydrobenzimidazolyl each optionally independently substituted with 1 to 3 substituents chosen from C_1-C_6 alkyl optionally substituted with 1 to 3 halogen atoms, C_1-C_6 alkoxy optionally substituted with 1 to 3 halogen atoms, C_3-C_6 cycloalkyl, phenoxy, halogen, cyano, dimethylaminoC_1-C_4alkyl, phenyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen, thienyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen and pyridinyl optionally substituted with 1 to 2 C_1-C_4 alkyl optionally substituted with halogen.

3. The compound according to claim 2 wherein

$\mathbf{R^1}$ is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyranyl, , bicylco(3.3.0)octanyl, or bicyclo[4.3.0]nonyl each optionally independently substituted with 1 to 3 substituents chosen from methyl, ethyl, pivaloyl, cyclopropyl, cyclobutyl, cyclohexyl, tetrahydropyranyl, tetrahydrofuranyl,

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pyrrolidinyl optionally substituted with methylsulfone, fluoro, chloro, bromo, oxo and hydroxy;

$\mathbf{R^2}$ and $\mathbf{R^3}$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, isobutyl, tert-butyl, or R^2 and R^3 together with the carbon to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or tetrahydropyranyl ring;

$\mathbf{R^4}$ is hydrogen;

$\mathbf{R^5}$ is phenyl, naphthyl, pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, indolyl, benzoxazolyl, benzopyrazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzimidazolyl, tetrahydrobenzoxazolyl, tetrahydrobenzothiazolyl, or tetrahydrobenzimidazolyl each optionally independently substituted with 1 to 3 substituents chosen from C_1-C_6 alkyl optionally substituted with 1 to 3 halogen atoms, C_1-C_6 alkoxy optionally substituted with 1 to 3 halogen atoms, C_3-C_6 cycloalkyl, phenoxy, halogen, cyano, dimethylaminoC_1-C_4alkyl, phenyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen, thienyl optionally substituted with 1 to 2 halogen atoms or C_1-C_4 alkyl optionally substituted with halogen and pyridinyl optionally substituted with 1 to 2 C_1-C_4 alkyl optionally substituted with halogen.

4. The compound according to claim 3 wherein

$\mathbf{R^1}$ is benzyl or phenethyl each optionally independently substituted with 1 to 3 substituents chosen from methyl, fluoro, chloro and bromo.

5. The compound according to claim 3 wherein

$\mathbf{R^1}$ is methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl or benzyl each optionally substituted with methyl, pivaloyl, cyclopropyl, cyclobutyl, cyclohexyl tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl (optionally substituted with methylsulfonyl)or chloro;

$\mathbf{R^2}$ and $\mathbf{R^3}$ are independently hydrogen, methyl, isopropyl, tert-butyl, or R^2 and R^3 together with the carbon to which they are attached form a cyclopropyl or cyclobutyl, ring;

$\mathbf{R^4}$ is hydrogen;

$\mathbf{R^5}$ is phenyl, pyridinyl, quinolinyl, isoquinolinyl, pyrazolyl, isoxazolyl, benzothiazolyl, thiadiazolyl, or thiazolyl each optionally independently substituted with 1 to 2 substituents chosen from, methyl, ethyl, tert-butyl, neopentyl, cyclohexyl, trifluoromethyl or phenyl optionally substituted with a chlorine atom.

6. A compound chosen from

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (4-tert-butyl-thiazol-2-yl)-amide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-N-naphthalen-2-yl-2-(propane-2-sulfonyl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-propionamide

2-Methyl-N-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-2-(propane-2-sulfonyl)-propionamide

N-Isoquinolin-3-yl-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-3-yl-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(propane-2-sulfonyl)-propionamide

2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

2-Methyl-2-(2-methyl-propane-2-sulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(2-methyl-propane-2-sulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

2-(1-Acetyl-piperidin-3-ylmethanesulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

2-(Butane-2-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-ethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methanesulfonyl-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2,2,2-trifluoro-ethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

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N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(hexane-3-sulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-ethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyanomethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(2,2-dimethyl-propane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-Methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((S)-5-oxo-pyrrolidin-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-((R)-5-oxo-pyrrolidin-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(piperidin-4-ylmethanesulfonyl)-propionamide

2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(piperidin-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(4-methyl-tetrahydro-pyran-4-sulfonyl)-propionamide

2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopropylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclobutylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-phenyl-propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-3-yl-thiazol-2-yl)-propionamide

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2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-2-yl-thiazol-2-yl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-2-yl-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-3-yl-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-2-yl-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-N-(2-methyl-5-thiophen-2-yl-2H-pyrazol-3-yl)-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(4-pyridin-4-yl-thiazol-2-yl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-N-(5-phenyl-pyridin-2-yl)-2-(propane-1-sulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(2,4-Dimethyl-5-phenyl-2H-pyrazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-thiazol-2-yl)-propionamide

N-(4-Cyclopropyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-[1,3,4]thiadiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

N-(4-Ethyl-pyridin-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-Benzooxazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(3-propyl-isoxazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-Isopropyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(2,4-Dimethyl-5-phenyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-naphthalen-1-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-methyl-pyridin-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(3-trifluoromethyl-phenyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-phenyl)-propionamide

2-Methyl-N-(2-methyl-5-phenyl-2H-pyrazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-Isoquinolin-3-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide

N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide

N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-3-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-2-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-4-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-Isopropyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide and

2-Methyl-N-(3-phenyl-1,2,4-thiadiazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

or the tautomers or the pharmaceutically acceptable salts thereof.

7. A compound chosen from

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-3-methyl-2-(propane-2-sulfonyl)-butyramide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(6-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(4-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-(hexane-3-sulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-Methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

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N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclopropylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cyclobutylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide

2-Methyl-2-(propane-2-sulfonyl)-N-quinolin-2-yl-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-3-yl-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Methyl-2-(propane-1-sulfonyl)-N-quinolin-2-yl-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide

N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-[1,3,4]thiadiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

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N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(3-propyl-isoxazol-5-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(3-trifluoromethyl-phenyl)-propionamide

N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(4-trifluoromethyl-phenyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide

N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide

N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-3-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-N-(4-pyridin-2-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide and

2-Methyl-N-(4-pyridin-4-yl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

or the tautomers or the pharmaceutically acceptable salts thereof.

8. A compound chosen from

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-2-sulfonyl)-propionamide

1-Cyclohexanesulfonyl-cyclobutanecarboxylic acid (5-tert-butyl-isoxazol-3-yl)-amide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(4-chloro-phenylmethanesulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide

2-Cyclohexanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(2-methyl-propane-2-sulfonyl)-propionamide

2-(Butane-2-sulfonyl)-N-(5-tert-butyl-isoxazol-3-yl)-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(4-tert-butyl-thiazol-2-yl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-(4-tert-Butyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-cyclopentanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(3,3-Dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-(3,3-dimethyl-2-oxo-butane-1-sulfonyl)-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cycloheptanesulfonyl-2-methyl-propionamide

2-Cyclohexylmethanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Methyl-2-(3-methyl-butane-1-sulfonyl)-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

2-Cycloheptanesulfonyl-2-methyl-N-(5-trifluoromethyl-pyridin-2-yl)-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide

N-(5-tert-Butyl-isoxazol-3-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide

N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-2-sulfonyl)-propionamide
N-(4-tert-Butyl-phenyl)-2-methyl-2-(propane-1-sulfonyl)-propionamide
N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(propane-1-sulfonyl)-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide
N-(5-tert-Butyl-isoxazol-3-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide
2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(propane-1-sulfonyl)-propionamide
N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide
N-(4-Cyclohexyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide
N-(5-tert-Butyl-4-methyl-thiazol-2-yl)-2-methyl-2-(propane-1-sulfonyl)-propionamide
N-Benzothiazol-2-yl-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
2-Methyl-N-(5-phenyl-[1,2,4]thiadiazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
2-Methyl-N-(5-methyl-4-phenyl-thiazol-2-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-(5-Ethyl-4-phenyl-thiazol-2-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-[3-(2,2-Dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
2-Methyl-N-quinolin-3-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-(4-tert-Butyl-phenyl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
2-Methyl-N-quinolin-2-yl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide
N-(5-tert-Butyl-1,3,4-thiadiazol-2-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide
2-Cyclopentanesulfonyl-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclobutylmethanesulfonyl-2-methyl-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopropylmethanesulfonyl-2-methyl-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionamide
2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclopentanesulfonyl-2-methyl-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-cyclohexylmethanesulfonyl-2-methyl-propionamide

2-(Butane-2-sulfonyl)-N-(3-tert-butyl-isoxazol-5-yl)-2-methyl-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-2-ylmethanesulfonyl)-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(2-methyl-propane-1-sulfonyl)-propionamide
1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
N-(3-tert-Butyl-isoxazol-5-yl)-2-(4-fluoro-phenylmethanesulfonyl)-2-methyl-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-2-ylmethanesulfonyl)-propionamide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-ylmethanesulfonyl)-propionamide
N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide and
N-[4-(4-Fluoro-phenyl)-thiazol-2-yl]-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
or the tautomers or the pharmaceutically acceptable salts thereof.

9. A compound chosen from
1-(Tetrahydro-pyran-4-sulfonyl)-cyclobutanecarboxylic acid (3-tert-butyl-isoxazol-5-yl)-amide
N-(3-tert-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-furan-3-sulfonyl)-propionamide
1-(Tetrahydro-pyran-4-ylmethanesulfonyl)-cyclobutanecarboxylic acid (5-phenyl-4H-1,2,4-triazol-3-yl)-amide
2-Methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-2-(tetrahydro-pyran-4-sulfonyl)-propionamide
1-(Tetrahydro-pyran-4-sulfonyl)-cyclobutanecarboxylic acid (5-phenyl-4H-1,2,4-triazol-3-yl)-amide
N-(3-tert-Butyl-isoxazol-5-yl)-2-(1-methanesulfonyl-pyrrolidin-3-ylmethanesulfonyl)-2-methyl-propionamide and
2-(1-Methanesulfonyl-pyrrolidine-3-sulfonyl)-2-methyl-N-(5-phenyl-4H-1,2,4-triazol-3-yl)-propionamide
or the tautomers or the pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1.

11. A method of treating a CB2 receptor-mediated disease or condition in an

animal subject comprising administering to said animal subject a therapeutically effective dose of the compound according to claim 1.

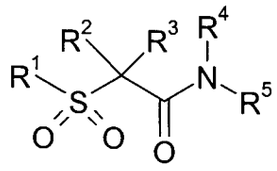
12. The method according to claim 11 wherein said CB2 receptor-mediated disease or condition is selected from the group consisting of an inflammatory disease and an autoimmune disease.

13. The method according to claim 11 wherein said CB2 receptor-mediated disease or condition is pain.

14. The method according to claim 10 wherein said CB2 receptor-mediated disease or condition is a lung disease, a rheumatic disease, an autoimmune disease, a musculoskeletal disease, an allergic disease, an allergic reaction, a vascular disease, a dermatological disease, a renal disease, a hepatic disease, a gastrointestinal disease, neurodegeneration eye disease, diseases of the ear, nose, and throat, neurological disease blood disease, tumors, endocrine diseases, organ and tissue transplantations and graft-versus-host diseases, severe states of shock, acute pain, visceral pain, spasm of the gastrointestinal tract or uterus, colics, neuropathic pain, inflammatory and nociceptive pain, cancer pain, headache, restenosis, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis, and pyrexia.

ABSTRACT

Compounds of formula (I)



are disclosed. Compounds according to the invention bind to and are agonists, antagonists or inverse agonists of the CB2 receptor, and are useful for treating inflammation. Those compounds which are agonists are additionally useful for treating pain.

COMPUESTOS QUE MODULAN EL RECEPTOR CB2

DATOS DE LA SOLICITUD

Esta solicitud reivindica los derechos de la solicitud provisional de Estados Unidos N° de serie 60/826.819 presentada el 25 de Septiembre de 2006.

ANTECEDENTES DE LA INVENCIÓN

1. CAMPO TÉCNICO

La presente invención se refiere a nuevos compuestos que modulan el receptor CB2 y su utilización como medicamentos.

2. INFORMACIÓN ANTECEDENTE

Los canabinoides son un grupo de aproximadamente 60 compuestos diferentes encontrados en la *Cannabis sativa* (también conocida como marihuana), siendo las moléculas más representativas el cannabinol, cannabidiol y Δ^9-tetrahidrocannabinol (THC). La utilización terapéutica del *Cannabis* puede datarse en las antiguas dinastías de China e incluye aplicaciones para varias enfermedades que van de la falta de apetito, emesis, calambres, dolor menstrual, espasticidad a reumatismo. La larga historia de la utilización del *Cannabis* ha conducido al desarrollo de varios fármacos. Por ejemplo, Marinol y Cesamet que se basan en el THC y su análogo la nabilona respectivamente, se utilizan como antieméticos y estimulantes del apetito. A pesar de los beneficios clínicos, la utilización terapéutica del cannabis está limitada por sus efectos psicoactivos, incluyendo alucinación, adicción y dependencia. El documento de Mechoulam R, ed., *Cannabinoids as Therapeutic Agents*, Boca Ratón, FL; CRC Press, 1986 proporciona una revisión de la utilización medicinal del cannabis.

Los efectos fisiológicos de los cannabinoides están mediados por al menos dos receptores acoplados a la proteína G, CB1 y CB2. Estudios auto-radiográficos han demostrado que los receptores CB1 se expresan principalmente en el sistema nervioso central, específicamente en el córtex cerebral, el hipocampo, los ganglios basales y el cerebelo.

También se encuentran en un grado menor en el sistema reproductor y en otros tejidos periféricos incluyendo los del sistema inmune. Los receptores CB1 regulan la liberación de neurotransmisores de las neuronas presinápticas y se cree que intervienen en la mayoría de los efectos eufóricos y otros efectos sobre el sistema nervioso central del *cannabis*, tales como la catalepsia inducida por THC, hipomovilidad e hipotermia, los cuales se ha demostrado que están totalmente ausentes en ratones con una deleción del gen del CB1 (Zimmer et al., Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci U S A. (1999) 96: 5780-5785.)

Los receptores CB2 se encuentran casi exclusivamente en el sistema inmune, con la mayor densidad en el bazo. Se calcula que el nivel de expresión del CB2 en las células inmunes es aproximadamente de 10 a 100 veces mayor que el del CB1. En el sistema inmune, el CB2 se encuentra en varios tipos de células, incluyendo células B, células NK, monocitos, células microgliales, neutrófilos, células T, células dentríticas y mastocitos, lo que sugiere que un amplio espectro de funciones inmunes puede regularse a través de los moduladores CB2 (Klein et al., The cannabinoid system and immune system. J Leukoc Biol (2003) 74: 486-496). Esto está basado en el descubrimiento de que el efecto inmunomodulador del THC está ausente en ratones deficientes en CB2 (Bicklet et al., Immunomodulation by cannabinoid is absent in mice deficient for the cannabinoid CB2 receptor. Eur J Pharmacol (2000) 396: 141-149). Se han desarrollado ligandos selectivos al CB2 y se han ensayado en base a sus efectos en varios procesos inflamatorios. Por ejemplo, en modelos animales de inflamación, se ha demostrado que los agonistas selectivos, agonistas inversos y antagonistas de CB2 son eficaces para suprimir la inflamación (Hanus et al., HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor, Proc Natl Acad Sci U S A. (1999) 96: 14228-14233, Ueda et al., Involvement of cannabinoid CB(2) receptor-mediated response and efficacy of cannabinoid CB(2) receptor inverse agonist, JTE-907, in cutaneous inflammation in mice, Eur J Pharmacol. (2005) 520: 164-171 y Smith et al., The anti-inflammatory activities of cannabinoid receptor ligands in mouse peritonitis models Eur J Pharmacol. (2001) 432: 107-119). Además, los agonistas selectivos del CB2 inhiben la gravedad de la enfermedad y la

espasticidad en modelos animales para la esclerosis múltiple (Baker et al., Cannabinoids control spasticity and tremor in a multiple sclerosis model, Nature (2000) 404: 84-87, Arevalo-Martin et al., Therapeutic action of cannabinoids in a murine model of multiple sclerosis, J Neurosci. (2003) 23:2511-2516). En conjunto, estos resultados apoyan la idea de que se pueden emplear moduladores del receptor del CB2 para el tratamiento de estados médicos que tengan un componente inflamatorio.

Además de la inflamación, se ha demostrado que los agonistas del CB2 inhiben el dolor y la emesis. Por ejemplo, agonistas selectivos del CB2 reducen la respuesta dolorosa inducida por estímulos térmicos y de otro tipo (Malan et al., CB2 cannabinoid receptor-mediated peripheral antinociception, Pain (2001) 93: 239-45 y Nackley et al., Selective activation of cannabinoid CB(2) receptors suppresses spinal fos protein expression and pain behavior in a rat model of inflammation, Neuroscience (2003) 119: 747-57). También se ha demostrado que la activación del CB2 inhibe la respuesta dolorosa neuropática (Ibrahim et al., Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS, Proc Natl Acad Sci U S A. (2003) 100: 10529-33). Finalmente, frente a datos anteriores que no encontraron CB2 en el cerebro, un artículo reciente ha demostrado la expresión del CB2 en el cerebro, con aproximadamente 1,5% del nivel en el bazo. En este artículo se muestra que la activación del CB2 es responsable del efecto antiemético del endocanabinoide (Van Sickle et al., Identification and functional characterization of brainstem cannabinoid CB2 receptors, Science 2005 310: 329-332). Los resultados anteriores confirman que los agonistas del CB2 se pueden utilizar para el tratamiento de dolor inflamatorio y neuropático, así como para el de la emesis.

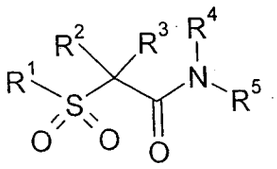
BREVE RESUMEN DE LA INVENCIÓN

La presente invención proporciona nuevos compuestos que se unen a y modulan el receptor CB2. La invención proporciona también un método y composiciones farmacéuticas para tratar la inflamación por medio de la administración de cantidades terapéuticas de estos compuestos. Finalmente, la invención proporciona un método y composiciones farmacéuticas

para tratar el dolor por medio de la administración de cantidades terapéuticas de los nuevos compuestos que son agonistas del CB2.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

En su aspecto genérico más amplio, la invención proporciona compuestos de la fórmula



(I)

en la que:

R^1 es alquilo C_{1-10}, alcoxi C_{1-10}, cicloalquilo C_{3-10}, anillo heterocíclico saturado de 3-10 miembros, bencilo o fenetilo cada uno opcionalmente sustituido de forma independiente con 1-3 sustituyentes elegidos a partir de alquilo C_{1-10} sustituido opcionalmente con 1 a 3 átomos de halógeno, cicloalquilo C_{3-10}, anillo heterocíclico saturado de 3-10 miembros sustituido opcionalmente con acilo, oxo o sulfona de metilo, acilo, ciano, fenilo, oxo, hidroxilo y halógeno;

R^2 y R^3 son independientemente hidrógeno o alquilo C_1-C_6; o R^2 y R^3 junto con el átomo de carbono al que están unidos forman un anillo heterocíclico o cicloalquilo de 3 a 6 miembros;

R^4 es hidrógeno o metilo;

R^5 es arilo o heteroarilo cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 sustituido opcionalmente con 1 a 3 átomos de halógeno o con un grupo heterociclilo, alcoxi C_1-C_6 opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C_3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C_1-C_4, fenilo opcionalmente sustituido con 1 a 2 átomos de halógeno o alquilo C_1-C_4 opcionalmente sustituido con halógeno, tienilo opcionalmente sustituido con 1 a 2 átomos de halógeno o

alquilo C_1-C_4 opcionalmente sustituido con halógeno y piridinilo opcionalmente sustituido con 1 a 2 alquilo C_1-C_4 opcionalmente sustituido con halógeno;

o un tautómero o una sal farmacéuticamente aceptable de los mismos.

En un primer aspecto subgenérico, la invención proporciona compuestos de la fórmula I en la que,

$\mathbf{R^1}$ es metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, tetrahidropiranilo, biciclo(3.3.0)octanilo, biciclo[4.3.0]nonilo, bencilo o fenetilo cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, tetrahidrofuranilo, tetrahidropiranilo, pirrolidinilo (sustituido opcionalmente con acilo, oxo o metilsulfonilo), piperidinilo (sustituido opcionalmente con acilo, oxo, o metilsulfona, acilo, ciano, fenilo, oxo, fluoro, cloro, bromo e hidroxilo;

$\mathbf{R^2}$ y $\mathbf{R^3}$ son independientemente hidrógeno, metilo, etilo, n-propilo, isopropilo, isobutilo, terc-butilo, o R^2 y R^3 junto con el carbono al que están unidos forman un anillo de ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o tetrahidropiranilo;

$\mathbf{R^4}$ es hidrógeno;

$\mathbf{R^5}$ es fenilo, naftilo, piridinilo, quinolinilo, isoquinolinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, triazolilo, oxadiazolilo, tiadiazolilo, indolilo, benzoxazolilo, benzopirazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzimidazolilo, tetrahidrobenzoxazolilo, tetrahidrobenzotiazolilo o tetrahidrobenzimidazolilo, cada uno opcionalmente sustituido independientemente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 que está sustituido opcionalmente con 1 a 3 átomos de halógeno, alcoxi C_1-C_6 que está opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C1-C4, fenilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno, tienilo que está sustituido opcionalmente con 1 a 2 átomos de

halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno y piridinilo que está sustituido opcionalmente con 1 a 2 alquilo C_1-C_4 opcionalmente sustituido con halógeno.

En un aspecto subgenérico adicional, la invención proporciona compuestos de la fórmula I en la que,

R^1 es metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, terc-butilo, n-pentilo, n-hexilo, n-heptilo, n-octilo, n-nonilo, n-decilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, tetrahidropiranilo, biciclo(3.3.0)octanilo, o biciclo[4.3.0]nonilo cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de metilo, etilo, pivaloilo, ciclopropilo, ciclobutilo, ciclohexilo, tetrahidropiranilo, tetrahidrofuranilo, pirrolidinilo opcionalmente sustituido con metilsulfona, fluoro, cloro, bromo, oxo e hidroxi;

R^2 y R^3 son independientemente hidrógeno, metilo, etilo, n-propilo, isopropilo, isobutilo, terc-butilo, o R^2 y R^3 junto con el carbono al que están unidos forman un anillo de ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o tetrahidropiranilo;

R^4 es hidrógeno;

R^5 es fenilo, naftilo, piridinilo, quinolinilo, isoquinolinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, triazolilo, oxadiazolilo, tiadiazolilo, indolilo, benzoxazolilo, benzopirazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzimidazolilo, tetrahidrobenzoxazolilo, tetrahidrobenzotiazolilo o tetrahidrobenzimidazolilo, cada uno opcionalmente sustituido independientemente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 que está sustituido opcionalmente con 1 a 3 átomos de halógeno, alcoxi C_1-C_6 que está opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C1-C4, fenilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno, tienilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno y piridinilo que está sustituido opcionalmente con 1 a 2 alquilo C1-C4 opcionalmente sustituido con halógeno.

En otro aspecto subgenérico, la invención proporciona compuestos de la fórmula I en la que,

R^1 es bencilo o fenetilo, cada uno opcionalmente sustituido independientemente con 1 a 3 sustituyentes elegidos de metilo, fluoro, cloro y bromo.

En otro aspecto subgenérico, la invención proporciona compuestos de la fórmula I en la que,

R^1 es metilo, etilo, n-propilo, isopropilo, terc-butilo, n-butilo, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, tetrahidropiranilo o bencilo, cada uno opcionalmente sustituido con metilo, pivaloilo, ciclopropilo, ciclobutilo, ciclohexilo, tetrahidropiranilo, tetrahidrofuranilo, pirrolidinilo opcionalmente sustituido con metilsulfonilo o cloro;

R^2 y R^3 son independientemente hidrógeno, metilo, isopropilo, terc-butilo, o R^2 y R^3 junto con el carbono al que están unidos forman un anillo de ciclopropilo o ciclobutilo;

R^4 es hidrógeno;

R^5 es fenilo, piridinilo, quinolinilo, isoquinolinilo, pirazolilo, isoxazolilo, benzotiazolilo, tiadiazolilo o tiazolilo cada uno opcionalmente sustituido de forma independiente con 1 a 2 sustituyentes elegidos de metilo, etilo, terc-butilo, neopentilo, ciclohexilo, trifluorometilo o fenilo opcionalmente sustituidos con un átomo de cloro.

El término "alquilo", o cualquier sustituyente que contiene un grupo alquilo tal como alcoxi o acilamino, se entenderá que tiene grupos alquilo ramificados o no ramificados, preferiblemente C_1-C_6 y se entenderá que están opcionalmente parcial o totalmente halogenados.

Los compuestos de fórmula I se pueden elaborar utilizando los métodos generales de síntesis descritos a continuación, los cuales también forman parte de la invención.

MÉTODOS GENERALES DE SÍNTESIS

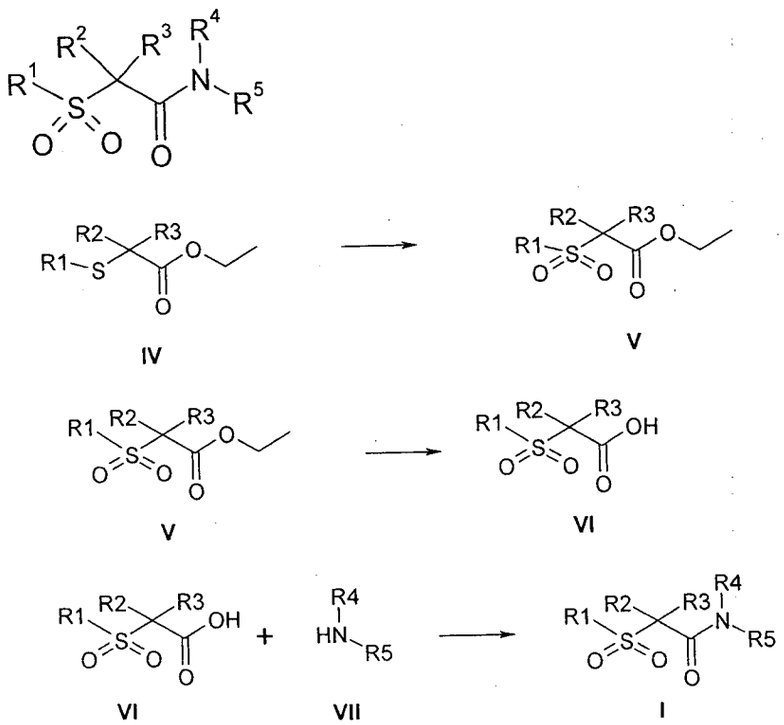
La invención también proporciona procedimientos para elaborar compuestos de Fórmula (I). En todos los métodos, a menos que se especifique otra cosa, R^1, R^2, R^3, R^4 y R^5 en

las fórmulas que se muestran a continuación tendrán el significado de R^1, R^2, R^3, R^4 y R^5 en la Fórmula (I) de la invención descrita anteriormente en este documento.

Las condiciones de reacción y los tiempos de reacción óptimos pueden variar dependiendo de los reactivos particulares usados. A menos que se especifique otra cosa, los disolventes, temperaturas, presiones y otras condiciones de reacción pueden seleccionarse fácilmente por un especialista habitual en la técnica. En la sección de Ejemplos de Síntesis se proporcionan procedimientos específicos. Típicamente, el progreso de la reacción puede controlarse por cromatografía de capa fina (TLC), si se desea, y los intermedios y productos pueden purificarse por cromatografía sobre gel de sílice y/o por recristalización.

Los ejemplos que se muestran a continuación son ilustrativos y, como se aprecia por un especialista en la técnica, los reactivos o condiciones particulares pueden modificarse cuando sea necesario para los compuestos individuales sin experimentación excesiva. Los materiales iniciales y los intermedios utilizados, en los métodos posteriores, o bien están disponibles comercialmente o se preparan fácilmente por los expertos en la técnica a partir de materiales disponibles comercialmente.

Los compuestos de fórmula (I) se pueden sintetizar por el método ilustrado en el Método A.

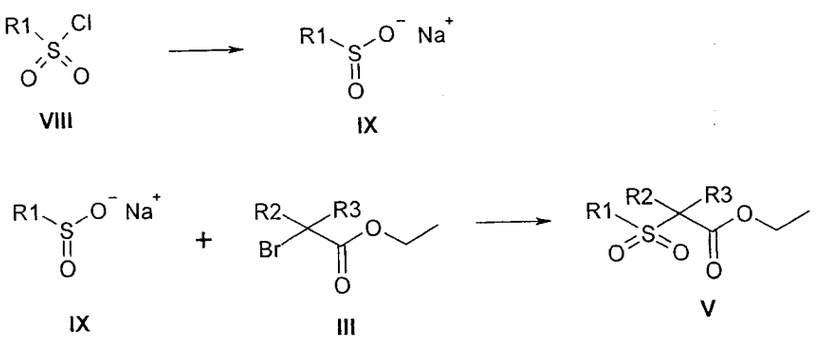


Método A

Como se ilustra en el Método A, la reacción de un tiol de fórmula II con un éster etílico de bromo de fórmula III, en un disolvente adecuado en presencia de una base adecuada, proporciona un tioéter de fórmula IV. La reacción del tioéter de fórmula IV con un agente oxidante adecuado proporciona la sulfona correspondiente de fórmula V. La hidrólisis del grupo éster de la sulfona de fórmula V en un disolvente adecuado en presencia de una base adecuada tal como hidróxido de litio, proporciona el ácido correspondiente de fórmula VI. Hacer reaccionar el ácido de fórmula VI con un reactivo tal como cloruro de tionilo o cloruro de oxalilo, proporciona el cloruro de ácido que después se hace reaccionar con una amina de fórmula VII en un disolvente adecuado en presencia de una base adecuada, para proporcionar un compuesto de fórmula (I). De forma alternativa, el ácido de fórmula VI también puede acoplarse con una amina de fórmula VII bajo condiciones de acoplamiento estándar, para proporcionar un compuesto de fórmula (I). En estas síntesis se pueden emplear reacciones de

acoplamiento peptídico convencionales conocidas en la técnica (véase por ejemplo M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag). Un ejemplo de condiciones de acoplamiento adecuadas es el tratamiento de una solución del ácido carboxílico en un disolvente adecuado tal como DMF con EDC, HOBT y una base tal como diisopropiletilamina, seguido de la amina deseada. Una modificación adicional del producto inicial de la fórmula (I) por métodos conocidos en la técnica e ilustrados en los ejemplos siguientes, se puede usar para preparar compuestos adicionales de esta invención.

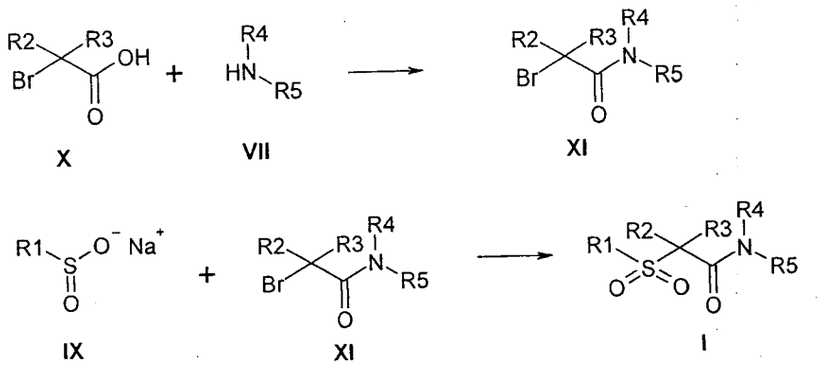
Los compuestos de fórmula (I) se pueden sintetizar también por el método ilustrado en el Método B.



Método B

Como se muestra en el Método B, el cloruro de sulfonilo de fórmula VIII se convierte a la correspondiente sal sódica de ácido sulfínico de fórmula IX, usando procedimientos presentados en la literatura. La reacción de la sulfona de fórmula IX con un bromoetil-éster de fórmula III en un disolvente adecuado, proporciona una sulfona de fórmula V. La sulfona de fórmula V se somete a la secuencia de reacciones como se muestra en el Método A, para proporcionar un compuesto de fórmula (I).

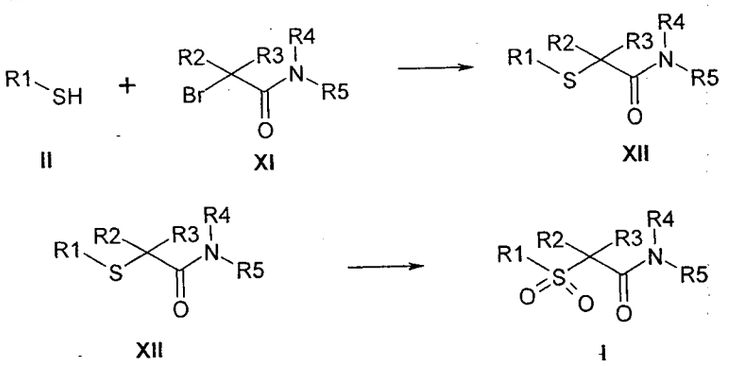
Los compuestos de fórmula (I) se pueden sintetizar por el método ilustrado en el Método C.



Método C

Como se ilustra en el Método C, hacer reaccionar el ácido de fórmula X con un reactivo tal como cloruro de tionilo o cloruro de oxalilo, proporciona el cloruro de ácido que después se hace reaccionar con una amina de fórmula VII en un disolvente adecuado en presencia de una base adecuada, para proporcionar un compuesto de fórmula (XI). Como alternativa, el ácido de fórmula X también puede acoplarse con una amina de fórmula VII en condiciones de acoplamiento convencionales, para proporcionar un compuesto de fórmula (XI). La reacción de la amida de fórmula XI con una sal de sodio del ácido sulfínico de fórmula IX, en un disolvente adecuado en presencia de una base adecuada, proporciona un compuesto de fórmula (I).

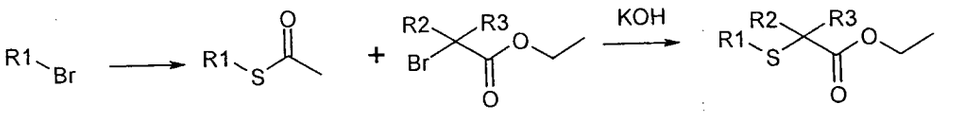
Los compuestos de Fórmula (I) pueden sintetizarse por el método que se ilustra en el Método D



Método D

Como se ilustra en el Método A, la reacción de un tiol de fórmula II con una bromoamida de fórmula XI, en un disolvente adecuado en presencia de una base adecuada, proporciona un tioéter de fórmula XII. Hacer reaccionar el tioéter de fórmula XII con un agente oxidante adecuado en un disolvente adecuado, proporciona un compuesto de fórmula (I).

Los compuestos de fórmula (I) se pueden sintetizar por el método ilustrado en el Método E.

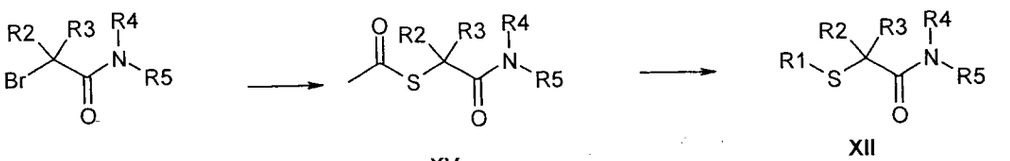


XIII XIV III IV

Método E

La reacción del bromuro inicial de fórmula XIII con un reactivo tal como tioacetato de potasio, en un disolvente adecuado, proporciona un éster de ácido tioacético de fórmula XIV. La reacción del éster de ácido tioacético XIV con el bromoetil-éster de fórmula III, en un disolvente adecuado en presencia de una base adecuada, proporciona el correspondiente éster de etilo de ácido sulfánico de fórmula IV que puede convertirse a un compuesto de fórmula (I) mediante la secuencia de etapas mostrada en el Método A.

Los compuestos de fórmula (I) se pueden sintetizar por el método ilustrado en el Método F.



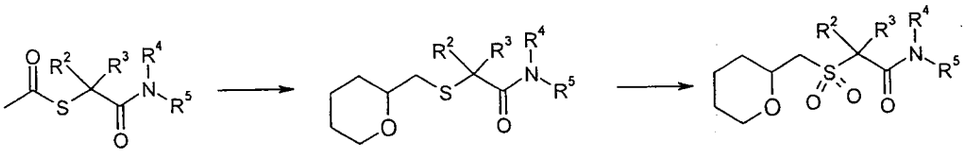
XI XV XII

Método F

La reacción de una bromoamida de fórmula XI con un reactivo tal como tioacetato de potasio, en un disolvente adecuado, proporciona un tiocompuesto de fórmula XV. La reacción del tiocompuesto de fórmula XV con el compuesto de bromo apropiado, en un disolvente

adecuado, en presencia de una base adecuada, proporciona la tioamida de fórmula XII que puede convertirse a un compuesto de fórmula (I) como en el Método D.

Los compuestos de Fórmula (I) pueden sintetizarse por el método que se ilustra en el Método G

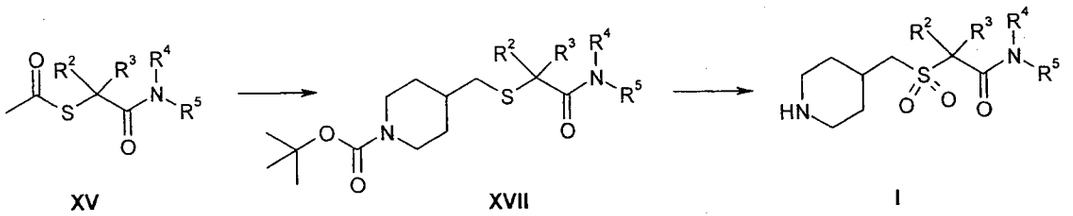


XV XVI I

Método G

La reacción de un tiocompuesto acilado de fórmula XV con bromometiltetrahidropirano en presencia de una base adecuada, tal como metóxido sódico, en un disolvente adecuado, proporciona un intermedio de fórmula XVI. La reacción del intermedio de fórmula XVI con un agente oxidante adecuado tal como peróxido de hidrógeno, proporciona un compuesto de fórmula I.

Los compuestos de Fórmula (I) pueden sintetizarse por el método que se ilustra en el Método H.

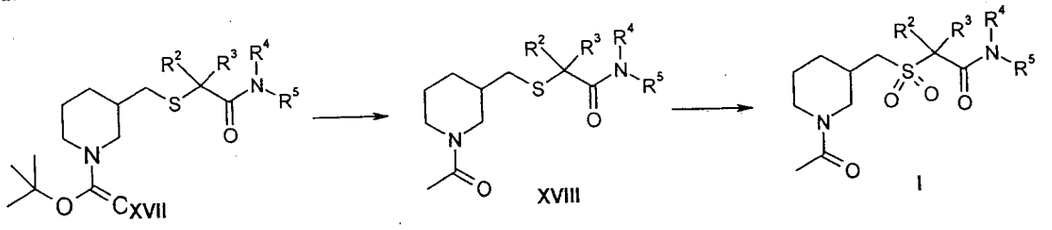


XV XVII I

Método H

Como se ilustra anteriormente, la reacción de un tiocompuesto acilado de fórmula XV con N-Boc-bromometilpiperidina, en presencia de una base adecuada, tal como metóxido sódico, en un disolvente adecuado, proporciona un intermedio de fórmula XVII. La eliminación del grupo protector en presencia de un ácido, y la oxidación en condiciones de reacción estándar, proporciona un compuesto de fórmula I.

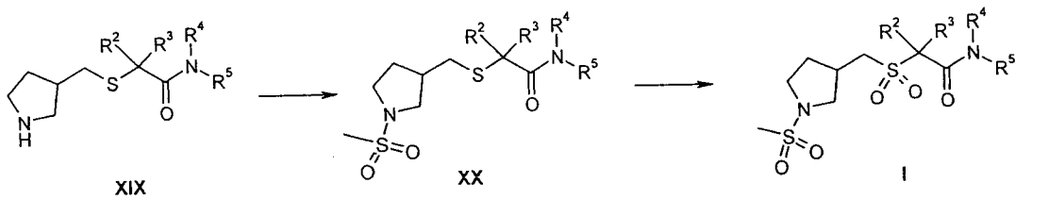
Los compuestos de Fórmula (I) pueden sintetizarse por el método que se muestra en el Método I.



Método I

Como se esboza anteriormente, la desprotección de una piperidina protegida por N-Boc de fórmula XVII, con un ácido adecuado seguido de acilación con un reactivo tal como anhídrido acético, en presencia de una base adecuada, proporciona un compuesto de fórmula XVIII. La reacción del intermedio de fórmula XVIII con un agente oxidante adecuado tal como ácido m-cloroperbenzóico, proporciona un compuesto de fórmula I.

Los compuestos de Fórmula (I) pueden sintetizarse por el método que se ilustra en el Método J.



Método J

Como se esboza en el método anterior J, la reacción de un compuesto de fórmula XIX con cloruro de sulfonilmetano, en presencia de una base adecuada, en un disolvente adecuado, proporciona un intermedio de fórmula XX. La reacción del intermedio de fórmula XX con un agente oxidante adecuado tal como ácido m-cloroperbenzóico, proporciona un compuesto de fórmula I.

Los compuestos de Fórmula (I) pueden sintetizarse por el método que se ilustra en el Método K.

I I

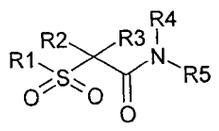
Método K

Un compuesto de fórmula I puede convertirse en otro compuesto de fórmula I como se muestra en el método K. La alquilación de un compuesto de fórmula 1 con un reactivo tal como yoduro de metilo, en presencia de una base adecuada tal como diisopropilamida de litio, proporciona un compuesto metilado de fórmula 1.

EJEMPLOS

La forma en la que se pueden preparar los compuestos de la invención se comprenderá adicionalmente por medio de los siguientes ejemplos.

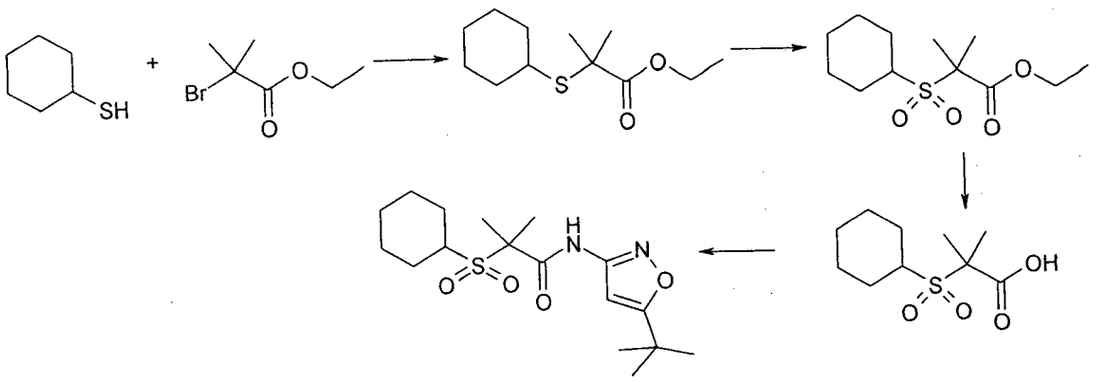
Procedimientos Experimentales para Compuestos de Fórmula I



I

<u>Método A</u>

Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida (Ejemplo 1 en la Tabla 17)



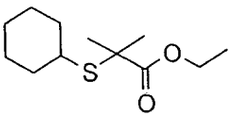
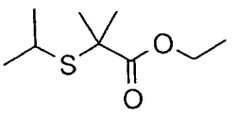
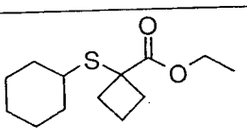
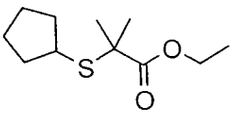
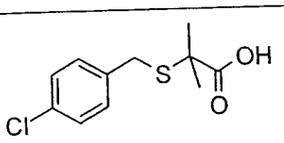
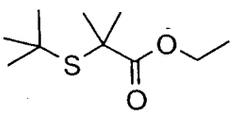
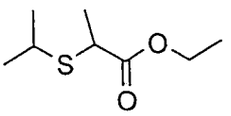
Etapa 1: Síntesis del éster de etilo del ácido 2-ciclohexilsulfanil-2-metil-propiónico

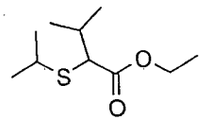
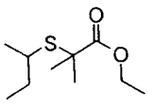
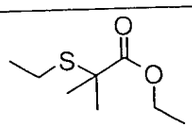
Preparado como se describe por adaptación de la siguiente referencia: Brown *et al. J. Med. Chem.* **1999**, *42*, 3785-3788

A una disolución de 2,5 g (21,5 mmol) de ciclohexiltiol en etanol (75 mL) se añadieron 1,2 g (21,5 mmol) de bolitas de KOH, seguido por 4,2 g (21,5 mmol) de α-bromoisobutirato de etilo. La reacción se calentó a reflujo durante 18 horas, después se enfrió a temperatura ambiente. El sólido (KBr) se separó por filtración y se aclaró con etanol (20 ml). El filtrado se concentró a presión reducida y el residuo se disolvió en DCM (50 mL). La fase orgánica se lavó con agua (2 x 20 mL). Los lavados acuosos se extrajeron de nuevo con DCM (10 mL). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4. La filtración y concentración a presión reducida proporcionó 4,15 g de éster de etilo de ácido 2-ciclohexilsulfanil-2-metil-propiónico.

Los siguientes tioéteres se sintetizaron de acuerdo con este procedimiento:

Tabla 1:

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	éster de etilo del ácido 2-ciclohexilsulfanil-2-metil-propiónico	84	231
	éster de etilo del ácido 2-isopropilsulfanil-2-metilpropiónico	83	191
	éster de etilo de ácido 1-ciclohexilsulfanil-ciclobutanocarboxílico	68	243
	éster de etilo del ácido 2-ciclopentilsulfanil-2-metil-propiónico	77	217
	ácido 2-(4-cloro-bencilsulfanil)-2-metil-propiónico	40*	245/247
	éster de etilo del ácido 2-terc-butilsulfanil-2-metilpropiónico	88	205
	éster de etilo del ácido 2-isopropilsulfanil-propiónico	50	177

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	éster de etilo del ácido 2-Isopropilsulfanil-3-metilbutírico	45	Estructura confirmada por 1H NMR
	éster de etilo de ácido 2-sec-Butilsulfanil-2-metil-propiónico	55	205
	éster de etilo del ácido 2-etilsulfanil-2-metil-propiónico	44	177

*La hidrólisis del éster de etilo se dio durante las condiciones de reacción

Etapa 2: Síntesis de éster de etilo del ácido 2-ciclohexanosulfonil-2-metil-propiónico

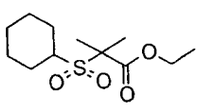
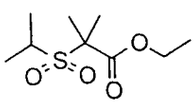
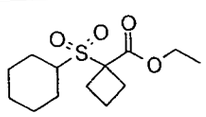
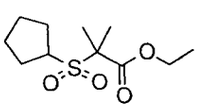
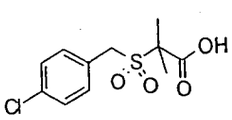
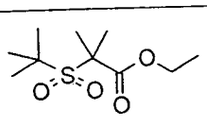
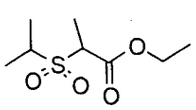
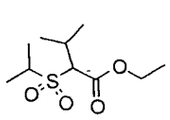
Preparado como se describe por adaptación de la siguiente referencia:

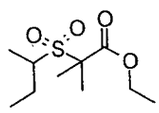
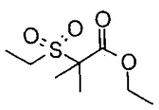
Aranapakam, V. et al. *J. Med. Chem.*, **2004**, *47*, 6255-6269.

A una disolución de 4,15 g (18 mmol) de éster de etilo del ácido 2-ciclohexilsulfanil-2-metil-propiónico en dioxano/agua (5/1, 40 mL) se añadió en una vez 33,2 g (54 mmol) de sal triple de monopersulfato de potasio (OXONE®). La suspensión blanca se agitó a temperatura ambiente durante 18 h. El sólido blanco se separó por filtración y se lavó con dioxano (10 mL). El filtrado se concentró a presión reducida para eliminar el disolvente orgánico. La disolución acuosa resultante se extrajo con DCM (3 x 40 mL). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró a presión reducida para proporcionar 3,47 g de éster de etilo de ácido 2-ciclohexanosulfonil-2-metil-propiónico.

Las siguientes sulfonas se sintetizaron de acuerdo con este procedimiento:

Tabla 2

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	éster de etilo de ácido 2-ciclohexanosulfonil-2-metil-propiónico	50	263
	éster de etilo de ácido 2-metil-2-(propano-2-sulfonil)-propiónico	75	223
	éster de etilo de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico	76	275
	éster de etilo de ácido 2-ciclopentanosulfonil-2-metil-propiónico	78	249
	ácido 2-(4-cloro-fenilmetanosulfonil)-2-metil-propiónico	81*	277/279, 294/296 [M+H_2O^+]
	éster de etilo de ácido 2-metil-2-(2-metil-propano-2-sulfonil)-propiónico	86	237
	éster de etilo de ácido 2-(propano-2-sulfonil)-propiónico	99	209
	éster de etilo de ácido 3-metil-2-(propano-2-sulfonil)-butírico	100	237

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	éster de etilo de ácido 2-(butano-2-sulfonil)-2-metil-propiónico	77	237
	éster de etilo de ácido 2-etanosulfonil-2-metil-propiónico	85	209

*Ácido 2-(4-cloro-bencilsulfanil)-2-metil-propiónico usado para la etapa de oxidación

Etapa 3: Síntesis de ácido 2-ciclohexanosulfonil-2-metil-propiónico

Se preparó como se describe por la adaptación de la siguiente referencia:

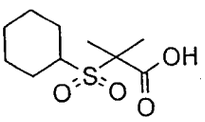
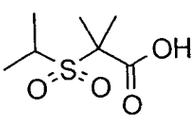
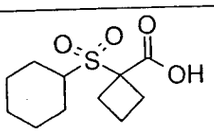
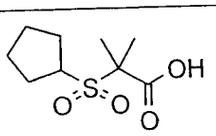
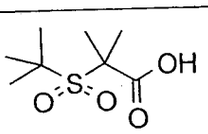
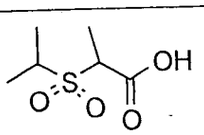
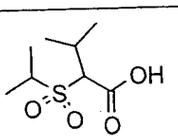
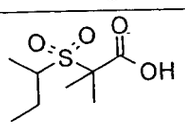
Troeger, Uhde., *J. Prakt. Chem.* **1899**, *59*, 320- 349

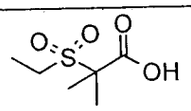
A una disolución de 3,47 g (13,2 mmol) de éster de etilo de ácido 2-ciclohexanosulfonil-2-metil-propiónico en THF/agua (4/1, 50 mL) se añadieron 1,11 g (26,4 mmol) de monohidrato de hidróxido de litio. La reacción se agitó a temperatura ambiente durante 18 h. La reacción se diluyó adicionalmente con agua (20 ml) y después se lavó con DCM (2 x 15 mL). La fase acuosa básica se enfrió en un baño de hielo y después se aciduló con una disolución de HCl acuosa 1M a pH 2. La fase acuosa ácida se extrajo con DCM (3 x 20 mL). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4 y se filtraron. La concentración del filtrado a presión reducida proporcionó 2,96 g de ácido 2-ciclohexanosulfonil-2-metil-propiónico.

Los siguientes ácidos se sintetizaron de acuerdo con este procedimiento:

Tabla 3:

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	ácido 2-ciclohexanosulfonil-2-metil-propiónico	64	258 [M+Na$^+$+H$^+$]
	ácido 2-metil-2-(propano-2-sulfonil)-propiónico	92	195, 212 [M+H$_2$O$^+$]
	ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico	89	247
	ácido 2-ciclopentanosulfonil-2-metil-propiónico	92	221
	ácido 2-metil-2-(2-metil-propano-2-sulfonil)-propiónico	69	209, 226 [M+H$_2$O$^+$]
	ácido 2-(propano-2-sulfonil)-propiónico	29	181
	ácido 3-metil-2-(propano-2-sulfonil)-butírico	32	209
	ácido 2-(butano-2-sulfonil)-2-metil-propiónico	78	209, 226 [M+H$_2$O$^+$]

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	ácido 2-etanosulfonil-2-metil-propiónico	89	198 [M+H_2O^+]

Etapa 4: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida

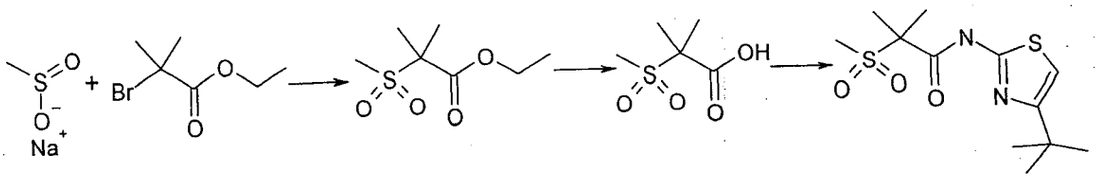
La activación de 100 mg (0,4 mmol) de ácido 2-ciclohexanosulfonil-2-metil-propiónico como el cloruro de ácido correspondiente se alcanzó mediante tratamiento con cloruro de tionilo (1 mL) a 80 °C durante 2 h. La reacción se enfrió a temperatura ambiente y se eliminó el exceso de cloruro de tionilo a presión reducida.

El cloruro de ácido en bruto se disolvió en DCM (0,5 ml) y se añadió a una disolución de 67 mg (0,48 mmol) de 3-amino-5-terc-butilisoxazol y N,N-diisopropiletilamina (83 ml, 0,48 mmol) en DCM (1 ml). La reacción se agitó a temperatura ambiente durante 18 h antes de evaporarse hasta sequedad. La mezcla de reacción se diluyó con DCM (4 mL) y se lavó con disolución acuosa saturada de $NaHCO_3$ (3 mL). Las fases orgánicas se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía en columna (sílice, eluyente: DCM, 0-5% de acetato de etilo) para dar 14 mg de N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida.

Los ejemplos enumerados en la Tabla 17, Método A, se hicieron según este procedimiento.

<u>Método B</u>

Síntesis de N-(4-terc-butil-tiazol-2-il)-2-metanosulfonil-2-metil-propionamida (Ejemplo 51 en la Tabla 17)



Etapa 1: Síntesis de éster de etilo del ácido 2-metanosulfonil-2-metil-propiónico

Se preparó como se describe por la adaptación de las siguientes referencias:

Faucher, A.-M. *et al. J. Med. Chem.* **2004**, *47*, 19-21.

Binsiti, C. *Eur. J. Med. Chem. Chim. Ther.* **2001**, *36*, 809-828.

Field, L.; Clark, R.D. *Org. Synth.* **1958**, *38*, 62-64.

Troeger; U., *J. Prakt. Chem.* **1899**, *59*, 320-349.

A una suspensión de 5 g (49 mmol) de metanosulfito sódico en DMF (50 mL) se añadió piridina (6,3 mL) y α-bromoisobutirato de etilo (2,9 mL). La reacción se agitó durante 18 h a 50 °C en nitrógeno. La mezcla de reacción se diluyó con acetato de etilo (250 mL), se lavó con $NaHCO_3$ acuoso saturado (2 x 100 mL), disolución de HCl acuoso 2M (50 mL), salmuera (1 x 50 mL) y se secó en Na_2SO_4. La filtración y concentración a presión reducida proporcionó 3,04 g de éster de etilo de ácido 2-metanosulfonil-2-metil-propiónico.

El compuesto no se ionizó en condiciones LCMS, así que la estructura se confirmó por espectroscopía ^{1}H-NMR: ^{1}H NMR (360 MHz, *CLOROFORMO-d*) δ ppm 1,33 (3 H, t, *J*=7,1 Hz), 1,66 (6 H, s), 3,06 (3 H, s), 4,28 (2 H, q, *J*=7,1 Hz).

Etapa 2: Síntesis de ácido 2-metanosulfonil-2-metil-propiónico

El ácido 2-metanosulfonil-2-metil-propiónico se preparó generalmente como se describe en la etapa 3, Método A:

A una disolución de 500 mg (2,6 mmol) de éster de etilo de ácido 2-metanosulfonil-2-metil-propiónico en THF/agua (4/1, 5 mL) se añadieron 270 mg (6,6 mmol) de monohidrato de hidróxido de litio. La reacción se agitó a temperatura ambiente durante 18 h. La reacción se diluyó adicionalmente con agua (20 mL) y después se lavó con DCM (2 x 15 mL). La fase

acuosa básica se enfrió en un baño de hielo y se aciduló con una disolución acuosa de HCl 1M a pH 2. La fase acuosa ácida se extrajo con isopropanol/cloroformo (1/1, 3 x 20 mL). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4 y se filtraron. La concentración del filtrado a presión reducida proporcionó 413 mg de ácido 2-metanosulfonil-2-metil-propiónico. El compuesto no se ionizó en condiciones LCMS, así que la estructura se confirmó por espectroscopía ^{1}H-NMR:

^{1}H-NMR (400 MHz, *DMSO-d_6*) δ ppm 1,49 (6 H, s), 3,08 (3 H, s).

Etapa 3: Síntesis de N-(4-terc-butil-tiazol-2-il)-2-metanosulfonil-2-metil-propionamida

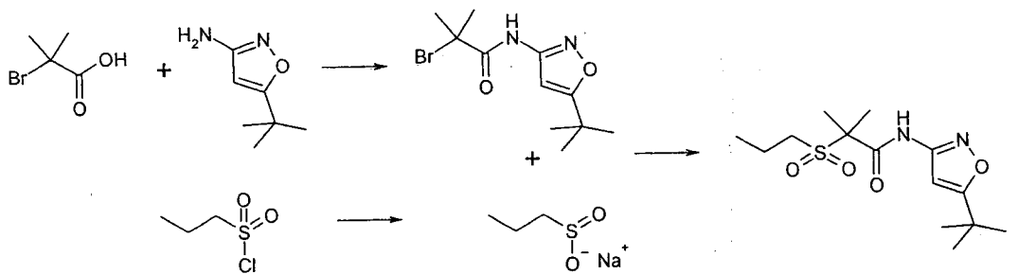
La activación de 97 mg (0,6 mmol) de ácido 2-metanosulfonil-2-metil-propiónico como el cloruro de ácido correspondiente se alcanzó mediante tratamiento con cloruro de tionilo (2 mL) a 80 °C durante 2 h. La reacción se enfrió a temperatura ambiente y se eliminó el exceso de cloruro de tionilo a presión reducida.

El cloruro de ácido en bruto se disolvió en DCM (2 mL) y se añadió a una solución de 91 mg (0,6 mmol) de 2-amino-4-terc-butiltiazol y N,N-diisopropiletilamina (0,13 mL) en DCM (1 mL). La reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con DCM, se lavó con una disolución acuosa saturada de $NaHCO_3$ (2 mL) y salmuera (2 mL) y se secó sobre Na_2SO_4. La filtración y concentración del filtrado proporcionó el producto en bruto. La purificación adicional por cromatografía de columna (sílice, eluyente: heptanos, 0-20% de acetato de etilo) dio 116 mg de N-(4-terc-butil-tiazol-2-il)-2-metanosulfonil-2-metil-propionamida.

Los ejemplos enumerados en la Tabla 17, Método B, se hicieron según este procedimiento.

Método C

Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida (Ejemplo 10 en Tabla 17)



Etapa 1: Síntesis de sal sódica de ácido 1-propanosulfínico

Se preparó como se describe por la adaptación de las siguientes referencias:

Faucher, A.-M. *et al. J. Med. Chem.* **2004**, *47*, 19-21.

Binsiti, C. *Eur. J. Med. Chem. Chim. Ther.* **2001**, *36*, 809-828.

Field, L.; Clark, R.D. *Org. Synth.* **1958**, *38*, 62-64.

A una disolución de 0,26 g (3,2 mmol) de $NaHCO_3$ y 0,4 g (3,2 mmol) de Na_2SO_3 en agua (1,5 mL), se añadieron 0,23 g (1,6 mmol) de cloruro de 1-propanosulfonilo. La reacción se calentó a 80 °C durante 3 h. El disolvente se eliminó a presión reducida. El material en bruto se suspendió en etanol hirviendo (20 mL) y los sólidos inorgánicos se eliminaron por filtración. El filtrado se concentró a presión reducida para dar 0,18 g de sal sódica de ácido 1-propanosulfínico.

Etapa 2: Síntesis de 2-bromo-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

Se preparó como se describe por la adaptación de las siguientes referencias: Katoh A. *et al. Heterocycles* **1999**, *50*, 299-308

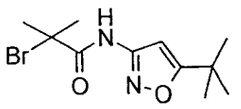
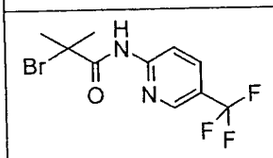
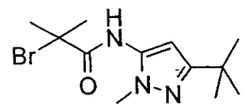
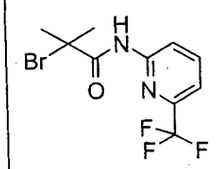
La activación de 5 g (30 mmol) de ácido 2-bromo-2-metil-propiónico como su cloruro de ácido correspondiente se alcanzó mediante tratamiento con cloruro de tionilo (10 mL) a 60

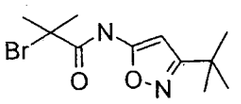
°C durante 2 h. La reacción se enfrió y se eliminó el exceso de cloruro de tionilo a presión reducida para dar el correspondiente cloruro de ácido.

A una disolución de 4,2 g (30 mmol) de 3-amino-5-terc-butilisoxazol y 5,2 mL (30 mmol) de N,N-diisopropiletilamina en DCM (20 mL) se añadió en gotas el cloruro de ácido, como disolución en DCM (15 mL). La reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se lavó con disolución acuosa saturada de $NaHCO_3$ (2 x 15 mL) y se separaron las fases. La fase orgánica se lavó adicionalmente con salmuera, se secó sobre $MgSO_4$, se filtró y concentró a presión reducida. El producto en bruto se purificó por cromatografía en columna ultrarrápida seca (sílice, eluyente: DCM, acetato de etilo al 0-20%) para producir 8,5 g de 2-bromo-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida.

Las siguientes amidas se sintetizaron de acuerdo con este procedimiento:

Tabla 4:

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	2-bromo-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida	97	289/291
	2-bromo-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	55	311/313
	2-bromo-N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-propionamida	51	302/304
	2-bromo-2-metil-N-(6-trifluorometil-piridin-2-il)-propionamida	72	311/313

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	2-bromo-N-(3-terc.-butil-isoxazol-5-il)-2-metil-propionamida	68	289/291

Etapa 3: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

Se preparó como se describe por la adaptación de las siguientes referencias:

Faucher, A.-M. *et al. J. Med. Chem.* **2004**, *47*, 19-21.

Troeger; Uhde; *J. Prakt. Chem.* **1899**, *59*, 320-349.

Binsiti, C. *Eur. J. Med. Chem. Chim. Ther.* **2001**, *36*, 809-828.

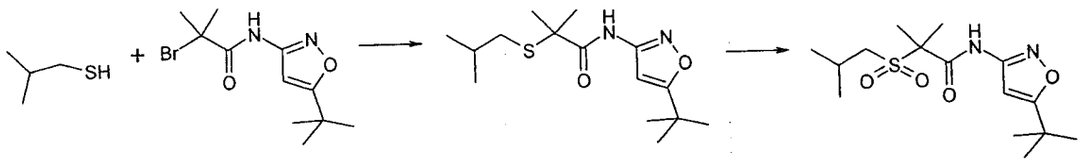
Field, L.; Clark, R.D. *Org. Synth.* **1958**, *38*, 62-64.

A una disolución de 160 mg (0,55 mmol) de 2-bromo-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida en DMF (3 mL) se añadieron 87 mg (0,71 mmol) de sal sódica de ácido 1-propanosulfínico de una sola vez. Se añadió piridina (48 µL) y la reacción se agitó a 50°C durante 18 h. La mezcla se aciduló con una disolución acuosa 1 M de HCl (1 mL) y se extrajo con éter dietílico (3 x 3 mL). Las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró a presión reducida. El material en bruto se purificó por cromatografía en columna (sílice, eluyente heptanos, 0-20% de acetato de etilo) para dar 86 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida.

Los ejemplos enumerados en la Tabla 17, Método C, se hicieron según este procedimiento.

Método D

Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida (Ejemplo 52 en Tabla 17)

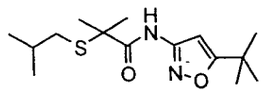
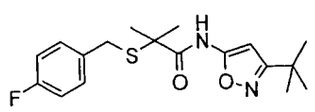


Etapa 1: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-isobutilsulfanil-2-metil-propionamida

A una disolución agitada de 82 µL (1,31 mmol) de 2-metil-1-propanotiol en etanol (2 mL) se añadieron 37 mg (0,65 mmol) de bolitas de KOH, seguido de 190 mg (0,65 mmol) de 2-bromo-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida (preparada como se describe en la etapa 2, Método B). La mezcla de reacción se calentó a reflujo durante 18 h. La reacción se enfrió a temperatura ambiente. El sólido (KBr) se separó por filtración y se aclaró con etanol (15 mL). El filtrado se concentró a presión reducida para dar 160 mg de N-(5-terc-butil-isoxazol-3-il)-2-isobutilsulfanil-2-metil-propionamida.

Las siguientes amidas se sintetizaron de acuerdo con este procedimiento:

Tabla 5:

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-isoxazol-3-il)-2-isobutilsulfanil-2-metil-propionamida	83	299
	N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-bencilsulfanil)-2-metil-propionamida	63	351

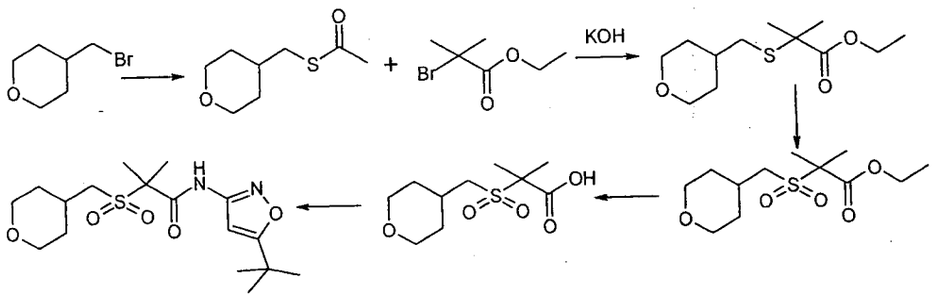
Etapa 2: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-isobutilsulfonil-2-metil-propionamida

A una disolución de 160 mg (0,54 mmol) de N-(5-terc-butil-isoxazol-3-il-)-2-isobutilsulfanil-2-metil-propionamida en dioxano/agua (5/1, 2,5 mL) se añadieron en una vez 0,99 g (1,61 mmol) de sal triple de monopersulfato de potasio (OXONE®). La suspensión blanca se agitó a temperatura ambiente durante 18 h. El sólido blanco se separó por filtración y se lavó con dioxano (5 mL). El filtrado se concentró a presión reducida para eliminar el disolvente orgánico. La disolución acuosa resultante se extrajo con DCM (2 x 5 mL). Los extractos orgánicos combinados se lavaron con disolución acuosa saturada de $NaHCO_3$ (5 mL), salmuera (5 mL), se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró a presión reducida. El residuo en bruto se purificó por cromatografía en columna (sílice, eluyente DMC, 0-10% de acetato de etilo) para dar 98 mg de N-(5-terc-butil-isoxazol-3-il)-2-isobutilsulfonil-2-metil-propionamida.

Los ejemplos enumerados en la Tabla 17, Método D, se prepararon de acuerdo con este procedimiento.

Método E

Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida (Ejemplo 56, Tabla 17)



Etapa 1: Síntesis del S-(tetrahidro-piran-4-ilmetil)-éster del ácido tioacético

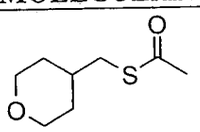
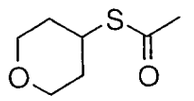
Preparado como se describe por adaptación de la siguiente referencia:

Watson, R.J. *et al. Tetrahedron Lett.* **2002**, *43*, 683-685.

A una disolución de 0,97 g (5,4 mmol) de 4-bromometiltetrahidropirano en DMF (9,7 mL) se añadieron 1,27 g (11,2 mmol) de tioacetato de potasio. La reacción se agitó a temperatura ambiente durante 3 h. Se añadió dietiléter (100 mL) y la mezcla de reacción se lavó con disolución acuosa saturada de $NaHCO_3$ (2 x 25 mL) y salmuera (25 mL). La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía de columna (sílice, eluyente: heptanos, 10 % de acetato de etilo) para dar 0,81 g de S-(tetrahidro-piran-4-ilmetil)éster de ácido tioacético.

Según este procedimiento, los siguientes tioacetatos se sintetizaron:

Tabla 6

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	S-(tetrahidro-piran-4-ilmetil)-éster de ácido tioacético	86	175
	S-(tetrahidro-piran-4-il)-éster de ácido tioacético	68	161

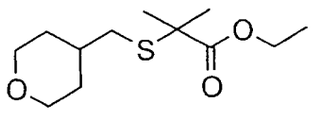
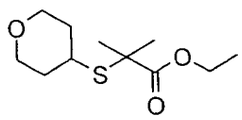
Etapa 2: Síntesis del éster de etilo del ácido 2-metil-2-(tetrahidro-piran-4-ilmetilsulfanil)-propiónico

Una disolución de 0,86 g (15,2 mmol) de hidróxido de potasio en etanol (78 mL, desgasificado y en nitrógeno) se añadió a 0,81 g (4,66 mmol) de S-(tetrahidro-piran-4-ilmetil)éster de ácido tioacético. La reacción se agitó a temperatura ambiente en nitrógeno durante 0,5 h. Después, se añadieron 2,1 mL (14,1 mmol) de α-bromoisobutirato de etilo y la reacción se agitó durante 4 h. El precipitado resultante se eliminó por filtración y el filtrado se concentró a presión reducida. El residuo se disolvió en DCM (100 mL) y se lavó con $NaHCO_3$ acuoso saturado (50

mL), salmuera (50 mL) y se secó sobre Na_2SO_4. La filtración y concentración del filtrado a presión reducida, seguido por cromatografía en columna del residuo (sílice, eluyente: heptanos, 0-20 % de acetato de etilo) dio 0,76 g de éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-ilmetilsulfanil)-propiónico.

Según este procedimiento, los siguientes ésteres de etilo se sintetizaron:

Tabla 7:

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-ilmetilsulfanil)-propiónico	66	247
	éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-ilsulfanil)-propiónico	75	233

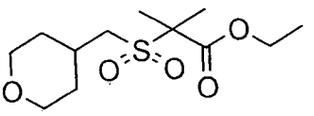
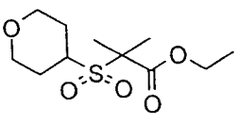
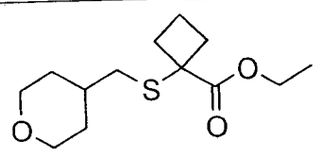
Etapa 3: Síntesis del éster de etilo del ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfanil)-propiónico

Preparado como se describe por adaptación del Método A, Etapa 2.

A una disolución de 0,76 g (3,1 mmol) de éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-ilmetilsulfanil)-propiónico en dioxano/agua (1/1, 10 mL) se añadió en una vez 4,1 g (6,6 mmol) de sal triple de monopersulfato de potasio (OXONE®). La suspensión blanca se agitó a temperatura ambiente durante 1 h. El sólido blanco se separó por filtración y se lavó con dioxano (5 mL). El filtrado se concentró a presión reducida para eliminar el disolvente orgánico. La mezcla resultante se diluyó con DCM (50 mL) y agua (5 mL). La fase orgánica se separó y se lavó con una mezcla de $NaHCO_3$ acuoso saturado/salmuera (1/1) (20 mL) y se secó sobre Na_2SO_4. La filtración y concentración a presión reducida proporcionó 0,77 g de éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propiónico.

Según este procedimiento, las siguientes sulfonas se sintetizaron:

Tabla 8:

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propiónico	90	279
	éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-sulfonil)-propiónico	84	265
	éster de etilo de ácido 1-(tetrahidro-piran-4-ilmetilsulfanil)-ciclobutanocarboxílico	77	259

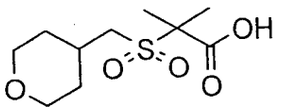
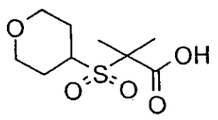
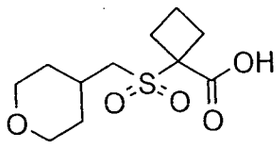
Etapa 4: Síntesis del ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propiónico

Preparado como se describe por adaptación del Método A, etapa 3.

A una disolución de 769 mg (2,77 mmol) de éster de etilo de ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propiónico en THF/agua (1/1, 10 mL) se añadieron 228 mg (5,43 mmol) de monohidrato de hidróxido de litio. La reacción se agitó a temperatura ambiente durante 18 h. La reacción se concentró a presión reducida. El residuo se disolvió en agua (10 mL) y se lavó con dietiléter (2 x 25 mL). La fase acuosa se enfrió en un baño de hielo y después se aciduló con una disolución acuosa de HCl 1M a pH 2. La fase acuosa ácida se extrajo con acetato de etilo (2 x 50 mL) y con isopropanol/cloroformo (3 x 50 mL). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se filtraron. La concentración del filtrado a presión reducida dio 734 mg de ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propiónico.

Los siguientes ácidos se sintetizaron de acuerdo con este procedimiento:

Tabla 9

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propiónico	100	251
	ácido 2-metil-2-(tetrahidro-piran-4-sulfonil)-propiónico	93	237
	ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico	80	263

Etapa 5: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

Preparado como se describe por adaptación del Método A, etapa 4.

La activación de 122 mg (0,49 mmol) de ácido 2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propiónico como su cloruro de ácido correspondiente se alcanzó mediante tratamiento con cloruro de tionilo (0,4 mL) a 50 °C durante 1 h. La reacción se enfrió a temperatura ambiente y se eliminó el exceso de cloruro de tionilo a presión reducida.

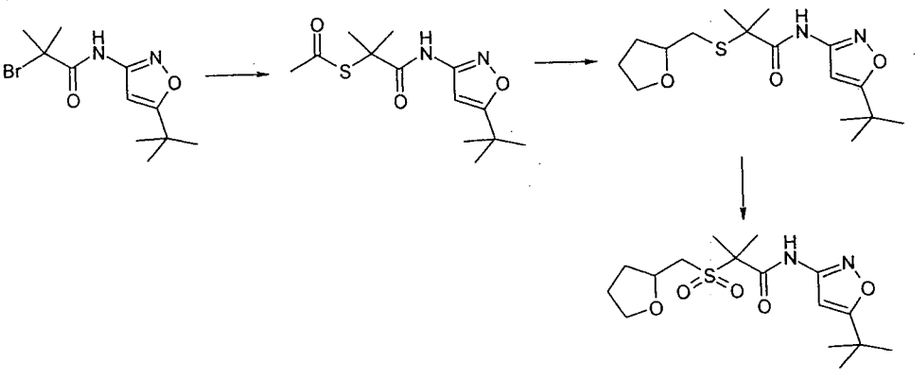
El cloruro de ácido en bruto se disolvió en DCM (2 ml) y se añadió a una solución de 63 mg (0,49 mmol) de 3-amino-5-terc-butilisoxazol y N,N-diisopropiletilamina (145 ml, 0,88 mmol) en DCM (2 mL). La reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con DCM (2 mL) y se lavó con una mezcla de disolución acuosa saturada de $NaHCO_3$/salmuera (1/1, 2 mL). La fase orgánica se secó sobre Na_2SO_4, se filtró y concentró a presión reducida. El producto en bruto se purificó por cromatografía de columna

(sílice, eluyente: heptanos, 0-20 % de acetato de etilo, después DCM, 0-20 % de acetato de etilo) para dar 41 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida.

Los ejemplos enumerados en la Tabla 17, Método E, se hicieron según este procedimiento.

Método F

Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-4-ilmetanosulfonil)-propionamida (Ejemplo 74, Tabla 17)

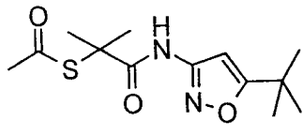
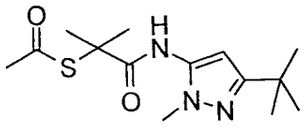
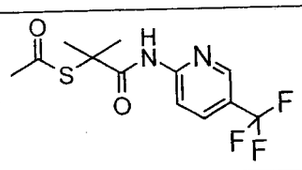
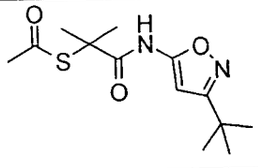


Etapa 1: Síntesis de S-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etil]éster de ácido tioacético

A una disolución de 200 mg (0,69 mmol) de 2-bromo-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida (preparada como se describe en el Método B, etapa 2) en DMF (3 mL) se añadieron 157 mg (1,4 mmol) de tioacetato de potasio. La reacción se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con dietiléter (5 mL) y se lavó con disolución acuosa de HCl 2M (5 mL). La fase orgánica se secó sobre Na_2SO_4. La filtración y concentración a presión reducida proporcionó 151 mg de S-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etil]éster de ácido tioacético.

Según este procedimiento, los siguientes tioacetatos se sintetizaron:

Tabla 10

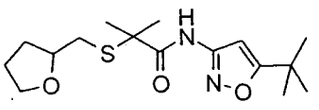
ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	S-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etil]éster de ácido tioacético	76	285
	S-[1-(5-terc-butil-2-metil-2H-pirazol-3-ilcarbamoil)-1-metil-etil]éster de ácido tioacético	73	298
	S-[1-metil-1-(5-trifluoro-metil-piridin-2-ilcarba-moil)-etil]éster de ácido tioacético	62	307
	S-[1-(3-terc.-butil-isoxazol-5-ilcarbamoil)-1-metil-etil]éster de ácido tioacético	62	285

Etapa 2: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetilsulfonil)-propionamida

A una disolución de 100 mg (0,35 mmol) de S-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etil]éster de ácido tioacético en etanol (2 mL), se añadieron 70 mg (0,42 mmol) de 2-(bromometil)tetrahidrofurano y 340 µL (1,05 mmol) de disolución de etóxido sódico (21% en etanol) a temperatura ambiente. La reacción se calentó a 50 °C durante 18 h. La mezcla de reacción se concentró a presión reducida y el producto en bruto se purificó por cromatografía en columna (sílice, eluyente: heptanos, 0-20 % de acetato de etilo) para dar 82 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetilsulfanil)-propionamida.

Los siguientes tioéteres se sintetizaron de acuerdo con este procedimiento:

Tabla 11

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetilsulfanil)-propionamida	71	327

Etapa 3 Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

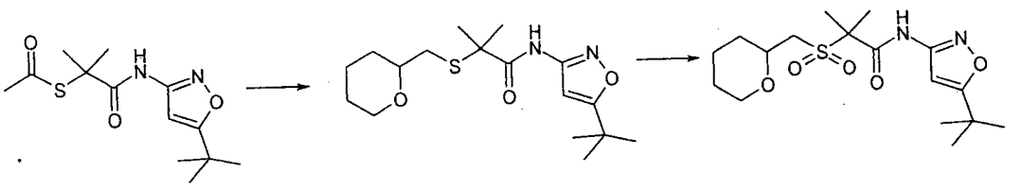
Preparado como se describe por adaptación del Método D, etapa 2.

A una disolución de 82 mg (0,25 mmol) de N-(5-terc-butil-isoxazol-3-il-)-2-metil-2-(tetrahidro-furan-2-ilmetilsulfanil)-propionamida en dioxano/agua (5/1, 4 mL) se añadieron en una vez 460 mg (0,75 mmol) de sal triple de monopersulfato de potasio (OXONE®). La suspensión blanca se agitó a temperatura ambiente durante 3 h. El sólido blanco se separó por filtración y se lavó con dioxano (5 mL). El filtrado se concentró a presión reducida para eliminar el disolvente orgánico. La disolución acuosa resultante se extrajo con DCM (2 x 5 mL). Los extractos orgánicos combinados se lavaron con disolución acuosa saturada de $NaHCO_3$ (5 mL), salmuera (5 mL), se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró a presión reducida. El residuo en bruto se purificó por cromatografía de columna (sílice, eluyente: DCM, 0-10 % de acetato de etilo) para dar 5 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida.

Los ejemplos enumerados en la Tabla 17, Método F, se hicieron según este procedimiento.

Método G

Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida (Ejemplo 82, Tabla 17)

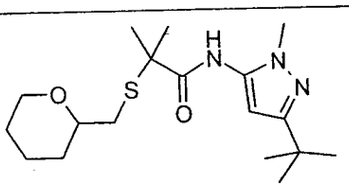


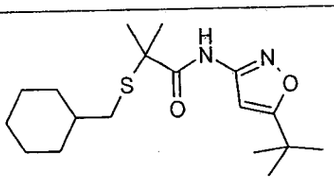
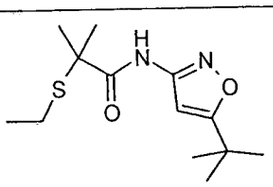
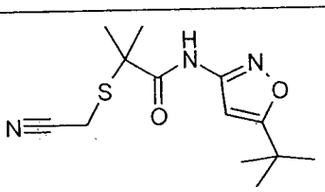
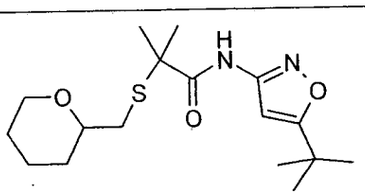
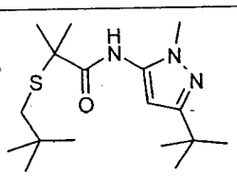
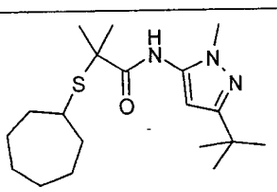
Etapa 1: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetilsulfanil)-propionamida

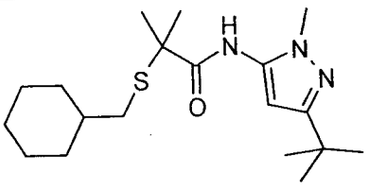
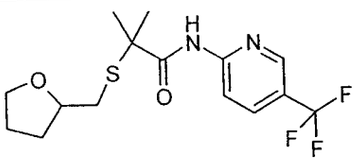
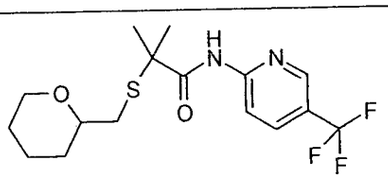
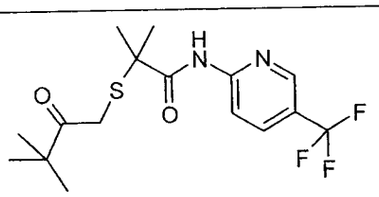
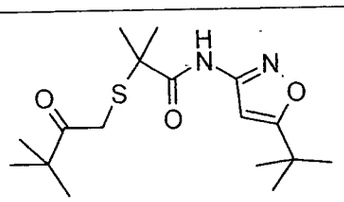
A una disolución de 100 mg (0,352 mmol) de S-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etil]éster de ácido tioacético (sintetizado según el Método F, etapa 1) en etanol (2 mL), se añadieron 126 mg (0,704 mmol) de 2-(bromometil)tetrahidropirano y 76 mg (1,41 mmol) de metóxido sódico a temperatura ambiente. La reacción se calentó a 130 °C durante 0,5 h en un microondas (CEM Discover). La mezcla de reacción se concentró a presión reducida. El residuo se disolvió en DCM (5 mL) y se lavó con disolución acuosa saturada de $NaHCO_3$ (5 mL). La fase orgánica se secó (Na_2SO_4), se filtró y concentró a presión reducida para dar 119 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetilsulfanil)-propionamida.

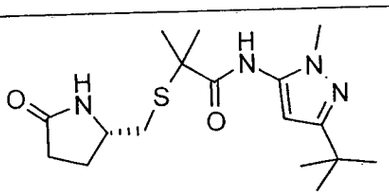
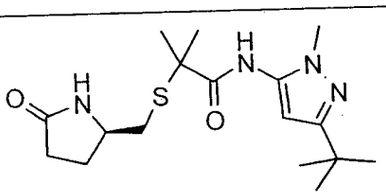
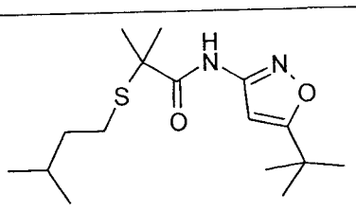
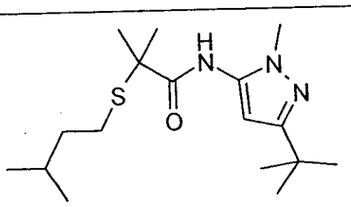
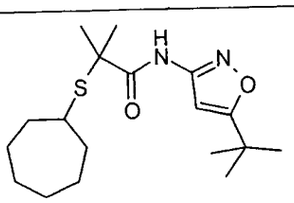
Los siguientes tioéteres se sintetizaron de acuerdo con este procedimiento:

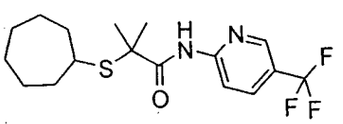
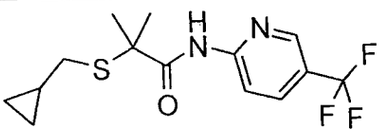
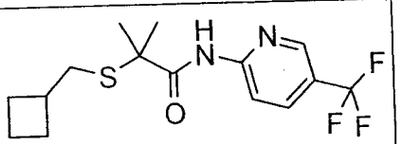
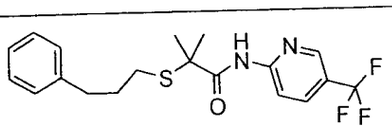
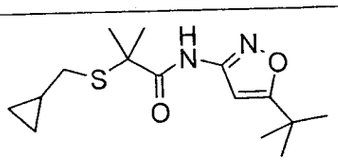
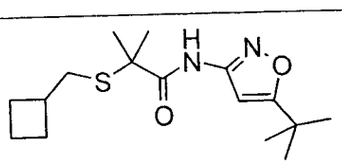
Tabla 12

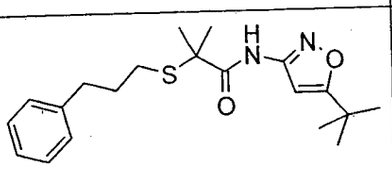
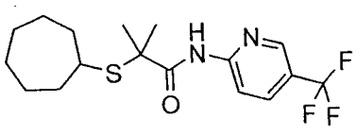
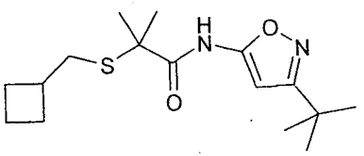
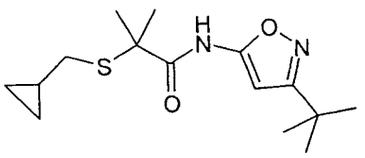
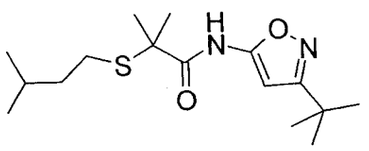
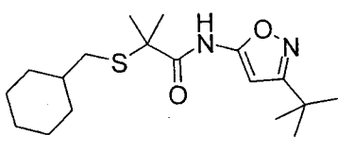
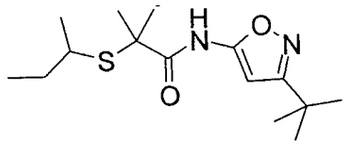
ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfanil)-propionamida	100	354

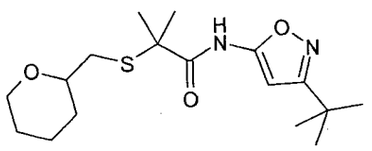
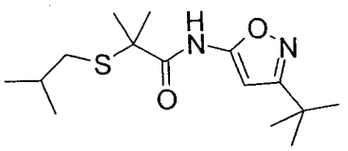
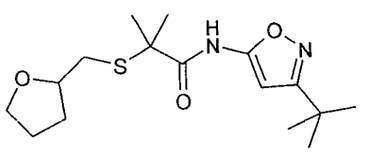
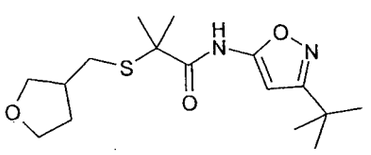
ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetilsulfanil-2-metil-propionamida	100	339
	N-(5-terc-butil-isoxazol-3-il)-2-etilsulfanil-2-metil-propionamida	90	271
	N-(5-terc-butil-isoxazol-3-il)-2-cianometilsulfanil-2-metil-propionamida	96	282
	N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetilsulfanil)-propionamida	100	341
	N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(2,2-dimetil-propilsulfanil)-2-metil-propionamida	63	326
	N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptilsulfanil-2-metil-propionamida	68	352

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetilsulfanil-2-metil-propionamida	95	352
	2-Metil-2-(tetrahidro-furan-2-ilmetilsulfanil)-N-(5-trifluorometil-piridin-2-il)-propionamida	53	349
	2-Metil-2-(tetrahidro-piran-2-ilmetilsulfanil)-N-(5-trifluorometil-piridin-2-il)-propionamida	54	363
	2-(3,3-Dimetil-2-oxo-butilsulfanil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	45	363
	N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butilsulfanil)-2-metil-propionamida	75	341

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((S)-5-oxo-pirrolidin-2-ilmetilsulfanil)-propionamida	85	353
	N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((R)-5-oxo-pirrolidin-2-ilmetilsulfanil)-propionamida	97	353
	N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butilsulfanil)-propionamida	70	313
	N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butilsulfanil)-propionamida	90	326
	N-(5-terc-butil-isoxazol-3-il)-2-cicloheptilsulfanil-2-metil-propionamida	89	339

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	2-cicloheptilsulfanil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	83	361
	2-ciclopropilmetilsulfanil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	100	319
	2-ciclobutilmetilsulfanil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	97	333
	2-metil-2-(3-fenil-propilsulfanil)-N-(5-trifluorometil-piridin-2-il)-propionamida	82	383
	N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetilsulfanil-2-metil-propionamida	74	297
	N-(5-terc-butil-isoxazol-3-il)-2-ciclobutilmetilsulfanil-2-metil-propionamida	77	311

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-fenil-propilsulfanil)-propionamida	86	361
	2-cicloheptilsulfanil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	83	361
	N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetilsulfanil-2-metil-propionamida	55	361
	N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetil-sulfanil-2-metil-propionamida	70	297
	N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butilsulfanil)-propionamida	50	313
	N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetil-sulfanil-2-metil-propionamida	50	339
	N-(3-terc-butil-isoxazol-5-il)-2-sec-butilsulfanil-2-metil-propionamida	73	299

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidropiran-2-ilmetilsulfanil)-propionamida	75	341
	N-(3-terc-butil-isoxazol-5-il)-2-isobutilsulfanil-2-metil-propionamida	73	299
	N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidrofuran-2-ilmetilsulfanil)-propionamida	100	327
	N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidrofuran-3-ilmetilsulfanil)-propionamida	100	327

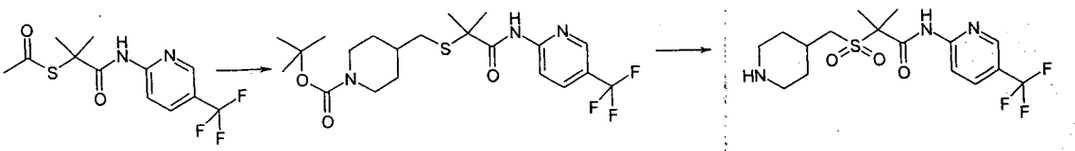
Etapa 3: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

A una disolución de 119 mg (0,365 mmol) de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetilsulfanil)-propionamida en ácido acético (1 mL) se añadieron 103 µL (1,83 mmol) de peróxido de hidrógeno (disolución al 50%, estabilizada en agua) y se calentó a 80 °C durante 50 minutos. La disolución incolora se apagó con etanol (2 mL) y se concentró a presión reducida. El material en bruto se purificó por LCMS de preparación activado por masa y el TFA residual se eliminó por filtración a través de un pequeño tapón de resina Ambersep 900-OH para dar 27 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida.

Los ejemplos enumerados en la Tabla 17, Método G, se prepararon de acuerdo con este procedimiento.

Método H

Síntesis de 2-metil-2-(piperidin-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida (Ejemplo 98, Tabla 17)

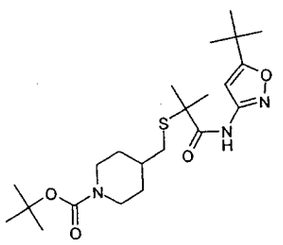
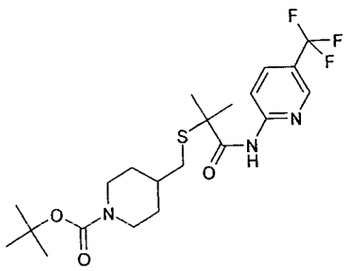
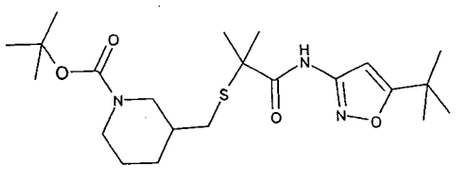
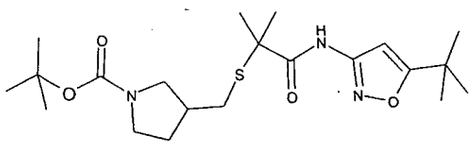


Etapa 1: Síntesis de terc-butiléster de ácido 4-[1-metil-1-(5-trifluorometil-piridin-2-ilcarbamoil)-etilsulfanilmetil]-piperidina-1-carboxílico

A una disolución de 200 mg (0,654 mmol) de S-[1-metil-1-(5-trifluorometil-piridin-2-ilcarbamoil)-etil]éster de ácido tioacético (sintetizado según el Método F, etapa 1) en etanol (2 mL), se añadieron 363 mg (1,31 mmol) de terc-butiléster de ácido 4-bromometil-piperidina-1-carboxílico y 141 mg (2,61 mmol) de metóxido sódico a temperatura ambiente. La reacción se calentó a 130 °C durante 0,5 h en un microondas (CEM Discover). La mezcla de reacción se concentró a presión reducida. El residuo se disolvió en DCM (4 mL) y se lavó con disolución acuosa saturada de $NaHCO_3$ (5 mL). La fase orgánica se secó sobre Na_2SO_4, se filtró y el filtrado se concentró a presión reducida para dar 375 mg de terc-butiléster de ácido 4-[1-metil-1-(5-trifluorometil-piridin-2-ilcarbamoil)-etilsulfanilmetil]-piperidina-1-carboxílico.

Según este procedimiento, los siguientes tioéteres se sintetizaron:

Tabla 13

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	terc-butiléster de ácido 4-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etilsulfanilmetil]-piperidina-1-carboxílico	89	462 [M+Na$^+$], 340 [M+H$^+$-$C_5H_8O_2$]
	terc-butiléster de ácido 4-[1-metil-1-(5-trifluorometil-piridin-2-ilcarbamoil)-etilsulfanilmetil]-piperidina-1-carboxílico	100	462 [M+H$^+$], 485 [M+Na$^+$]
	terc-butiléster de ácido 3-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etilsulfanilmetil]-piperidina-1-carboxílico	88	462 [M+Na$^+$], 340 [M+H$^+$-$C_5H_8O_2$]
	terc-butiléster de ácido 3-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etilsulfanilmetil]-piperidina-1-carboxílico	30	426 [M+H$^+$], 448 [M+Na$^+$], 326 [M+H$^+$-$C_5H_8O_2$]

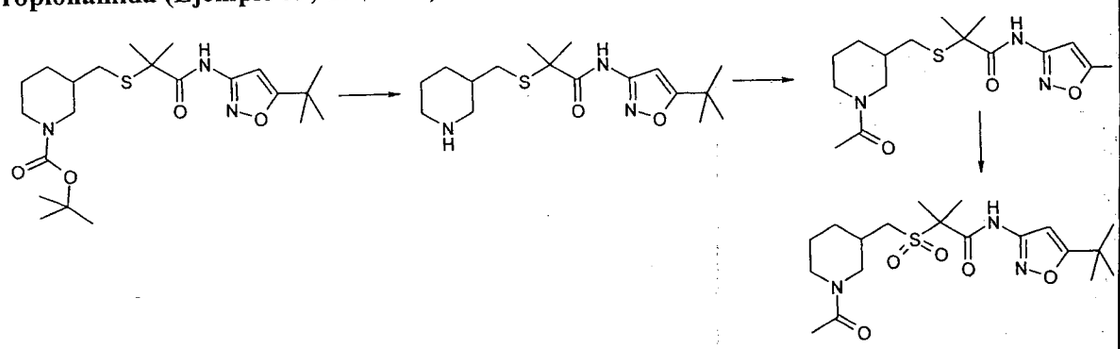
Etapa 2: Síntesis de 2-metil-2-(piperidin-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

A una disolución de 375 mg (0,81 mmol) de terc-butiléster de ácido 4-[1-metil-1-(5-trifluorometil-piridin-2-ilcarbamoil)-etilsulfanilmetil]-piperidina-1-carboxílico en ácido acético (1 mL) se añadieron 241 µL (4,26 mmol) de peróxido de hidrógeno (disolución al 50%, estabilizada en agua) y se calentó a 80 °C durante 50 minutos. La disolución incolora se apagó con etanol (2 mL) y se concentró a presión reducida. El material en bruto se trató con una disolución de TFA al 10% en DCM (5 mL) durante 16 h. Los disolventes se eliminaron a presión reducida. El residuo se purificó por LC de preparación activado por masa y el TFA residual se eliminó por filtración a través de un pequeño tapón de resina Ambersep 900-OH para dar 24,8 mg de 2-metil-2-(piperidin-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)propionamida.

Los ejemplos que se muestran en la Tabla 17, Método H, se prepararon de acuerdo con este procedimiento.

Método I

Síntesis de 2-(1-acetil-piperidin-3-ilmetanesulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida (Ejemplo 39, Tabla 17)



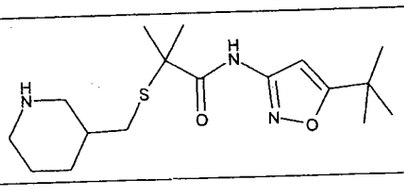
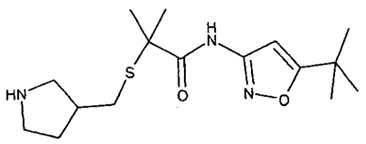
Etapa 1: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(piperidin-3-ilmetilsulfanil)-propionamida

A una disolución de 288 mg (0,65 mmol) de terc-butiléster de ácido 3-[1-(5-terc-butil-isoxazol-3-ilcarbamoil)-1-metil-etilsulfanilmetil]-piperidina-1-carboxílico (sintetizado según

el Método H, etapa 1) en DCM (5 mL) se añadieron 1,1 mL de HCl (disolución 2M en dioxano). La reacción se agitó a temperatura ambiente durante 16 h. La mezcla se diluyó con disolución acuosa saturada de $NaHCO_3$ (5 mL), la fase orgánica se separó y se secó sobre Na_2SO_4. La filtración y concentración del filtrado a presión reducida proporcionó 175 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(piperidin-3-ilmetilsulfanil)-propionamida.

Según este procedimiento, los siguientes tioéteres se sintetizaron:

Tabla 14

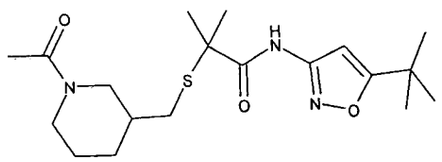
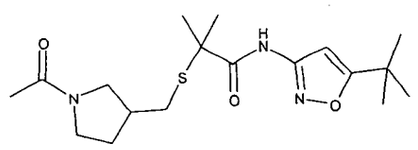
ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(piperidin-3-ilmetilsulfanil)-propionamida	79	340
	N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(pirrolidin-3-ilmetilsulfanil)-propionamida	89	326

Etapa 2: Síntesis de 2-(1-acetil-piperidin-3-ilmetilsulfanil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

Una disolución de 175 mg (0,52 mmol) de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(piperidin-3-ilmetilsulfanil)-propionamida, 0,18 mL (1,04 mmol) de N,N-diisopropiletilamina y anhídrido acético (1,5 mL) se calentaron durante 0,5 h a 100 °C en un microondas (CEM discover). El disolvente se eliminó a presión reducida. El residuo se disolvió en DCM (5 mL) y se lavó con disolución acuosa saturada de $NaHCO_3$ (5 mL). La fase orgánica se secó sobre Na_2SO_4, se filtró y el filtrado se concentró a presión reducida para proporcionar 183 mg de 2-(1-acetil-piperidin-3-ilmetilsulfanil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida, que se usó en la siguiente etapa sin purificación adicional.

Las siguientes amidas se sintetizaron de acuerdo con este procedimiento:

Tabla 15

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	2-(1-acetil-piperidin-3-ilmetilsulfanil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida	92	382
	2-(1-acetil-pirrolidin-3-ilmetilsulfanil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida	80	368

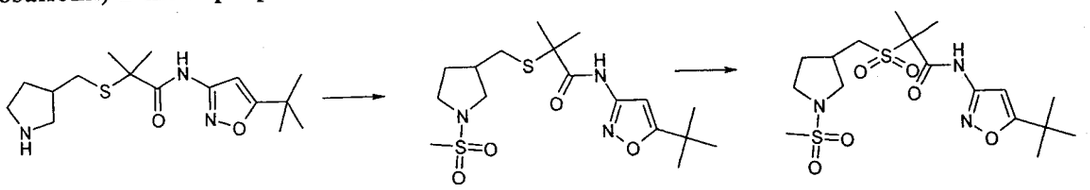
Etapa 3: Síntesis de 2-(1-acetil-piperidin-3-ilmetanosulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

A una disolución de 183 mg (0,48 mmol) de 2-(1-acetil-piperidin-3-ilmetilsulfanil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida en DCM (5 mL) se añadieron 123 mg (0,72 mmol) de ácido *m*-cloroperoxibenzóico. La reacción se agitó a temperatura ambiente hasta completarse. Entonces se añadieron 774 mg (2,4 mmol) de poli(estireno de aminometileno) a la reacción y la mezcla se agitó durante 18h. Las resinas se separaron por filtración y se aclararon con DCM. El filtrado se concentró a presión reducida y se purificó por LCMS de preparación activado por masa (a pH neutro) para proporcionar 34 mg de 2-(1-acetil-piperidin-3-ilmetanosulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

Los ejemplos enumerados en la Tabla 17, Método I, se prepararon de acuerdo con este procedimiento.

Método J

Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida (Ejemplo 127, Tabla 17)

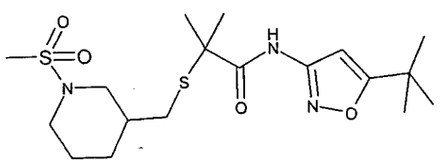


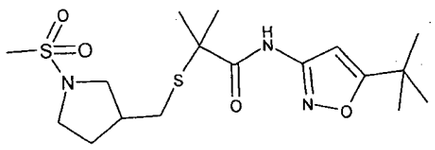
Etapa 1: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetilsulfanil)-2-metil-propionamida

A una disolución de 172 mg (0,52 mmol) de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(pirrolidin-3-ilmetilsulfanil)-propionamida (preparada según el Método I, etapa 1) y 0,18 mL (1,04 mmol) de N,N-diisopropiletilamina en THF, se añadieron 0,16 mL (2,11 mmol) de cloruro de metanosulfonilo. La reacción se calentó en un microondas a 90 °C durante 0,5 h. La mezcla se concentró a presión reducida. El residuo se disolvió en DCM (5 mL) y se lavó con disolución acuosa saturada de $NaHCO_3$ (5 mL). La fase orgánica se secó sobre Na_2SO_4, se filtró y el filtrado se concentró a presión reducida para proporcionar 168 mg de N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetilsulfanil)-2-metil-propionamida, que se usó en la siguiente etapa sin purificación adicional.

Las siguientes sulfonamidas se sintetizaron de acuerdo con este procedimiento:

Tabla 16

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-piperidin-3-ilmetilsulfanil)-2-metil-propionamida	73	418

ESTRUCTURA MOLECULAR	NOMBRE	RENDIMIENTO [%]	m/z [M+H$^+$]
	N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetilsulfanil)-2-metil-propionamida	78	404

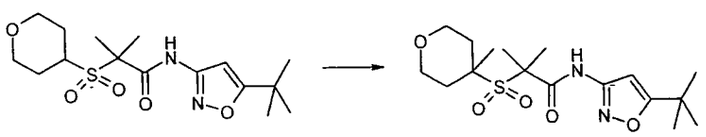
Etapa 2: Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfanil)-2-metil-propionamida

A una disolución de 168 mg (0,41 mmol) de N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetilsulfanil)-2-metil-propionamida en DCM (5 mL) se añadieron 107 mg (0,63 mmol) de ácido *m*-cloroperoxibenzóico. La reacción se agitó a temperatura ambiente hasta completarse. Entonces se añadieron 672 mg (2,08 mmol) de poli(estireno de aminometileno) a la reacción y la mezcla se agitó durante 18 h. Las resinas se separaron por filtración y se aclararon con DCM. El filtrado se concentró a presión reducida y el residuo se purificó por LCMS de preparación activado por masa (a pH neutro) para proporcionar 37 mg de N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida.

Los ejemplos enumerados en la Tabla 17, Método J, se prepararon de acuerdo con este procedimiento.

<u>Método K</u>

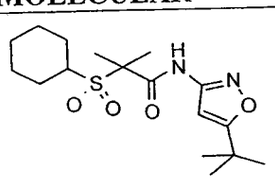
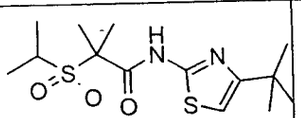
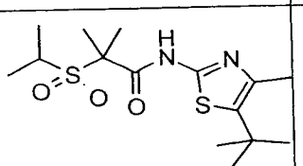
Síntesis de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(4-metil-tetrahidro-piran-4-sulfonil)-propionamida (Ejemplo 100, Tabla 17)

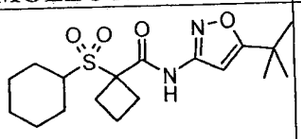
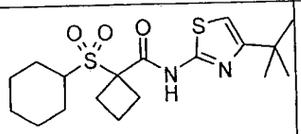
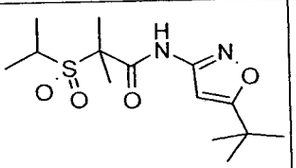
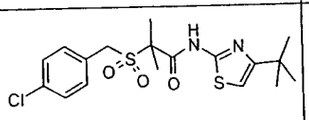
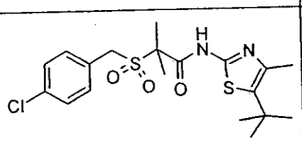
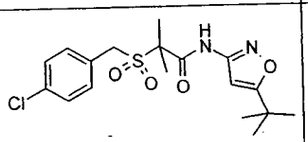
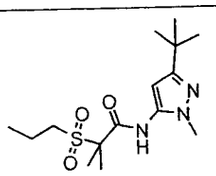


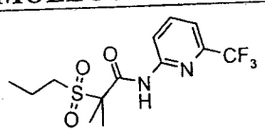
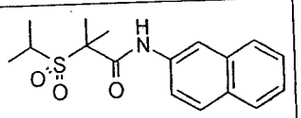
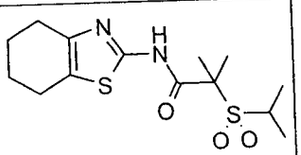
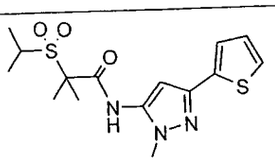
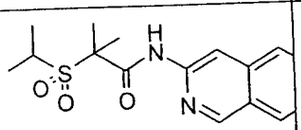
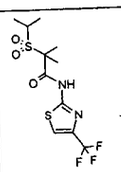
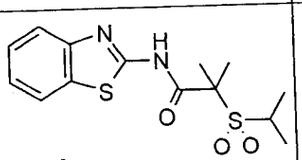
A una disolución de 202 mg (0,56 mmol) de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida (preparada según el Método E) en THF anhidro (10 mL) a -78 °C en atmósfera de nitrógeno, se añadieron 0,8 mL (1,4 mmol) de diisopropilamida de litio (disolución 1,8 M en THF/heptano/etilbenceno) y la reacción se agitó a -78 °C durante 0,5 h. Después se añadieron 0,1 mL (1,6 mmol) de yoduro de metilo en una vez y se continuó la agitación durante 0,5 h adicionales a -78 °C, antes de que la reacción se calentara a temperatura ambiente. Después de 18 h a temperatura ambiente la reacción se apagó mediante la adición de disolución acuosa saturada de NH_4Cl (25 mL). La mezcla se extrajo con acetato de etilo (3 x 25 mL). Los extractos orgánicos se combinaron, se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró a presión reducida y el residuo se purificó por LCMS de preparación activado por masa para proporcionar 31 mg de N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(4-metil-tetrahidro-piran-4-sulfonil)-propionamida.

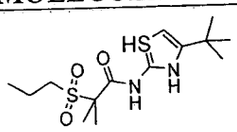
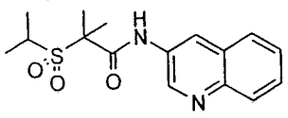
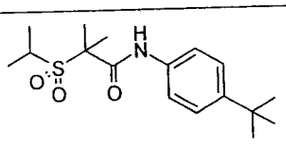
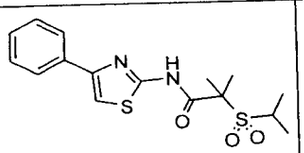
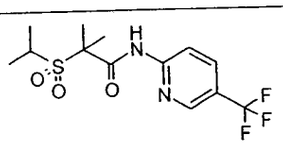
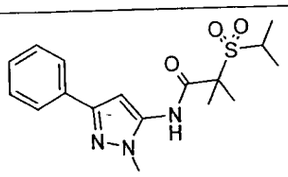
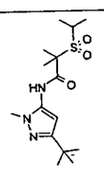
Los ejemplos enumerados en la Tabla 17, Método K, se prepararon de acuerdo con este procedimiento.

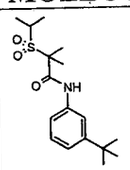
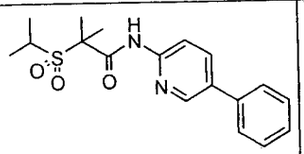
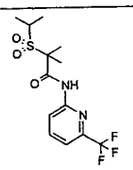
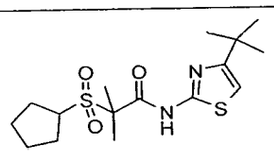
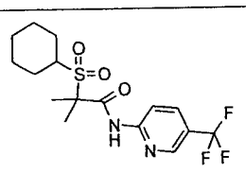
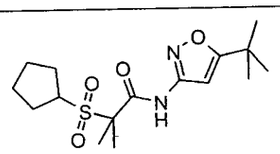
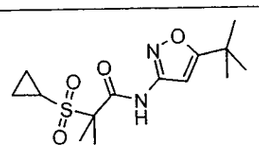
Tabla 17: EJEMPLOS

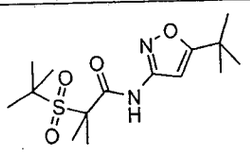
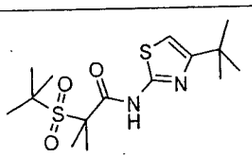
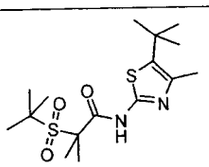
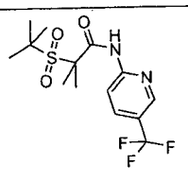
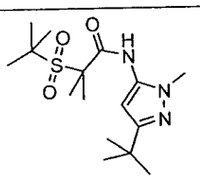
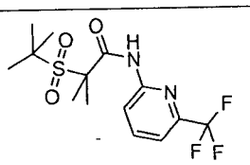
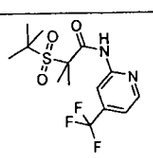
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
1		N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida	357	A
2		N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida	333	A
3		N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida	347	A

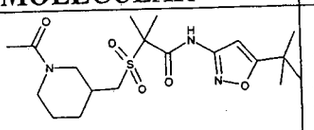
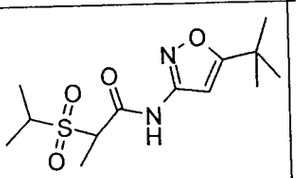
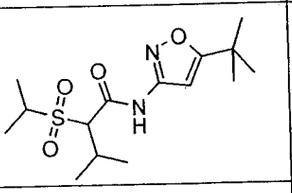
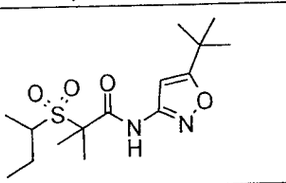
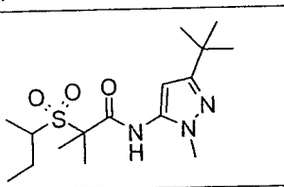
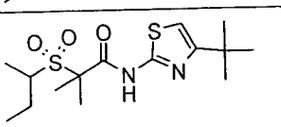
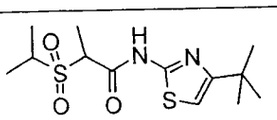
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
4		(5-terc-butil-isoxazol-3-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico	369	A
5		(4-terc-butil-tiazol-2-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico	385	A
6		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida	317	A
7		N-(4-terc-butil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida	415/417	A
8		N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida	429/431	A
9		N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida	399/401	A
10		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida	317	C

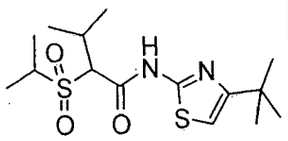
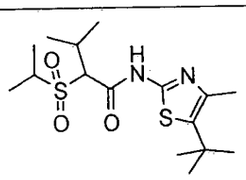
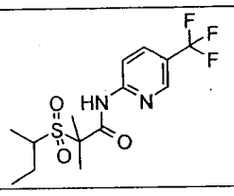
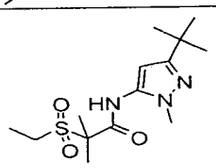
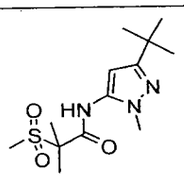
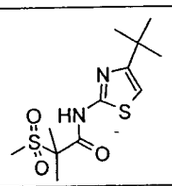
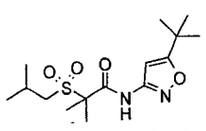
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
11		2-metil-2-(propano-1-sulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida	339	A
12		2-metil-N-naftalen-2-il-2-(propano-2-sulfonil)-propionamida	320,25	A
13		2-metil-2-(propano-2-sulfonil)-N-(4,5,6,7-tetrahidrobenzotiazol-2-il)-propionamida	331,35	A
14		2-metil-N-(2-metil-5-tiofen-2-il-2H-pirazol-3-il)-2-(propano-2-sulfonil)-propionamida	356,21	A
15		N-isoquinolin-3-il-2-metil-2-(propano-2-sulfonil)-propionamida	321,27	A
16		2-metil-2-(propano-2-sulfonil)-N-(4-trifluorometil-tiazol-2-il)-propionamida	345,13	A
17		N-benzotiazol-2-il-2-metil-2-(propano-2-sulfonil)-propionamida	327,23	A

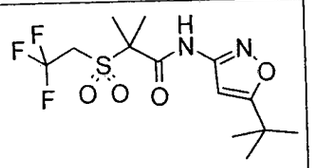
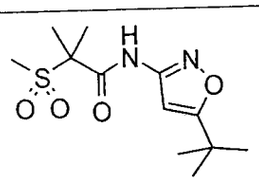
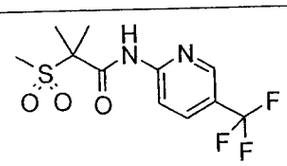
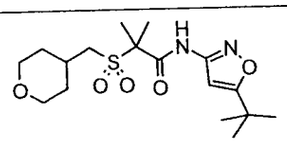
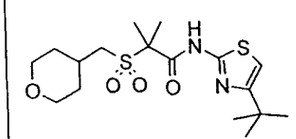
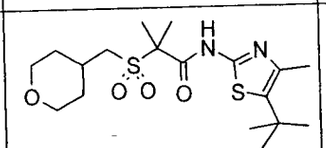
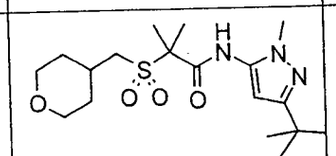
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
18		N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	333	A
19		2-metil-2-(propano-2-sulfonil)-N-quinolin-3-il-propionamida	321,36	A
20		N-(4-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida	326,27	A
21		2-metil-N-(4-fenil-tiazol-2-il)-2-(propano-2-sulfonil)-propionamida	353,26	A
22		2-metil-2-(propano-2-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	339,23	A
23		2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(propano-2-sulfonil)-propionamida	350,33	A
24		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida	330,29	A

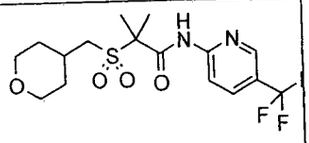
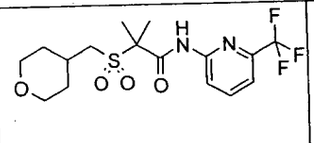
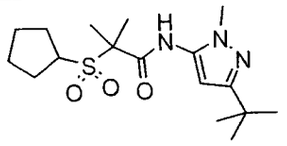
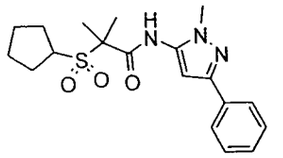
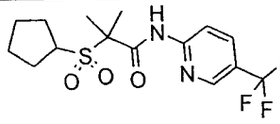
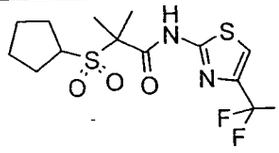
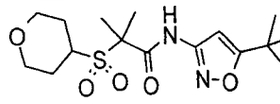
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
25		N-(3-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida	326,27	A
26		2-metil-N-(5-fenil-piridin-2-il)-2-(propano-2-sulfonil)-propionamida	347,31	A
27		2-metil-2-(propano-2-sulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida	339,18	A
28		N-(4-terc-butil-tiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida	359	A
29		2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	379	A
30		N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida	343	A
31		N-(5-terc-butil-isoxazol-3-il)-2-ciclopropanosulfonil-2-metil-propionamida	315	C

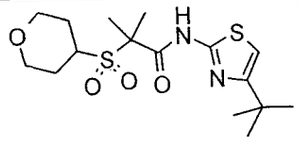
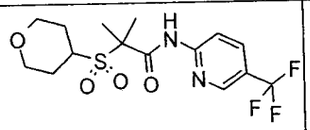
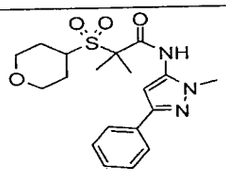
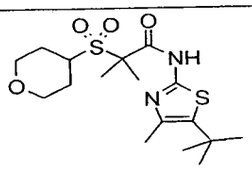
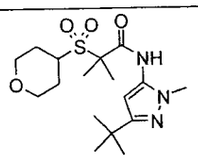
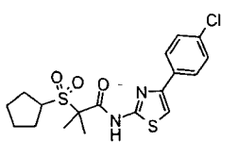
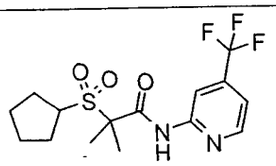
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
32		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida	331	A
33		N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida	347	A
34		N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida	361	A
35		2-metil-2-(2-metil-propano-2-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	353	A
36		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida	344	A
37		2-metil-2-(2-metil-propano-2-sulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida	353	A
38		2-metil-2-(2-metil-propano-2-sulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida	353	A

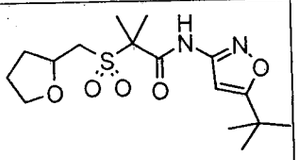
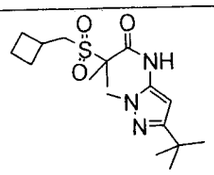
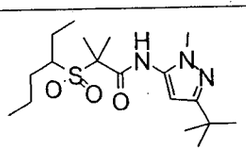
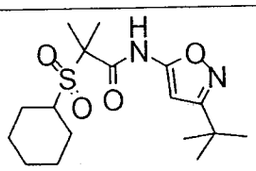
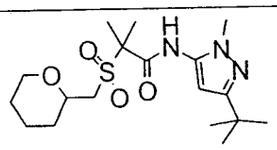
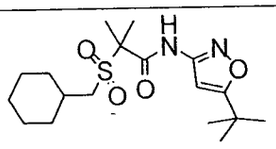
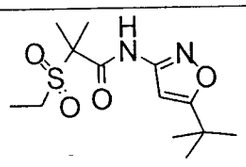
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
39		2-(1-acetil-piperidin-3-ilmetanosulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida	414	I
40		N-(5-terc-butil-isoxazol-3-il)-2-(propano-2-sulfonil)-propionamida	303	A
41		N-(5-terc-butil-isoxazol-3-il)-3-metil-2-(propano-2-sulfonil)-butiramida	331	A
42		2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida	331	A
43		2-(butano-2-sulfonil)-N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-propionamida	344	A
44		2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida	347	A
45		N-(4-terc-butil-tiazol-2-il)-2-(propano-2-sulfonil)-propionamida	319	A

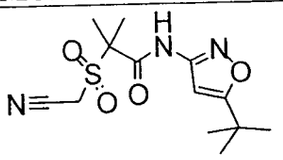
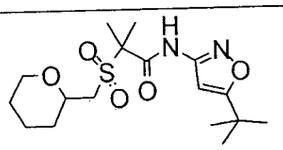
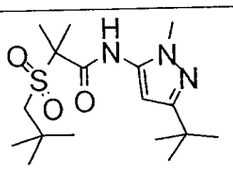
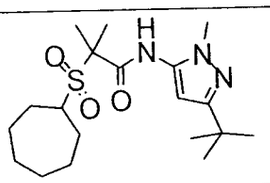
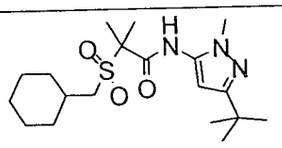
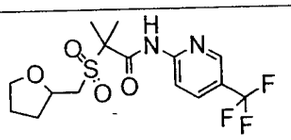
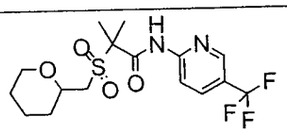
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
46		N-(4-terc-butil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida	347	A
47		N-(5-terc-butil-4-metil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida	361	A
48		2-(butano-2-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	353	A
49		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-etanosulfonil-2-metil-propionamida	316	A
50		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metanosulfonil-2-metil-propionamida	302	B
51		N-(4-terc-butil-tiazol-2-il)-2-metanosulfonil-2-metil-propionamida	305	B
52		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida	331	D

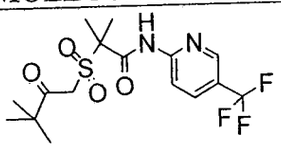
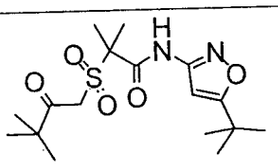
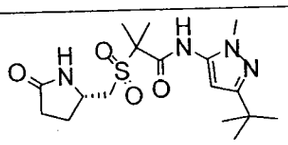
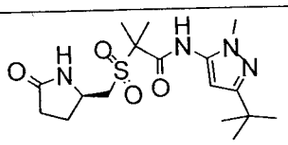
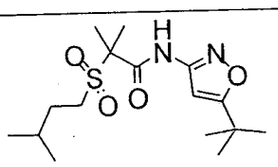
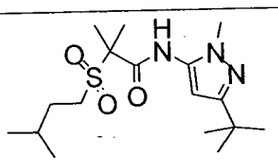
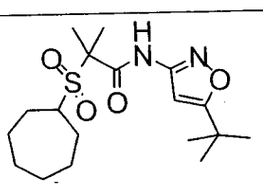
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
53		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2,2,2-trifluoro-etanosulfonil)-propionamida	357	B
54		N-(5-terc-butil-isoxazol-3-il)-2-metanosulfonil-2-metil-propionamida	289	B
55		2-metanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	311	B
56		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	373	E
57		N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	389	E
58		N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	403	E
59		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	386	E

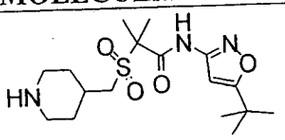
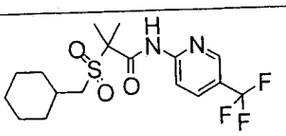
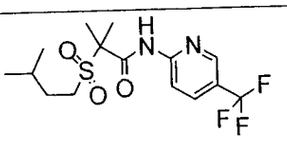
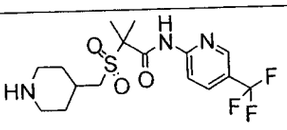
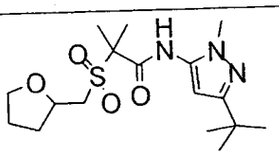
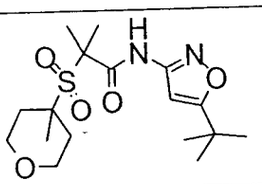
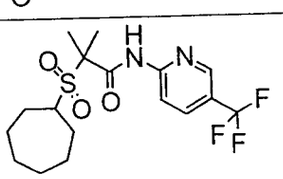
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
60		2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	395	E
61		2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida	395	E
62		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida	356	A
63		2-ciclopentanosulfonil-2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-propionamida	376	A
64		2-ciclopentanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	365	A
65		2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-tiazol-2-il)-propionamida	371	A
66		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	359	E

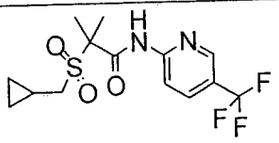
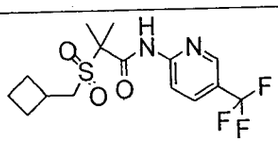
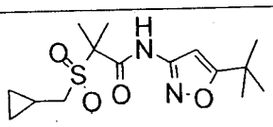
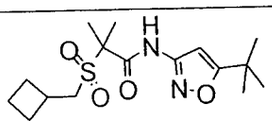
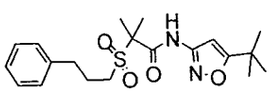
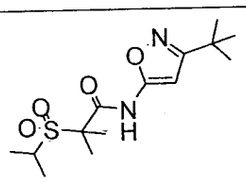
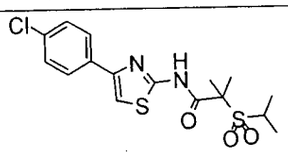
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
67		N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	375	E
68		2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	381	E
69		2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(tetrahidro-piran-4-sulfonil)-propionamida	392	E
70		N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	389	E
71		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	372	E
72		N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida	413/415	A
73		2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-piridin-2-il)-propionamida	365	A

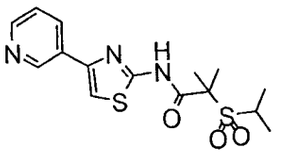
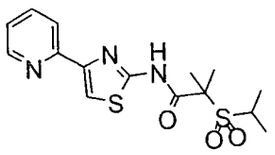
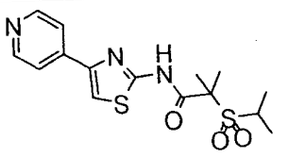
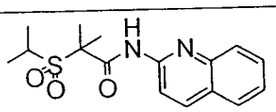
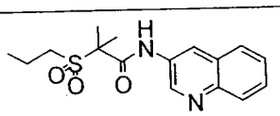
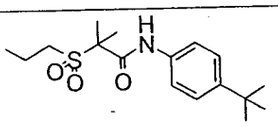
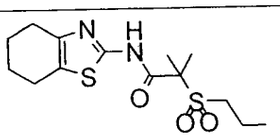
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
74		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida	359	F
75		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida	356	F
76		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(hexano-3-sulfonil)-2-metil-propionamida	372	F
77		N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida	357	A
78		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida	386	G
79		N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida	371	G
80		N-(5-terc-butil-isoxazol-3-il)-2-etanosulfonil-2-metil-propionamida	303	G

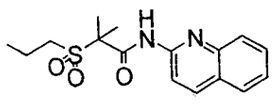
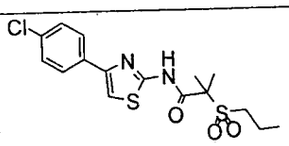
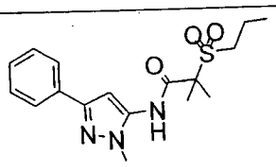
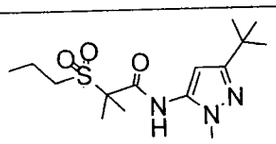
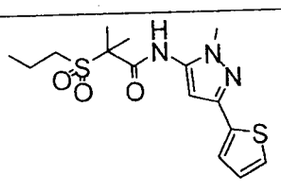
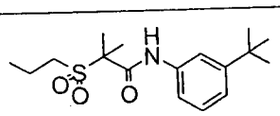
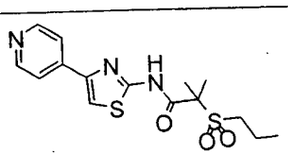
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
81		N-(5-terc-butil-isoxazol-3-il)-2-cianometanosulfonil-2-metil-propionamida	314	G
82		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida	373	G
83		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(2,2-dimetil-propano-1-sulfonil)-propionamida	358	G
84		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida	384	G
85		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida	384	G
86		2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	381	G
87		2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	395	G

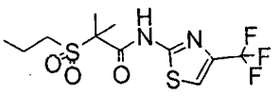
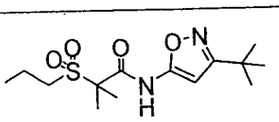
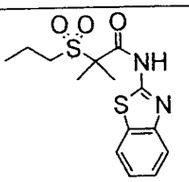
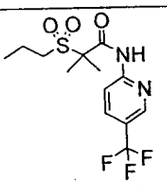
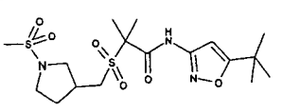
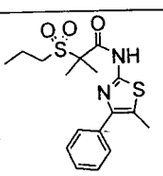
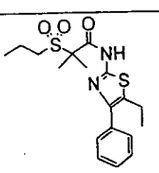
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
88		2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	395	G
89		N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida	373	G
90		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((S)-5-oxo-pirrolidin-2-ilmetanosulfonil)-propionamida	385	G
91		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((R)-5-oxo-pirrolidin-2-ilmetanosulfonil)-propionamida	385	G
92		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida	345	G
93		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida	358	G
94		N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida	371	G

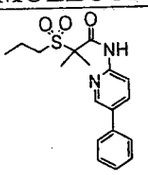
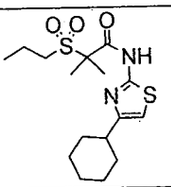
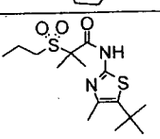
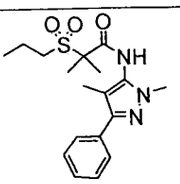
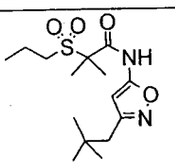
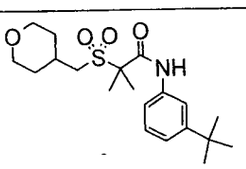
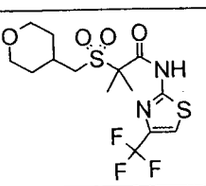
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
95		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(piperidin-4-ilmetanosulfonil)-propionamida	372	H
96		2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	393	G
97		2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	367	G
98		2-metil-2-(piperidin-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	394	H
99		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida	372	G
100		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(4-metil-tetrahidro-piran-4-sulfonil)-propionamida	373	K
101		2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	393	G

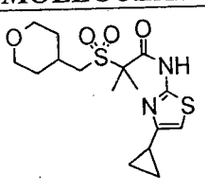
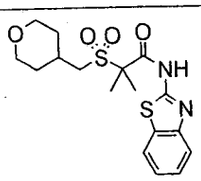
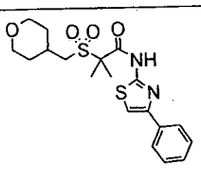
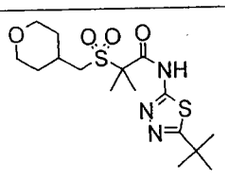
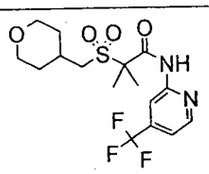
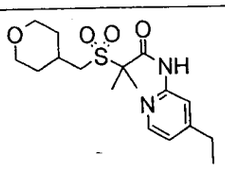
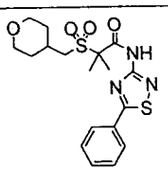
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
102		2-ciclopropilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	351	G
103		2-ciclobutilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	365	G
104		N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida	329	G
105		N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida	343	G
106		N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-fenil-propano-1-sulfonil)-propionamida	393	G
107		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-2-sulfonil)-propionamida	317	A
108		N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida	387/389	A

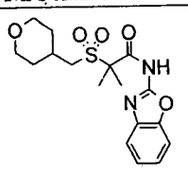
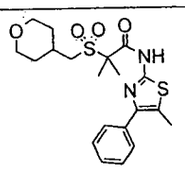
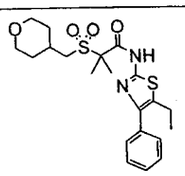
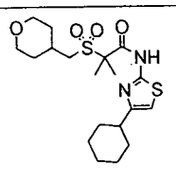
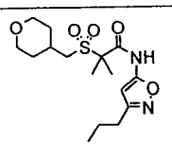
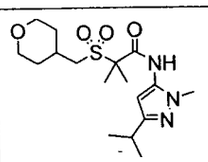
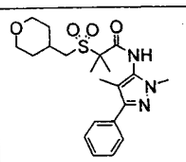
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
109		2-metil-2-(propano-2-sulfonil)-N-(4-piridin-3-il-tiazol-2-il)-propionamida	354	A
110		2-metil-2-(propano-2-sulfonil)-N-(4-piridin-2-il-tiazol-2-il)-propionamida	354	A
111		2-metil-2-(propano-2-sulfonil)-N-(4-piridin-4-il-tiazol-2-il)-propionamida	354	A
112		2-metil-2-(propano-2-sulfonil)-N-quinolin-2-il-propionamida	321	A
113		2-metil-2-(propano-1-sulfonil)-N-quinolin-3-il-propionamida	321	A
114		N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida	326	A
115		2-metil-2-(propano-1-sulfonil)-N-(4,5,6,7-tetrahidrobenzotiazol-2-il)-propionamida	331	A

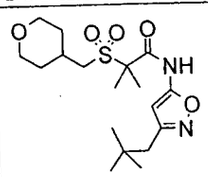
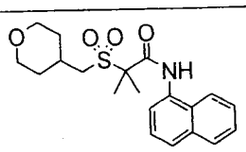
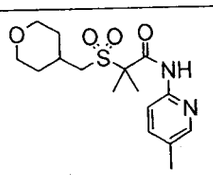
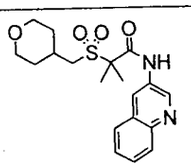
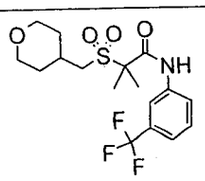
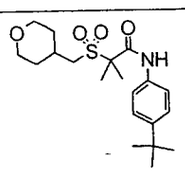
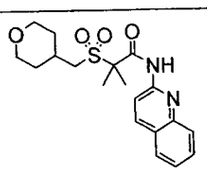
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
116		2-metil-2-(propano-1-sulfonil)-N-quinolin-2-il-propionamida	321	A
1117		N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida	387/389	A
118		2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(propano-1-sulfonil)-propionamida	350	A
119		N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida	330	A
120		2-metil-N-(2-metil-5-tiofen-2-il-2H-pirazol-3-il)-2-(propano-1-sulfonil)-propionamida	356	A
121		N-(3-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida	326	A
122		2-metil-2-(propano-1-sulfonil)-N-(4-piridin-4-il-tiazol-2-il)-propionamida	354	A

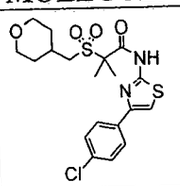
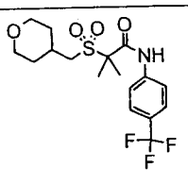
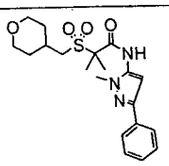
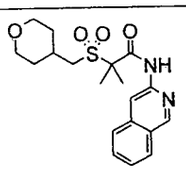
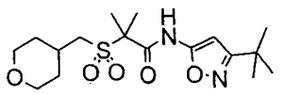
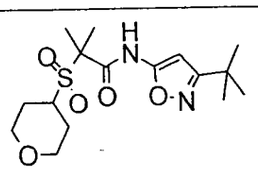
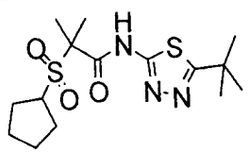
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
123		2-metil-2-(propano-1-sulfonil)-N-(4-trifluorometil-tiazol-2-il)-propionamida	345	A
124		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida	317	A
125		N-benzotiazol-2-il-2-metil-2-(propano-1-sulfonil)-propionamida	327	A
126		2-metil-2-(propano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	339	A
127		N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida	436	J
128		2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propano-1-sulfonil)-propionamida	367	A
129		N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	381	A

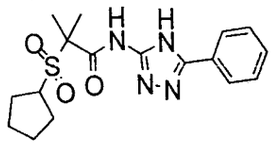
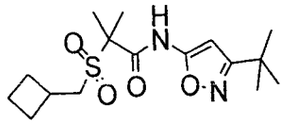
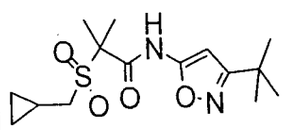
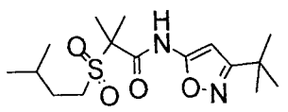
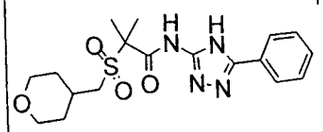
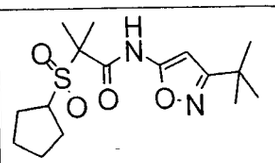
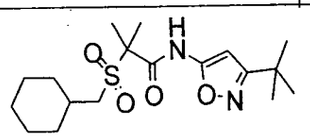
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
130		2-metil-N-(5-fenil-piridin-2-il)-2-(propano-1-sulfonil)-propionamida	347	A
131		N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	359	A
132		N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	347	A
133		N-(2,4-dimetil-5-fenil-2H-pirazol-3-il)-2-metil-2(propano-1-sulfonil)-propionamida	364	A
134		N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(propano-1-sulfonil)-propionamida	331	A
135		N-(3-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	382	E
136		2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-tiazol-2-il)-propionamida	401	E

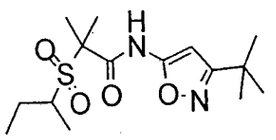
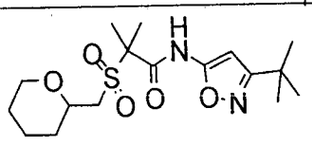
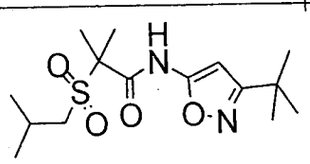
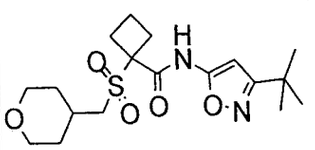
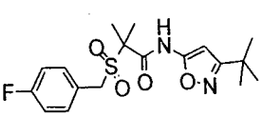
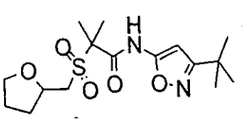
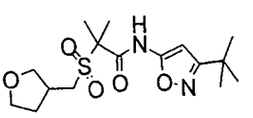
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
137		N-(4-ciclopropil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	373	E
138		N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	383	E
139		2-metil-N-(4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	409	E
140		N-(5-terc-butil-[1,3,4]tiadiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	390	E
141		2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida	395	E
142		N-(4-etil-piridin-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	355	E
143		2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	410	E

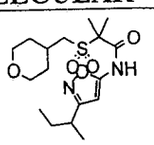
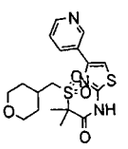
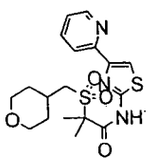
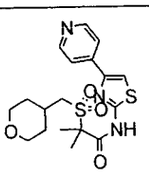
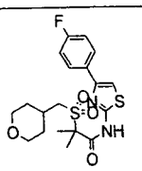
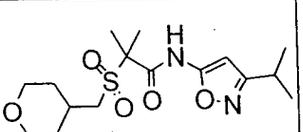
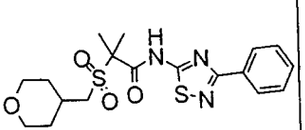
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
144		N-benzooxazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	367	E
145		2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	423	E
146		N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	437	E
147		N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	415	E
148		2-metil-N-(3-propil-isoxazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	359	E
149		N-(5-isopropil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	372	E
150		N-(2,4-dimetil-5-fenil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	420	E

nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
151		N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	387	E
152		2-metil-N-naftalen-1-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	376	E
153		2-metil-N-(5-metil-piridin-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	341	E
154		2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	377	E
155		2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(3-trifluorometil-fenil)-propionamida	394	E
156		N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	382	E
157		2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	377	E

nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
158		N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	443	E
159		2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-fenil)-propionamida	394	E
160		2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	406	E
161		N-isoquinolin-3-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	377	E
162		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	373	E
163		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	359	E
164		N-(5-tert-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida	360	A

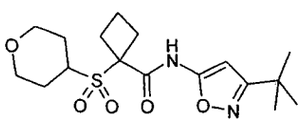
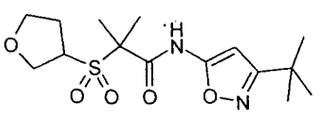
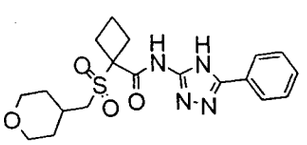
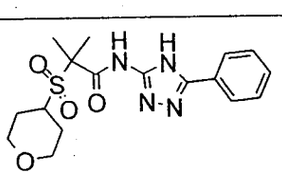
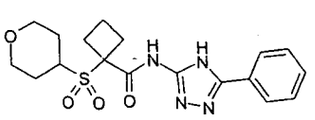
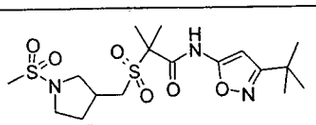
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
165		2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida	363	A
166		N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida	343	G
167		N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida	329	G
168		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida	345	G
169		2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	393	E
170		N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida	343	A
171		N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida	371	G

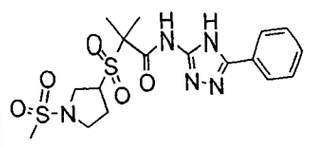
nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H$^+$]	Método
172		2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida	331	G
173		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida	373	G
174		N-(3-terc-butyl-isoxazol-5-il)-2-metil-2-(2-metil-propan-1-sulfonil)-propionamida	331	G
175		(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico	385	E
176		N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida	383	D
177		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida	359	G
178		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida	359	G

nº	ESTRUCTURA MOLECULAR	NOMBRE	m/z [M+H⁺]	Método
179		(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico	373	E
180		2-metil-N-(4-piridin-3-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	410	E
181		2-metil-N-(4-piridin-2-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	410	E
182		2-metil-N-(4-piridin-4-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	410	E
183		N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	427	E
184		N-(3-isopropil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	359	E
185		2-metil-N-(3-fenil-1,2,4-tiadiazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	410	E

Los siguientes compuestos también se pueden preparar de acuerdo con los procedimientos antes descritos:

Tabla 18: Ejemplos

Nº	ESTRUCTURA MOLAR	NOMBRE
186		(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-sulfonil)-ciclobutanocarboxílico
187		N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-sulfonil)-propionamida
188		(5-fenil-4H-1,2,4-triazol-3-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico
189		2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-sulfonil)-propionamida
190		(5-fenil-4H-1,2,4-triazol-3-il)-amida del ácido 1-(tetrahidro-piran-4-sulfonil)-ciclobutanocarboxílico
191		N-(3-terc-butil-isoxazol-5-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida

192		2-(1-metanosulfonil-pirrolidin-3-sulfonil)-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida

Valoración de las Propiedades Biológicas

Las propiedades biológicas de los compuestos de la fórmula I se evaluaron utilizando los ensayos descritos a continuación.

A. Enlace a los receptores CB1 y CB2 humanos:

Método experimental:

Se consiguieron membranas CB2 y se prepararon a partir de células HEK293 EBNA transfectadas establemente con ADNc del receptor CB2 humano (Perkin Elmer Life and Analytical Sciences). Se aislaron las membranas CB1 a partir de células HEK co-transfectadas establemente con ADNc del receptor CB1 humano y Gα16. La preparación de membrana se unió a gotas de centelleo (gotas de Ysi-Poli-L-lisina SPA, GE Healthcare) durante 4 horas a temperatura ambiente en tampón de ensayo que contenía Tris 50 mM, pH 7,5, EDTA 2,5 mM, $MgCl_2$ 5 mM, Albúmina de Suero Bovino libre de ácidos grasos al 0,8%. La membrana sin unir se eliminó lavando en tampón de ensayo. La mezcla membrana–gota se añadió en placas de ensayo de 96 pocillos en cantidades de 15 ug de membrana por pocillo (CB2) o 2,5 ug por pocillo (CB1) y 1 mg de gota SPA por pocillo. Se añadieron los compuestos a la mezcla de membrana-gota en concentraciones dosis-respuesta que variaban de $1x10^{-5}$ M a $1x10^{-10}$ M con DMSO al 0,25%, final. La reacción de competición se inició con la adición de ^{3}H-CP55940 (Perkin Elmer Life and Analytical Sciences) a una concentración final de 1,5 nM (CB2) o 2,5 nM (CB1). La reacción se incubó a temperatura ambiente durante 18 horas y se midió con un lector de placas TopCount NXT. Se determinó el enlace total y el no específico en ausencia y en presencia de Win 55212 1,25 uM (Sigma). Los valores de la CI50 para cada compuesto se

calcularon como la concentración del compuesto que inhibe en 50% el enlace específico del ligando marcado radiactivamente con el receptor, utilizando el modelo logístico de cuatro parámetros XLFit 4.1. Los valores de la CI50 se convirtieron en valores de la constante de inhibición (Ki) utilizando la ecuación de Cheng-Prusoff.

B. Modulación mediada por CB2R de la síntesis de AMPc:

Se evaluó la actividad agonista o agonista inversa frente al CB2 de los compuestos de la invención de acuerdo con el siguiente método experimental. Se supone que los compuestos que mostraron unirse al CB2 mediante el ensayo de unión descrito anteriormente pero que no presentaron modulación mediada por el CB2R de la síntesis del AMPc mediante este ensayo, son antagonistas del CB2.

Método experimental:

Se pusieron en placas células CHO que expresan el CB2R humano (Euroscreen) con una densidad de 5.000 células por pocillo en placas de 384 pocillos y se incubaron durante la noche a 37°C. Después de eliminar el medio, las células se trataron con los compuestos de ensayo diluidos con tampón de estimulación que contenía IBMX 1 mM, BSA al 0,25% y forscolina 10 µM. La mezcla de ensayo se incubó durante 30 minutos a 37°C. Las células se sometieron a lisis y se midió la concentración de AMPc utilizando un kit DiscoverX –XS cAMP, siguiendo el protocolo del fabricante. En este estado, los agonistas disminuirán la producción de AMPc inducida por forscolina mientras que los agonistas inversos aumentarán adicionalmente la producción de AMPc inducida por forscolina. La CE50 de los agonistas se calculó como sigue. La cantidad máxima de AMPc producida por la forscolina comparada con el nivel de AMPc inhibido por el CP55940 1 µM se define como 100%. El valor de la CE50 de cada compuesto de ensayo se determinó como la concentración a la que se inhibió 50% de la síntesis de AMPc estimulada por la forscolina. Se analizaron los datos utilizando un modelo logístico de cuatro parámetros. (Modelo 205 de XLfit 4.0).

C. Modulación mediada por el CB1R de la síntesis del AMPc:

Se evaluó la actividad agonista o agonista inversa frente al CB1 de los compuestos de la invención de acuerdo con el siguiente método experimental. Se supone que los compuestos que mostraron enlazarse al CB1 mediante el ensayo de enlace descrito anteriormente pero que no presentaron modulación mediada por el CB1R de la síntesis del AMPc mediante este ensayo, son antagonistas del CB1.

Método experimental:

Se pusieron en placas células CHO que expresan el CB1R humano (Euroscreen) con una densidad de 5.000 células por pocillo en placas de 384 pocillos y se incubaron durante la noche a 37°C. Después de eliminar el medio, las células se trataron con los compuestos de ensayo diluidos con tampón de estimulación que contenía IBMX 1 mM, BSA al 0,25% y forscolina 10 µM. La mezcla de ensayo se incubó durante 30 minutos a 37°C. Las células se sometieron a lisis y se midió la concentración de AMPc utilizando un kit DiscoverX –XS cAMP, siguiendo el protocolo del fabricante. En este estado, los agonistas disminuirán la producción de AMPc inducida por forscolina mientras que los agonistas inversos aumentarán adicionalmente la producción de AMPc inducida por forscolina. Las CE50 de los agonistas se calcularon como sigue. La cantidad máxima de AMPc producida por la forscolina comparada con el nivel de AMPc inhibido por el CP55940 1 uM se define como 100%. El valor de la CE50 de cada compuesto de ensayo se determinó como la concentración a la que se inhibió el 50% de la síntesis de AMPc estimulada por la forscolina. Se analizaron los datos utilizando un modelo logístico de cuatro parámetros. (Modelo 205 de XLfit 4.0).

Compuestos que tienen actividad agonista

NOMBRE	**CB2 EC_{50} [nM]**
N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida	0,2

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida	25,8
(5-terc-butil-isoxazol-3-il)-amida del ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico	0,5
(4-terc-butil-tiazol-2-il)-amida del ácido 1-ciclohexanosulfonol-coclobutanocarboxílico	11,7
N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida	12,1
N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida	16,6
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida	61,9
N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	19,2
N-(4-terc-butil-tiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida	19,0
2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	11,8
N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida	2,4
N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida	61,1
N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida	10,7
2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida	18,7
2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida	14,4
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida	44,6
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	4,5
N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	23,0
N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	0,2
2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	72,3
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	0,7
N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	12,4
2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	62,4
N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	0,3
N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida	1,5
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida	70,5

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida	33,0
N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida	0,0
N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida	0,6
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida	0,2
N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida	6,5
N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida	23,8
2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	41,5
N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida	39,8
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida	0,2
N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida	15,4
N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida	0,1
2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	15,4
2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida	19,9
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(4-metil-tetrahidro-piran-4-sulfonil)-propionamida	9,4
2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida	7,1
N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida	34,3
N-(5-terc-butil-isoxazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida	3,4
N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida	44,9
N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida	12,3
N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida	13,0
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida	89,7
N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida	44,1

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propani-1-sulfonil)-propionamida	52,2
N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	10,8
N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	31,1
N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida	7,2
N-(3-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	14,3
N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	27,9
2-metil-N-(4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	7,1
2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	17,6
2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	2,5
N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	2,0
N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	8,3
N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	74,3
2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	86,0
N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	3,3
2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	5,8
N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	2,2
N-isoquinolin-3-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	99,1
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	4,0
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida	0,1
N-(5-terc-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida	18,6
2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida	3,8
N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida	3,7
N-(3-terv-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida	12,5

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida	0,04
2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	1,7
N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida	0,9
N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida	0,1
2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida	3,3
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida	0,2
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida	1,6
(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico	6,2
N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida	17,0
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida	31,5
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida	18,5
N-(3-sec-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	20,0
N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida	5,5

Mediante el uso de los ensayos descritos anteriormente se encontró que los siguientes compuestos presentan actividad agonista y por lo tanto son particularmente muy adecuados para el tratamiento del dolor así como para el tratamiento de la inflamación.

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida

(5-terc-butil-isoxazol-3-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico

(4-terc-butil-tiazol-2-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida

2-metil-N-naftalen-2-il-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4,5,6,7-tetrahidrobenzotiazol-2-il)-propionamida

2-metil-N-(2-metil-5-tiofen-2-il-2H-pirazol-3-il)-2-(propano-2-sulfonil)-propionamida

N-isoquinolin-3-il-2-metil-2-(propano-2-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-quinolin-3-il-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-N-(4-fenil-tiazol-2-il)-2-(propano-2-sulfonil)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(propano-2-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

2-metil-2-(2-metil-propano-2-sulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(2-metil-propano-2-sulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida

2-(1-acetil-piperidin-3-ilmetanosulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-3-metil-2-(propano-2-sulfonil)-butiramida

2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

N-(5-terc-butil-4-metil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

2-(butano-2-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-etanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metanosulfonil-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2,2,2-trifluoro-etanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-tiazol-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(hexano-3-sulfonil)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-etanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cianometanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(2,2-dimetil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((S)-5-oxo-pirrolidin-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((R)-5-oxo-pirrolidin-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(piperidin-4-ilmetanosulfonil)-propionamida

2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(piperidin-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(4-metil-tetrahidro-piran-4-sulfonil)-propionamida

2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclopropilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclobutilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-fenil-propano-1-sulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4-piridin-3-il-tiazol-2-il)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4-piridin-2-il-tiazol-2-il)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4-piridin-4-il-tiazol-2-il)-propionamida

2-metil-2-(propano-2-sulfonil)-N-quinolin-2-il-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-3-il-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4,5,6,7-tetrahidro-benzotiazol-2-il)-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-2-il-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-N-(2-metil-5-tiofen-2-il-2H-pirazol-3-il)-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4-piridin-4-il-tiazol-2-il)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4-trifluorometil-tiazol-2-il)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propano-1-sulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-N-(5-fenil-piridin-2-il)-2-(propano-1-sulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(2,4-dimetil-5-fenil-2H-pirazol-3-il)-2-metil-2(propano-1-sulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-tiazol-2-il)-propionamida

N-(4-ciclopropil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-[1,3,4]tiadiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida

N-(4-etil-piridin-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-benzooxazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(3-propil-isoxazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-isopropil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(2,4-dimetil-5-fenil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-naftalen-1-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-piridin-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(3-trifluorometil-fenil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-fenil)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-isoquinolin-3-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico

N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida

N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide

N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-piridin-3-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-piridin-2-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-piridin-4-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-isopropil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(3-fenil-1,2,4-tiadiazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida.

De los compuestos anteriores se prefieren los siguientes:

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida

(5-terc-butil-isoxazol-3-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

N-(5-terc-butil-4-metil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(hexano-3-sulfonil)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclopropilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclobutilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-quinolin-2-il-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-3-il-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-2-il-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propano-1-sulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-[1,3,4]tiadiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(3-propil-isoxazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(3-trifluorometil-fenil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-fenil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(2-metil-propanio-1-sulfonil)-propionamida

(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico

N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida

N-(3-sec-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-piridin-3-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-piridin-2-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-piridin-4-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

De los compuestos anteriores, los más preferidos son los siguientes:

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida

(5-terc-butil-isoxazol-3-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico

N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propano-1-sulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico

N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida

N-(3-sec-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamidas

N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

USO TERAPÉUTICO

Como puede demostrarse mediante los ensayos descritos anteriormente, los compuestos de la invención son útiles para modular la función del receptor CB2. Debido a este hecho, estos compuestos tienen uso terapéutico para tratar estados de enfermedad y dolencias mediadas por la función del receptor CB2 o que se podrían beneficiar de la modulación de la función del receptor CB2.

Como los compuestos de la invención modulan la función del receptor CB2, tienen una actividad anti-inflamatoria e inmunosupresora muy útil y se pueden usar en pacientes como fármacos, particularmente en forma de composiciones farmacéuticas como se propone a continuación para el tratamiento de estados de enfermedad y dolencias.

Como se indica anteriormente, aquellos compuestos que son agonistas del CB2 se pueden emplear para el tratamiento del dolor.

Los compuestos agonistas, antagonistas y agonistas inversos, de acuerdo con la invención, se pueden usar en pacientes como fármacos para el tratamiento de los siguientes estados de enfermedad o indicaciones que se acompañan por procesos inflamatorios:

(i) Enfermedades pulmonares: por ejemplo, asma, bronquitis, rinitis alérgica, enfisema, síndrome de dificultad respiratoria del adulto (ARDS), enfermedad del colombófilo, pulmón del granjero, enfermedad pulmonar obstructiva crónica (COPD), asma que incluye asma alérgica (atópica o no atópica) además de broncoconstricción inducida por el ejercicio, asma ocupacional, exacerbación vírica o bacteriana del asma, otras asmas no alérgicas y "síndrome del niño resollante", neumoconiosis, que incluye aluminosis, antracosis, asbestosis, calicosis, ptilosis, siderosis, silicosis, tabacosis y bisinosis;

(ii) Enfermedades reumáticas o enfermedades autoinmunes o enfermedades musculoesqueléticas: todas las formas de enfermedades reumáticas, especialmente artritis reumatoide, fiebre reumática aguda y polimialgia reumática; artritis reactiva; enfermedades reumáticas de tejidos blandos; enfermedades inflamatorias de tejidos blandos de otros orígenes; síntomas artríticos en enfermedades articulares degenerativas (artrosis); tendinitis, bursitis, osteoartritis, artritis traumática;

colagenosis de cualquier origen, por ejemplo lupus eritematoso sistémico, escleroderma, polimiositis, dermatomiositis, síndrome de Sjögren, enfermedad de Still, síndrome de Felty; y osteoporosis y otras enfermedades de resorción ósea.

(iii) Enfermedades alérgicas: todas las formas de reacciones alérgicas, por ejemplo edema angioneurótico, fiebre del heno, picaduras de insectos, reacciones alérgicas a fármacos, derivados de la sangre, agentes de contraste, etc. choque anafiláctico (anafilaxis), urticaria, edema angioneurótico y dermatitis por contacto.

(iv) Enfermedades vasculares: panarteritis nodosa, poliarteritis nodosa, periarteritis nodosa, arteritis temporal, granulomatosis de Wegner, artritis de células gigantes, aterosclerosis, daño por reperfusión y eritema nodoso;

(v) Enfermedades dermatológicas: por ejemplo, dermatitis, soriasis; quemaduras solares, quemaduras, eczema;

(vi) Enfermedades renales: por ejemplo síndrome nefrótico; y todos los tipos de nefritis, por ejemplo, glomerulonefritis; pancreatitis;

(vii) Enfermedades hepáticas: por ejemplo, desintegración aguda de las células del hígado; hepatitis aguda de distintos orígenes, por ejemplo viral, tóxica, inducida por fármacos; y hepatitis crónicamente agresiva y/o crónicamente intermitente.

(viii) Enfermedades gastrointestinales: por ejemplo, enfermedades inflamatorias del intestino, síndrome del intestino irritable, enteritis regional (enfermedad de Crohn), colitis ulcerosa; gastritis; úlcera aftosa, enfermedad celiaca, ileitis regional, enfermedad de reflujo gastroesofágico.

(ix) Neuroprotección: por ejemplo en el tratamiento de la neurodegeneración después de un ictus; parada cardiaca; derivación pulmonar; lesión traumática cerebral; lesión de la médula espinal o similares;

(x) Enfermedades del ojo: queratitis alérgica, uveitis o iritis; conjuntivitis; blefaritis; neuritis del nervio óptico; coroiditis; glaucoma y oftalmia simpatética.

(xi) Enfermedades del área del oído, nariz y garganta (ENT): por ejemplo tinitus; rinitis alérgica o fiebre del heno; otitis externa; producidas por eczema de contacto, infección, etc.; y otitis media;

(xii) Enfermedades neurológicas: por ejemplo edema cerebral, particularmente edema cerebral relacionado con un tumor; esclerosis multiple; encefalomielitis aguda meningitis; lesión aguda de la médula espinal; trauma; demencia, particularmente demencia degenerativa (incluyendo demencia senil, enfermedad de Alzheimer; enfermedad de Parkinson y enfermedad de Creutzfeldt-Jacob; enfermedad de Huntington, enfermedad de Pick; enfermedad de las neuronas motoras), demencia vascular (incluyendo demencia por multi-infarto) así como demencia asociada con lesiones que ocupan el espacio intracraneal; infecciones y enfermedades relacionadas (incluyendo infección por VIH); síndrome de Guillain-Barre; miastenia grave, ictus; y diversas formas de crisis, por ejemplo, espasmos de nutación;

(xiii) Enfermedades de la sangre: anemia hemolítica adquirida; anemia aplástica y trombocitopenia idiopática.

(xiv) Enfermedades tumorales: leucemia linfática aguda; enfermedad de Hodgkin, linfoma maligno; linfogranulomatosis; linfosarcoma; tumores sólidos malignos; metástasis extensiva;

(xv) Enfermedades endocrinas: oftalmopatía endocrina; orbitopatía endocrina; crisis tirotóxica; Tiroiditis de Quervain; tiroiditis de Hashimoto; Morbus Basedow; tiroiditis granulomatosa; estruma linfomatosa y enfermedad de Graves; diabetes de tipo I (diabetes dependiente de insulina).

(xvi) Trasplantes de órganos y tejidos y enfermedades de injerto contra hospedador;

(xvii) Estados graves de choque, por ejemplo, choque séptico, choque anafiláctico y síndrome de respuesta inflamatoria sistémica (SIRS);

(xviii) Dolor agudo, tal como dolor dental, dolor perioperatorio o post-operatorio, dolor traumático, dolor muscular, dolor en piel quemada, quemadura solar, neuralgia trigeminal, quemadura solar; espasmos del tracto gastrointestinal o del útero, cólicos.

(xix) Dolor visceral, tal como dolor asociado con dolor pélvico crónico, pancreatitis, úlcera péptica, cistitis intersticial, cólico renal, angina, dismenorrea, menstruación, dolor ginecológico, síndrome del intestino irritable (IBS), dispepsia no ulcerosa, dolor de pecho no cardiaco, isquemia de miocardio.

(xx) Dolor neuropático, tal como dolor lumbar bajo, neuralgia no herpética, neuralgia post-herpética, neuropatía diabética, lesión de los nervios, dolor neuropático relacionado con el síndrome de inmunodeficiencia adquirida (SIDA), traumatismo craneal, mononeuropatía traumática dolorosa, dolor inducido por toxinas y quimioterapia, dolor de miembro fantasma, polineuropatía dolorosa, síndrome de dolor talámico, dolor post-ataque, lesión del sistema nervioso central, dolor post-quirúrgico, dolor de muñón, dolor por movimiento repetitivo, dolor inducido por síndrome de post-masectomía, esclerosis múltiple, avulsiones de raíz, síndrome de post-toracotomía, dolor neuropático asociado con hiperalgesia y alodinia.

(xxi) Dolor inflamatorio/nociceptivo inducido por o asociado con trastornos tales como osteoartritis, artritis reumatoide, enfermedad reumática, tenosinovitis, gota, vulvodinia, dolor miofascial (lesión muscular, fibromialgia), tendonitis, osteoartritis, artritis juvenil, espondilitis, artritis gotosa, artritis soriática, dolor musculoesquelético, fibromialgia, esguinces y tensiones, dolor mantenido simpatéticamente, miositis, dolor asociado con migraña, dolor de dientes, gripe y otras infecciones víricas tales como constipado común, fiebres reumáticas, lupus eritematoso sistémico.

(xxii) Dolor de cáncer inducido o asociado con tumores tales como leucemia linfática; enfermedad de Hodgkin, linfoma maligno; linfogranulomatosis; linfosarcoma; tumores sólidos malignos; metástasis extensiva;

(xxiii) Dolor de cabeza, tales como cefalalgia histamínica, migraña con o sin aura, dolor de cabeza de tipo tensional, dolor de cabeza con diferentes orígenes, trastornos con dolor de cabeza incluyendo uso profiláctico y agudo;

(xxiv) otros diversos estados de enfermedad o dolencias que incluyen, restenosis después de angioplastia coronaria transluminal percutánea, dolor agudo y crónico,

aterosclerosis, daño por reperfusión, fallo cardiaco congestivo, infarto de miocardio, daño térmico, daño secundario de múltiples órganos por trauma, enterocolitis necrotizante y síndromes asociados con hemodiálisis, leucoforesis, y transfusión de granulocitos, sarcoidosis, gingivitis, pirexia, edema resultante de trauma asociado con quemaduras, esguinces o fracturas, edema cerebral y angioedema. Diabetes tales como vasculopatía diabética, neuropatía diabética, retinopatía diabética, resistencia posterior a la capilaridad o síntomas diabéticos asociados con insulitis (por ejemplo, hiperglicemia, diuresis, proteinuria y excreción urinaria aumentada de nitritos y calicreina).

Otras indicaciones incluyen: epilepsia, choque séptico, por ejemplo como agentes antihipovolémicos y/o antihipotensivos, cáncer, sepsis, osteoporosis, hiperplasia prostática benigna y vejiga hiperactiva, pruritis, vitiligo, trastornos gastrointestinales generales, molestias de la motilidad visceral en las regiones respiratoria, genitourinaria, gastrointestinal o vascular, heridas, quemaduras, daño en tejidos y fiebre post-operatoria, síndromes asociados con prurito.

Además de ser útil para el tratamiento humano, estos compuestos también son útiles para tratamiento veterinario de animales de compañía, animales exóticos y animales de granja, incluyendo mamíferos, roedores y similares.

Para el tratamiento de las enfermedades y estados descritos anteriormente, una dosis terapéuticamente eficaz estará generalmente en el intervalo de aproximadamente 0,01 mg a aproximadamente 100 mg/kg de peso corporal por dosis de un compuesto de la invención; preferiblemente, de aproximadamente 0,1 mg a aproximadamente 20 mg/kg de peso corporal por dosis. Por ejemplo, para la administración a una persona de 70 kg, el intervalo de dosificación sería de aproximadamente 0,7 mg a aproximadamente 7.000 mg por dosis de un compuesto de la invención, preferiblemente de aproximadamente 7,0 mg a aproximadamente 1.400 mg por dosis. Puede requerirse cierto grado de optimización de la dosis rutinaria para determinar un nivel y un patrón de dosificación óptimos. El ingrediente activo se puede administrar de 1 a 6 veces al día.

Terapia de combinación

Estos compuestos también se pueden emplear en terapias de combinación con los siguientes compuestos:

fármacos antiinflamatorios no esteroidales (NSAID) que incluyen inhibidores de COX-2 tales como derivados de ácido propiónico (alminoprofeno, benoxaprofeno, ácido buclóxico, carprofeno, fenhufeno, fenoprofeno, flurbiprofeno, ibuprofeno, indoprofeno, cetoprofeno, miroprofeno, naproxeno, oxaprozina, pirprofeno, pranoprofeno, suprofeno, ácido tiaprofénico y tioxaprofeno), derivados de ácido acético (indometacina, acemetacina, alclofenac, clidanac, diclofenac, fenclofenac, ácido fenclózico, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetina, zidometacina y zomepirac), derivados de ácido fenámico (ácido meclofenámico, ácido mefenámico y ácido tolfenámico), derivados de ácido bifenilcarboxílico, oxicams (isoxicam, meloxicam, piroxicam, sudoxicam y tenoxican), salicilatos (ácido acetilsalicílico, sulfasalicina) y las pirazolonas (apazona, bezpiperilona, feprazona, mofebutazona, oxifenbutazona, fenilbutazona), y los coxibs (celecoxib, valecoXID, rofecoxib y etoricoxib);

agonistas del receptor opiáceo, tales como morfina, propoxifeno (Darvon), tramadol y buprenorfina;

bloqueadores del canal de sodio, tales como carbamazepina, mexiletina, lamotrigina, pregabalina, tectina, NW-1029 y CGX-1002;

bloqueantes del canal de calcio tipo N tales como Ziconotida, NMED-160, SPI-860;

moduladores serotonérgicos y noradrenérgicos, tales como SR-57746, paroxetina, duloxetina, clonidina, amitriptilina y citalopram;

corticosteroides tales como betametasona, budesonida, cortisona, dexametasona, hidrocortisona, metilprednisolona, prednisolona, prednisona y triamcinolona;

antagonistas del receptor H1 de la histamina, tales como bromofeniramina, clorfeniramina, dexclorfeniramina, triprolidina, clemastina, difenhidramina, difenilpiralina,

tripelenamina, hidroxizina, metadiazina, prometazina, trimeprazina, azatadina, ciproheptadina, antazolina, feniramina, pirilamina, astemizol, terfenadina, loratadina, cetirizina, desloratadina, fexofenadina y levocetiricina;

antagonistas del receptor H2 de la histamina tales como cimetidina, famotidina y ranitidina;

inhibidores de la bomba de protones tales como omeprazol, pantoprazol y esomeprazol;

antagonistas de leucotrieno e inhibidores de 5-lipoxigenasa tales como zafirlukast, montelukast, pranlukast y zileuton;

anestésicos locales tales como ambroxol, lidocaina;

agonistas y antagonistas de VR1 tales como NGX-4010, WL-1002, ALGRX-4975, WL-10001, AMG-517;

agonistas del receptor de acetilcolina nicotínica tales como ABT-202, A-366833, ABT-594; BTG-102, A-85380, CGX1204;

antagonistas del receptor de P2X3 tales como A-317491, ISIS-13920, AZD-9056;

agonistas y antagonistas del NGF, tales como RI-724, RI-1024, AMG-819, AMG-403 y PPH 207;

antagonistas de NK1 y NK2, tales como DA-5018, R-116301; CP-728663, ZD-2249;

antagonistas del NMDA, tales como NER-MD-11, CNS-5161, EAA-090, AZ-756 y CNP-3381;

moduladores del canal de potasio tales como CL-888, ICA-69673, retigabina;

moduladores de GABA tal como lacosamida;

moduladores serotonérgicos y noradrenérgicos, tales como SR-57746, paroxetina, duloxetina, clonidina, amitriptilina, citalopram y flibanserina; y

combinación con fármacos anti-migraña como sumatriptan, zolmitriptan, naratriptan, eletriptan.

Administración general y composiciones farmacéuticas

Cuando se usan como agentes farmacéuticos, los compuestos de la invención típicamente se administran en forma de una composición farmacéutica. Tales composiciones pueden prepararse usando procedimientos bien conocidos en la técnica farmacéutica y comprenden al menos un compuesto de la invención. Los compuestos de la invención también pueden administrarse solos o en combinación con adyuvantes que aumentan la estabilidad de los compuestos de la invención, facilitan la administración de composiciones farmacéuticas que los contienen en ciertas realizaciones, proporcionan una mayor disolución o dispersión, aumentan la actividad inhibidora, proporcionan una terapia auxiliar y similares. Los compuestos de acuerdo con la invención pueden usarse por sí mismos o junto con otras sustancias activas de acuerdo con la invención, opcionalmente también junto con otras sustancias farmacológicamente activas. En general, los compuestos de esta invención se administran en una cantidad terapéutica o farmacéuticamente eficaz, aunque se pueden administrar en cantidades menores para diagnóstico u otros propósitos.

La administración de los compuestos de la invención, en forma pura o en una composición farmacéutica apropiada, puede realizarse usando cualquiera de los modos aceptados de administración de composiciones farmacéuticas. De esta manera, la administración puede ser por ejemplo, por vía oral, bucal (por ejemplo, por vía sublingual), nasal, parenteral, tópica, transdérmica, vaginal o rectal, en forma de un sólido, semisólido, polvo liofilizado o en formas de dosificación líquida, tal como, por ejemplo, en forma de comprimidos, supositorios, píldoras, cápsulas de gelatina dura y cápsulas elásticas de gelatina blanda, polvos, disoluciones, suspensiones o aerosoles, o similares, preferiblemente en formas de dosificación unitaria adecuadas para una simple administración de dosificaciones precisas. Las composiciones farmacéuticas generalmente incluirán un vehículo o excipiente farmacéutico convencional y un compuesto de la invención como el/un agente activo y,

además, pueden incluir otros agentes medicinales, agentes farmacéuticos, transportes, adyuvantes, diluyentes, vehículos o combinaciones de los mismos. Dichos excipientes, vehículos o aditivos farmacéuticamente aceptables, así como los métodos para preparar composiciones farmacéuticas para distintos modos de administración son bien conocidos por los expertos en la técnica. El estado de la técnica se muestra, por ejemplo, por *Remington: The Science and Practice of Pharmacy*, 20ª Edición, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; *Handbook of Pharmaceutical Additives*, Michael & Irene Ash (eds.), Gower, 1995; *Handbook of Pharmaceutical Excipients*, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel y N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5ª ed., Lea y Febiger, 1990; cada uno de los cuales se incorpora en esta memoria como referencia en su integridad para describir mejor el estado de la técnica.

Como podría esperar un experto de la técnica, las formas de los compuestos de la invención utilizados en una formulación farmacéutica particular se elegirán (por ejemplo, sales) de forma que posean características físicas adecuadas (por ejemplo, solubilidad en agua) que son necesarias para que la formulación sea eficaz.

Las composiciones farmacéuticas adecuadas para la administración bucal (sub-lingual) incluyen grageas que comprenden un compuesto de la presente invención en una base aromatizada, normalmente sacarosa, y goma arábiga o tragacanto, y pastillas que comprenden el compuesto en una base inerte tal como gelatina y glicerina o sacarosa y goma arábiga.

Las composiciones farmacéuticas adecuadas para la administración parenteral comprenden preparados acuosos estériles de un compuesto de la presente invención. Estos preparados preferiblemente se administran por vía intravenosa, aunque la administración también puede realizarse por medio de inyección subcutánea, intramuscular o intradérmica. Las formulaciones farmacéuticas inyectables se basan generalmente en disolución salina estéril inyectable, disolución salina de fosfato tamponada, suspensiones oleaginosas u otros vehículos inyectables conocidos en la técnica y que generalmente se hacen estériles e isotónicos con la sangre. Las formulaciones farmacéuticas inyectables pueden proporcionarse por lo tanto como una disolución o suspensión inyectable estéril en un diluyente o disolvente

no tóxico parenteralmente aceptable, incluyendo 1,3-butanodiol, agua, disolución de Ringer, disolución isotónica de cloruro de sodio, aceites fijos, tales como mono- o diglicéridos sintéticos, ácidos grasos, tales como ácido oleico, y similares. Dichas formulaciones farmacéuticas inyectables se formulan de acuerdo con la técnica conocida usando agentes de dispersión o fijación y agentes de suspensión adecuados. Las formulaciones inyectables generalmente contendrán de 0,1 a 5% p/p de un compuesto de la invención.

Las formas de dosificación sólida para administración oral de los compuestos incluyen cápsulas, comprimidos, píldoras, polvos y gránulos. Para dicha administración oral, una composición farmacéuticamente aceptable que contiene uno o más compuestos de la invención se forma por medio de la incorporación de cualquiera de los excipientes empleados normalmente, tales como, por ejemplo, calidades farmacéuticas de manitol, lactosa, almidón, almidón pregelatinizado, estearato de magnesio, sacarina sódica, talco, derivados de éter de celulosa, glucosa, gelatina, sacarosa, citrato, galato de propilo y similares. Tales formulaciones farmacéuticas sólidas pueden incluir formulaciones, como es bien conocido en la técnica, para proporcionar la liberación prolongada o sostenida del fármaco en el tracto gastrointestinal mediante cualquier número de mecanismos que incluyen, pero sin estar limitados a ellos, liberación sensible al pH de la forma de dosificación basada en el cambio de pH del intestino delgado, erosión lenta del comprimido o la cápsula, retención en el estómago basada en las propiedades físicas de la formulación, bioadhesión de la forma de dosificación a la capa mucosa del tracto intestinal o liberación enzimática del fármaco activo de la forma de dosificación.

Las formas de dosificación líquidas para la administración oral de los compuestos incluyen emulsiones, microemulsiones, disoluciones, suspensiones, jarabes y elixires, que contienen opcionalmente adyuvantes farmacéuticos en un vehículo, tal como, por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, etanol y similares. Estas composiciones también pueden contener adyuvantes adicionales tales como agentes humectantes, emulsionantes, de suspensión, edulcorantes, aromatizantes y perfumantes.

Las formas de dosificación tópicas de los compuestos incluyen pomadas, pastas, cremas, lociones, geles, polvos, disoluciones, nebulizaciones, inhalaciones, pomadas oculares, gotas oculares u óticas, vendajes impregnados y aerosoles, y pueden contener aditivos convencionales apropiados tales como conservantes, disolventes para facilitar la penetración del fármaco y emolientes en pomadas y cremas. La aplicación tópica puede realizarse una vez o más veces al día dependiendo de las consideraciones médicas habituales. Además, los compuestos preferidos para la presente invención se pueden administrar de forma intranasal mediante la utilización tópica de vehículos intranasales adecuados. Las formulaciones también pueden contener vehículos convencionales compatibles, tales como bases de cremas o pomadas y etanol o alcohol oleílico para lociones. Dichos vehículos pueden estar presentes en una cantidad de aproximadamente 1% hasta aproximadamente 98% de la formulación, más habitualmente formarán parte de hasta aproximadamente 80% de la formulación.

También es posible la administración transdérmica. Las composiciones farmacéuticas adecuadas para la administración transdérmica pueden presentarse como parches discretos adaptados para mantenerse en contacto íntimo con la epidermis del receptor durante un periodo de tiempo prolongado. Para administrarse en forma de un sistema de liberación transdérmica, la administración de la dosificación será, por supuesto, continua mejor que intermitente a lo largo del régimen de dosificación. Dichos parches contienen adecuadamente un compuesto de la invención en una solución acuosa y opcionalmente tamponada, disuelto y/o disperso en un adhesivo, o disperso en un polímero. Una concentración adecuada del compuesto activo es de aproximadamente 1% a 35%, preferiblemente de aproximadamente 3% a 15%.

Para la administración por inhalación, los compuestos de la invención se liberan convenientemente en forma de pulverización en aerosol a partir de un dispositivo de pulverización con bomba que no requiere de gas propulsor o de un envase presurizado o un nebulizador mediante el uso de un propulsor adecuado, por ejemplo diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, tetrafluoroetano, heptafluoropropano, dióxido de carbono u otro gas adecuado. En cualquier caso, la unidad de dosificación de nebulización

en aerosol puede determinarse proporcionando una válvula para liberar una cantidad medida de manera que el inhalador de dosis medida resultante (MDI) se use para administrar los compuestos de la invención de una forma reproducible y controlada. Tales dispositivos de inhalación, nebulización o atomización son conocidos en la técnica anterior, por ejemplo en las publicaciones internacionales PCT N° WO 97/12687 (particularmente su figura 6, que es la base del nebulizador comercial RESPIMAT®); WO 94/07607; WO 97/12683; y WO 97/20590, a las que se hace referencia por el presente documento y cada una de las que se incorporan en este documento como referencia en su totalidad.

La administración rectal puede realizarse utilizando supositorios de dosis unitarias en los que el compuesto está mezclado con sólidos solubles o insolubles en agua de bajo punto de fusión tales como grasas, manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diversos pesos moleculares o ésteres de ácidos grasos de polietilenglicoles, o similares. El compuesto activo normalmente es un componente minoritario, con frecuencia de aproximadamente 0,05 a 10% en peso, siendo el resto el componente base.

En todas las composiciones farmacéuticas anteriores, los compuestos de la invención se formulan con un vehículo o excipiente aceptable. Por supuesto, los vehículos o excipientes usados deben ser aceptables en el sentido de ser compatibles con los otros ingredientes de la composición y no deben ser perjudiciales para el paciente. El vehículo o excipiente puede ser un sólido o un líquido, o ambos, y preferiblemente se formula con el compuesto de la invención como una composición de dosis unitaria, por ejemplo, un comprimido, que puede contener de 0,05% a 95% en peso del compuesto activo. Tales vehículos o excipientes incluyen cargas inertes o diluyentes, aglutinantes, lubricantes, agentes disgregantes, retardantes de disolución, aceleradores de la resorción, agentes de absorción y agentes colorantes. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o β-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como goma arábiga, tragacanto o alginato sódico, carboximetilcelulosa, polietilenglicol, ceras y similares. Los lubricantes incluyen oleato de sodio, estearato de sodio, estearato de magnesio, benzoato

de sodio, acetato de sodio, cloruro de sodio y similares. Los agentes disgregantes incluyen almidón, metilcelulosa, agar, bentonita, goma xantana y similares.

Los vehículos y excipientes farmacéuticamente aceptables comprenden todos los aditivos anteriores y similares.

Ejemplos de Formulaciones Farmacéuticas

A. COMPRIMIDOS	
Componente	**Cantidad por comprimido (mg)**
sustancia activa	100
Lactosa	140
almidón de maíz	240
polivinilpirrolidona	15
estearato de magnesio	5
TOTAL	500

Se mezclan la sustancia activa molida finamente, la lactosa y una pequeña cantidad del almidón de maíz. La mezcla se tamiza, después se humedece con una disolución de polivinilpirrolidona en agua, se amasa, se granula en húmedo y se seca. Los gránulos, el almidón de maíz restante y el estearato de magnesio se tamizan y se mezclan juntos. La mezcla se comprime para producir comprimidos de la forma y el tamaño adecuados.

B. COMPRIMIDOS	
Componente	**Cantidad por comprimido (mg)**
sustancia activa	80
Lactosa	55

almidón de maíz	190
polivinilpirrolidona	15
estearato de magnesio	2
celulosa microcristalina	35
carboximetil almidón sódico	23
TOTAL	400

Se mezclan la sustancia activa molida finamente, una pequeña cantidad del almidón de maíz, la lactosa, la celulosa microcristalina y la polivinilpirrolidona, la mezcla se tamiza y se trata con el resto del almidón de maíz y agua para formar un gránulo que se seca y se tamiza. Se añaden el almidón de carboximetil-sodio y el estearato de magnesio y se mezclan y la mezcla se comprime para formar comprimidos de un tamaño adecuado.

C. COMPRIMIDOS CON REVESTIMIENTO	
Componente	**Cantidad por comprimido (mg)**
sustancia activa	5
lactosa	30
almidón de maíz	41,5
polivinilpirrolidona	3
estearato de magnesio	0,5
TOTAL	90

Se mezclan minuciosamente la sustancia activa, el almidón de maíz, la lactosa y la polivinilpirrolidona y se humedece con agua. La masa húmeda se empuja a través de un tamiz con un tamaño de malla de 1 mm, se seca a aproximadamente 45°C y los gránulos se pasan después por el mismo tamiz. Después de mezclar el estearato de magnesio, se comprimen los núcleos convexos de los comprimidos con un diámetro de 6 mm en una máquina de

elaboración de comprimidos. Los núcleos de los comprimidos así producidos se revisten mediante un método conocido con un agente de recubrimiento que consiste esencialmente en azúcar y talco. Los comprimidos revestidos terminados se pulen con cera.

D. CÁPSULAS	
Componente	**Cantidad por cápsula (mg)**
sustancia activa	50
almidón de maíz	268,5
estearato de magnesio	1,5
TOTAL	320

Se mezclan la sustancia y el almidón de maíz y se humedecen con agua. La masa húmeda se tamiza y se seca. Los gránulos secos se tamizan y se mezclan con estearato de magnesio. La mezcla terminada se envasa en cápsulas de gelatina dura de tamaño 1.

E. DISOLUCIÓN EN AMPOLLAS	
Componente	**Cantidad por ampolla**
sustancia activa	50 mg
cloruro sódico	50 mg
Agua inyectable	5 mL

La sustancia activa se disuelve en agua a su propio pH u opcionalmente a pH 5,5 a 6,5 y se añade cloruro de sodio para hacerla isotónica. La solución obtenida se filtra libre de pirógenos y el filtrado se transfiere en condiciones asépticas al interior de ampollas que después se esterilizan y se cierran herméticamente por fusión. Las ampollas contienen 5 mg, 25 mg y 50 mg de sustancia activa.

F. SUPOSITORIOS	
Componente	**Cantidad por supositorio (mg)**
sustancia activa	50
grasa sólida	1650
TOTAL	1700

Se funde la grasa dura. Se dispersa homogéneamente en ella la sustancia activa a 40°C. La mezcla se enfría a 38°C y se vierte en moldes de supositorio ligeramente enfriados.

G. AEROSOL DE DOSIFICACIÓN	
Componente	**Cantidad**
sustancia activa	0,005
trioleato de sorbitán	0,1
Monofluorotriclorometano y difluorodiclorometano (2:3)	hasta 100

La suspensión se transfiere a un recipiente de aerosol convencional con una válvula de dosificación. Preferiblemente, se suministran 50 µL de suspensión en cada pulverización. La sustancia activa también puede dosificarse en dosis superiores si se desea (por ejemplo, 0,02% en peso).

H. POLVO PARA INHALACIÓN	
Componente	**Cantidad**
sustancia activa	1,0 mg
lactosa monohidrato	hasta 25 mg

I. POLVO PARA INHALACIÓN	
Componente	**Cantidad**
sustancia activa	2,0 mg.
lactosa monohidrato	hasta 25 mg

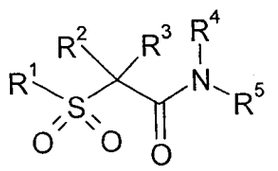
J. POLVO PARA INHALACIÓN	
Componente	**Cantidad**
sustancia activa	1,0 mg
lactosa monohidrato	hasta 5 mg

K. POLVO PARA INHALACIÓN	
Componente	**Cantidad**
sustancia activa	2,0 mg.
lactosa monohidrato	hasta 5 mg

En los Ejemplos H, I, J y K, el polvo para inhalación se produce de manera convencional mezclando juntos los ingredientes individuales.

REIVINDICACIONES

1. Un compuesto de la fórmula (I)



(I)

en el que:

R^1 es alquilo C_{1-10}, alcoxi C_{1-10}, cicloalquilo C_{3-10}, anillo heterocíclico saturado de 3-10 miembros, bencilo o fenetilo, cada uno opcionalmente sustituido de forma independiente con 1-3 sustituyentes elegidos a partir de alquilo C_{1-10} sustituido opcionalmente con 1 a 3 átomos de halógeno, cicloalquilo C_{3-10}, anillo heterocíclico saturado de 3-10 miembros sustituidos opcionalmente con acilo, oxo o sulfona de metilo, acilo, ciano, fenilo, oxo, hidroxilo y halógeno;

R^2 y R^3 son independientemente hidrógeno o alquilo C_1-C_6; o R^2 y R^3 junto con el átomo de carbono al que están unidos forman un anillo heterocíclico o cicloalquilo de 3 a 6 miembros;

R^4 es hidrógeno o metilo;

R^5 es arilo o heteroarilo cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 sustituido opcionalmente con 1 a 3 átomos de halógeno o con un grupo heterocíclico, alcoxi C_1-C_6 opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C_3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C_1-C_4, fenilo opcionalmente sustituido con 1 a 2 átomos de halógeno o alquilo C_1-C_4 opcionalmente sustituido con halógeno, tienilo opcionalmente sustituido con 1 a 2 átomos de halógeno o alquilo C_1-C_4 opcionalmente sustituido con halógeno y piridinilo opcionalmente sustituido con 1 a 2 alquilo C_1-C_4 opcionalmente sustituido con halógeno;

o un tautómero o una sal farmacéuticamente aceptable de los mismos.

2. El compuesto de acuerdo con la reivindicación 1, en el que

R^1 es metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, tetrahidropiranilo, biciclo(3.3.0)octanilo, biciclo[4.3.0]nonilo, bencilo o fenetilo, cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, tetrahidrofuranilo, tetrahidropiranilo, pirrolidinilo (sustituido opcionalmente con acilo, oxo o metilsulfonilo), piperidinilo (sustituido opcionalmente con acilo, oxo o metilsulfona, acilo, ciano, fenilo, oxo, fluoro, cloro, bromo e hidroxilo ;

R^2 y R^3 son independientemente hidrógeno, metilo, etilo, n-propilo, isopropilo, isobutilo, terc-butilo, o R^2 y R^3 junto con el carbono al que están unidos forman un anillo de ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o tetrahidropiranilo;

R^4 es hidrógeno;

R^5 es fenilo, naftilo, piridinilo, quinolinilo, isoquinolinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, triazolilo, oxadiazolilo, tiadiazolilo, indolilo, benzoxazolilo, benzopirazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzimidazolilo, tetrahidrobenzoxazolilo, tetrahidrobenzotiazolilo, o tetrahidrobenzimidazolilo, cada uno opcionalmente sustituido independientemente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 que está sustituido opcionalmente con 1 a 3 átomos de halógeno, alcoxi C_1-C_6 que está opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C_3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C_1-C_4, fenilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno, tienilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno y piridinilo que está sustituido opcionalmente con 1 a 2 alquilo C_1-C_4 sustituido opcionalmente con halógeno.

3. El compuesto de acuerdo con la reivindicación 2, en el que

R^1 es metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, terc-butilo, n-pentilo, n-hexilo, n-heptilo, n-octilo, n-nonilo, n-decilo, ciclopropilo, ciclobutilo, ciclopentilo,

ciclohexilo, cicloheptilo, ciclooctilo, tetrahidropiranilo, biciclo(3.3.0)octanilo, o biciclo[4.3.0]nonilo, cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de metilo, etilo, pivaloilo, ciclopropilo, ciclobutilo, ciclohexilo, tetrahidropiranilo, tetrahidrofuranilo, pirrolidinilo opcionalmente sustituido con metilsulfona, fluoro, cloro, bromo, oxo e hidroxi;

R^2 y R^3 son independientemente hidrógeno, metilo, etilo, n-propilo, isopropilo, isobutilo, terc-butilo, o R^2 y R^3 junto con el carbono al que están unidos forman un anillo de ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o tetrahidropiranilo;

R^4 es hidrógeno;

R^5 es fenilo, naftilo, piridinilo, quinolinilo, isoquinolinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, triazolilo, oxadiazolilo, tiadiazolilo, indolilo, benzoxazolilo, benzopirazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzimidazolilo, tetrahidrobenzoxazolilo, tetrahidrobenzotiazolilo, o tetrahidrobenzimidazolilo, cada uno opcionalmente sustituido independientemente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 que está sustituido opcionalmente con 1 a 3 átomos de halógeno, alcoxi C_1-C_6 que está opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C_3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C_1-C_4, fenilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno, tienilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno y piridinilo que está sustituido opcionalmente con 1 a 2 alquilo C_1-C_4 opcionalmente sustituido con halógeno.

4. El compuesto de acuerdo con la reivindicación 3, en el que

R^1 es bencilo o fenetilo, cada uno opcionalmente sustituido independientemente con 1 a 3 sustituyentes elegidos de metilo, fluoro, cloro o bromo.

5. El compuesto de acuerdo con la reivindicación 3, en el que

R^1 es metilo, etilo, n-propilo, isopropilo, terc-butilo, n-butilo, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, tetrahidropiranilo o bencilo cada uno opcionalmente sustituido con metilo, pivaloilo, ciclopropilo, ciclobutilo, ciclohexilo, tetrahidropiranilo, tetrahidrofuranilo, pirrolidinilo (opcionalmente sustituido con metilsulfonilo) o cloro;

R^2 y R^3 son independientemente hidrógeno, metilo, isopropilo, terc-butilo, o R^2 y R^3 junto con el carbono al que están unidos forman un anillo de ciclopropilo o ciclobutilo;

R^4 es hidrógeno;

R^5 es fenilo, piridinilo, quinolinilo, isoquinolinilo, pirazolilo, isoxazolilo, benzotiazolilo, tiadiazolilo o tiazolilo, cada uno opcionalmente sustituido de forma independiente con 1 a 2 sustituyentes elegidos de metilo, etilo, terc-butilo, neopentilo, ciclohexilo, trifluorometilo o fenilo opcionalmente sustituidos con un átomo de cloro.

6. Un compuesto elegido entre:

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida

(5-terc-butil-isoxazol-3-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico

(4-terc-butil-tiazol-2-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida

2-metil-N-naftalen-2-il-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4,5,6,7-tetrahidrobenzotiazol-2-il)-propionamida

2-metil-N-(2-metil-5-tiofen-2-il-2H-pirazol-3-il)-2-(propano-2-sulfonil)-propionamida

N-isoquinolin-3-il-2-metil-2-(propano-2-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-quinolin-3-il-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-N-(4-fenil-tiazol-2-il)-2-(propano-2-sulfonil)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(propano-2-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

2-metil-2-(2-metil-propano-2-sulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(2-metil-propano-2-sulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida

2-(1-acetil-piperidin-3-ilmetanosulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-3-metil-2-(propano-2-sulfonil)-butiramida

2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

N-(5-terc-butil-4-metil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

2-(butano-2-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-etanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metanosulfonil-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2,2,2-trifluoro-etanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-tiazol-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(hexano-3-sulfonil)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-etanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cianometanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(2,2-dimetil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((S)-5-oxo-pirrolidin-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-((R)-5-oxo-pirrolidin-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(piperidin-4-ilmetanosulfonil)-propionamida

2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(piperidin-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(4-metil-tetrahidro-piran-4-sulfonil)-propionamida

2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclopropilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclobutilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-fenil-propano-1-sulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4-piridin-3-il-tiazol-2-il)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4-piridin-2-il-tiazol-2-il)-propionamida

2-metil-2-(propano-2-sulfonil)-N-(4-piridin-4-il-tiazol-2-il)-propionamida

2-metil-2-(propano-2-sulfonil)-N-quinolin-2-il-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-3-il-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4,5,6,7-tetrahidrobenzotiazol-2-il)-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-2-il-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-N-(2-metil-5-tiofen-2-il-2H-pirazol-3-il)-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4-piridin-4-il-tiazol-2-il)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(4-trifluorometil-tiazol-2-il)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propano-1-sulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-N-(5-fenil-piridin-2-il)-2-(propano-1-sulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(2,4-dimetil-5-fenil-2H-pirazol-3-il)-2-metil-2(propano-1-sulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-tiazol-2-il)-propionamida

N-(4-ciclopropil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-[1,3,4]tiadiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-piridin-2-il)-propionamida

N-(4-etil-piridin-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-benzooxazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(3-propil-isoxazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-isopropil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(2,4-dimetil-5-fenil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-naftalen-1-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-piridin-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(3-trifluorometil-fenil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-fenil)-propionamida

2-metil-N-(2-metil-5-fenil-2H-pirazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-isoquinolin-3-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico

N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida
N-(3-sec-Butyl-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide
N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
2-metil-N-(4-piridin-3-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
2-metil-N-(4-piridin-2-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
2-metil-N-(4-piridin-4-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
N-(3-isopropil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
2-metil-N-(3-fenil-1,2,4-tiadiazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida.
o los tautómeros o las sales farmacéuticamente aceptables de los mismos.

7. Un compuesto elegido entre:
N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida
N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida
N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida
(5-terc-butil-isoxazol-3-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-2-sulfonil)-propionamida
N-(4-terc-butil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida
N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida
N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida
N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida
N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida
N-(4-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida
N-(3-terc-butil-fenil)-2-metil-2-(propano-2-sulfonil)-propionamida
N-(4-terc-butil-tiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida
2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

N-(5-terc-butil-4-metil-tiazol-2-il)-3-metil-2-(propano-2-sulfonil)-butiramida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(6-trifluorometil-piridin-2-il)-propionamida

2-ciclopentanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida

2-ciclopentanosulfonil-2-metil-N-(4-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-(hexano-3-sulfonil)-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclopropilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-ciclobutilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-2-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida

2-metil-2-(propano-2-sulfonil)-N-quinolin-2-il-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-3-il-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

2-metil-2-(propano-1-sulfonil)-N-quinolin-2-il-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propano-1-sulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-[1,3,4]tiadiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(3-propil-isoxazol-5-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(3-trifluorometil-fenil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(4-trifluorometil-fenil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(5-terc-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida
2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida
2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida
2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(2-metil-propanio-1-sulfonil)-propionamida
(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico
N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida
N-(3-sec-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
2-metil-N-(4-piridin-3-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
2-metil-N-(4-piridin-2-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
2-metil-N-(4-piridin-4-il-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
o los tautómeros o las sales farmacéuticamente aceptables de los mismos.

8. Un compuesto elegido entre:
N-(5-terc-butil-isoxazol-3-il)-2-ciclohexanosulfonil-2-metil-propionamida
N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-2-sulfonil)-propionamida
(5-terc-butil-isoxazol-3-il)-amida de ácido 1-ciclohexanosulfonil-ciclobutanocarboxílico
N-(5-terc-butil-4-metil-tiazol-2-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(4-cloro-fenilmetanosulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

2-ciclohexanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopentanosulfonil-2-metil-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(2-metil-propano-2-sulfonil)-propionamida

2-(butano-2-sulfonil)-N-(5-terc-butil-isoxazol-3-il)-2-metil-propionamida

2-(butano-2-sulfonil)-N-(4-terc-butil-tiazol-2-il)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-(4-terc-butil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

2-metil-2-(tetrahidro-piran-4-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-ciclopentanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-ciclohexanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida

2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(3,3-dimetil-2-oxo-butano-1-sulfonil)-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-2-metil-2H-pirazol-3-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-cicloheptanosulfonil-2-metil-propionamida

2-ciclohexilmetanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

2-metil-2-(3-metil-butano-1-sulfonil)-N-(5-trifluorometil-piridin-2-il)-propionamida

2-cicloheptanosulfonil-2-metil-N-(5-trifluorometil-piridin-2-il)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-2-sulfonil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(propano-1-sulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(propano-1-sulfonil)-propionamida

N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-isoxazol-3-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(propano-1-sulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(4-ciclohexil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-(5-terc-butil-4-metil-tiazol-2-il)-2-metil-2-(propano-1-sulfonil)-propionamida

N-benzotiazol-2-il-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-fenil-[1,2,4]tiadiazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-(5-metil-4-fenil-tiazol-2-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(5-etil-4-fenil-tiazol-2-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[3-(2,2-dimetil-propil)-isoxazol-5-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-3-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-(4-terc-butil-fenil)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

2-metil-N-quinolin-2-il-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

N-[4-(4-cloro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-sulfonil)-propionamida
N-(5-terc-butil-1,3,4-tiadiazol-2-il)-2-ciclopentanosulfonil-2-metil-propionamida
2-ciclopentanosulfonil-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclobutilmetanosulfonil-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclopropilmetanosulfonil-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(3-metil-butano-1-sulfonil)-propionamida
2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclopentanosulfonil-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-ciclohexilmetanosulfonil-2-metil-propionamida
2-(butano-2-sulfonil)-N-(3-terc-butil-isoxazol-5-il)-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-2-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(2-metil-propano-1-sulfonil)-propionamida
(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico
N-(3-terc-butil-isoxazol-5-il)-2-(4-fluoro-fenilmetanosulfonil)-2-metil-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-2-ilmetanosulfonil)-propionamida
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-ilmetanosulfonil)-propionamida
N-(3-sec-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamidas
N-[4-(4-fluoro-fenil)-tiazol-2-il]-2-metil-2-(tetrahidro-piran-4-ilmetanosulfonil)-propionamida

o los tautómeros o las sales farmacéuticamente aceptables de los mismos.

9. Un compuesto elegido de

(3-terc-butil-isoxazol-5-il)-amida del ácido 1-(tetrahidro-piran-4-sulfonil)-ciclobutanocarboxílico
N-(3-terc-butil-isoxazol-5-il)-2-metil-2-(tetrahidro-furan-3-sulfonil)-propionamida

(5-fenil-4H-1,2,4-triazol-3-il)-amida del ácido 1-(tetrahidro-piran-4-ilmetanosulfonil)-ciclobutanocarboxílico
2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-2-(tetrahidro-piran-4-sulfonil)-propionamida
(5-fenil-4H-1,2,4-triazol-3-il)-amida del ácido 1-(tetrahidro-piran-4-sulfonil)-ciclobutanocarboxílico
N-(3-terc-butil-isoxazol-5-il)-2-(1-metanosulfonil-pirrolidin-3-ilmetanosulfonil)-2-metil-propionamida y
2-(1-metanosulfonil-pirrolidini-3-sulfonil)-2-metil-N-(5-fenil-4H-1,2,4-triazol-3-il)-propionamida
o los tautómeros o las sales farmacéuticamente aceptables de los mismos.

10. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de acuerdo con la reivindicación 1.

11. Un método para el tratamiento de una enfermedad o afección mediada por el receptor CB2 en un sujeto animal, que comprende administrar a dicho sujeto animal una dosis terapéuticamente eficaz del compuesto según la reivindicación 1.

12. El método de acuerdo con la reivindicación 11, en el que dicha enfermedad o afección mediada por el receptor CB2 se selecciona entre el grupo que consiste en una enfermedad inflamatoria y una enfermedad autoinmune.

13. El método de acuerdo con la reivindicación 11, en el que dicha enfermedad o afección mediada por el receptor CB2 es dolor.

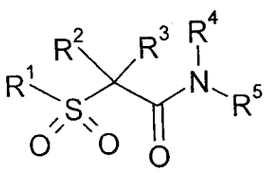
14. El método de acuerdo con la reivindicación 10, en el que dicha enfermedad o afección mediada por el receptor CB2 es una enfermedad pulmonar, una enfermedad reumática, una enfermedad autoinmune, una enfermedad musculoesquelética, una enfermedad alérgica, una

reacción alérgica, una enfermedad vascular, una enfermedad dermatológica, una enfermedad renal, una enfermedad hepática, una enfermedad gastrointestinal, enfermedad de eurodegeneración ocular, enfermedad del oído, la nariz y la garganta, enfermedad neurológica, enfermedad sanguínea, tumores, enfermedades endocrinas, transplantes de órganos y tejidos y enfermedades de injerto contra hospedador, estados graves de choque, dolor agudo, dolor visceral, espasmo del tracto gastrointestinal o del útero, cólicos, dolor neuropático, dolor inflamatorio y nociceptivo, dolor de cáncer, dolor de cabeza, restenosis, aterosclerosis, lesión de reperfusión, insuficiencia cardiaca congestiva, infarto de miocardio, lesión térmica, lesión multiorgánica provocada por traumatismo, enterocolitis necrotizante y síndromes asociados con la hemodiálisis, leucoferesis y transfusión de granulocitos, sarcoidosis, gingivitis y pirexia.

RESUMEN

COMPUESTOS QUE MODULAN EL RECEPTOR CB2

Se describen compuestos de fórmula (I)



Compuestos según la invención se enlazan a y son agonistas, antagonistas o agonistas inversos del receptor CB2, y son útiles para tratar la inflamación. Los compuestos que son agonistas, son adicionalmente útiles para tratar el dolor.

WPCL9255 IID.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
9-396PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2007/078341	13/09/2007	25/09/2006
Applicant		
BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

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INTERN IONAL SEARCH REPORT

Inter. onal application No
PCT/US2007/078341

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C317/44 A61K31/16 A61P29/00 A61P37/00 C07D213/75
C07D215/38 C07D217/22 C07D231/40 C07D261/12 C07D277/46
C07D277/82 C07D309/04 C07D403/12 C07D405/12 C07D407/12

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)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/080040 A (UNIVERSITÀ DEGLI STUDI DI SIENA) 3 August 2006 (2006-08-03) page 3, line 14 - page 4, line 8; claims 1,44-46; table I	1-14
X	M.C. SEIDEL, ET AL.: "Heterocyclic rearrangements. XII. The formation of a formylbenzofuran oxide from a nitroanthril" JOURNAL OF ORGANIC CHEMISTRY, vol. 35, no. 5, May 1970 (1970-05), pages 1662-1664, XP002464462 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US compound 11	1-3,5

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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 document 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
16 January 2008	31/01/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, Russell

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERN IONAL SEARCH REPORT

Inter. onal application No
PCT/US2007/078341

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M.-Y. CHANG, ET AL.: "Reaction of different alpha-sulphonyl acetamides with methyl acrylate" TETRAHEDRON, vol. 58, no. 25, 17 June 2002 (2002-06-17), pages 5075-5080, XP004366431 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL ISSN: 0040-4020 compound A4-3	1-3,5
X	J. STRATING, ET AL.: "Additions nucléophiles au bis-tertiobutyl-sulfonyl-acetylène, II. Proprötös du groupe sulfonyle XLIV" RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS., vol. 73, no. 9/10, September 1954 (1954-09), pages 709-716, XP002464463 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL page 716, last paragraph	1-3,5
X	R. LESSER, ET AL.: "Über das Homo-beta-oxy-thionaphthen (4-keto-iso-thiochroman)" BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, vol. 56, no. 7, 4 July 1923 (1923-07-04), pages 1642-1648, XP002464464 VERLAG CHEMIE, WEINHEIM, DE page 1648, lines 10-21	1,2,4,5
X	US 4 859 707 A (T. LOFTSSON, ET AL.) 22 August 1989 (1989-08-22) examples 4,7	1-3,5
X	US 5 475 130 A (M. SATO, ET AL.) 12 December 1995 (1995-12-12) compounds 15,16	1-3
X	US 2005/182108 A1 (J.R. CARSON, ET AL.) 18 August 2005 (2005-08-18) example 2A	1-3
X	US 6 359 009 B1 (R.E. DIEHL, ET AL.) 19 March 2002 (2002-03-19) example 21	1-3,5
P,X	WO 2006/100502 A (STERIX) 28 September 2006 (2006-09-28) page 148, lines 1-11; claims 1,58,59	1,10-12, 14

2

INTERN ONAL SEARCH REPORT

Information on patent family members

Inter. onal application No
PCT/US2007/078341

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006080040 A	03-08-2006	EP 1846364 A1	24-10-2007
US 4859707 A	22-08-1989	NONE	
US 5475130 A	12-12-1995	AT 137744 T	15-05-1996
		CA 2096970 A1	27-05-1992
		DE 69119434 D1	13-06-1996
		DE 69119434 T2	12-09-1996
		DK 559898 T3	19-08-1996
		EP 0559898 A1	15-09-1993
		ES 2088574 T3	16-08-1996
		GR 3020257 T3	30-09-1996
		WO 9209572 A1	11-06-1992
US 2005182108 A1	18-08-2005	NONE	
US 6359009 B1	19-03-2002	NONE	
WO 2006100502 A	28-09-2006	CA 2598589 A1	28-09-2006
		EP 1861384 A1	05-12-2007

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Industria y Comercio
SUPERINTENDENCIA

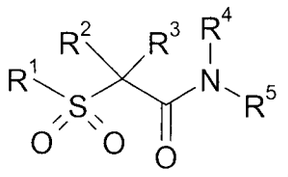
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int Cl: **C07C 317/044**
22) Fecha de solicitud:	(71)Solicitante(s) **BOEHRINGER INTELHEIM INTERNATIONAL GMBH**
(30) Prioridad (31) ***Prioridad*** (32) ***Fecha*** (33) ***País*** **60/826,819** **25/09/2006** **US**	(72) Inventor(es) **ANGELA BERRY Y OTROS**
	(74) Apoderado: **EMILIO FERRERO**
(85) Fecha limite inicio fase nacional: 25/04/2009 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 13/09/2007 No. de solicitud PCT/US2007/078341	(87) Publicación internacional Fecha: 03/04/2008 N° publicación: ***WO 2008/039645 A1***

(54) Titulo: **COMPUESTOS QUE MODULAN EL RECEPTOR CB2**

Reivindicación(es):

1. Un compuesto de la fórmula (I)



(I)

en el que:

R^1 es alquilo C_{1-10}, alcoxi C_{1-10}, cicloalquilo C_{3-10}, anillo heterocíclico saturado de 3-10 miembros, bencilo o fenetilo, cada uno opcionalmente sustituido de forma independiente con 1-3 sustituyentes elegidos a partir de alquilo C_{1-10} sustituido opcionalmente con 1 a 3 átomos de halógeno, cicloalquilo C_{3-10}, anillo heterocíclico saturado de 3-10 miembros sustituidos opcionalmente con acilo, oxo o sulfona de metilo, acilo, ciano, fenilo, oxo, hidroxilo y halógeno;

R^2 y R^3 son independientemente hidrógeno o alquilo C_1-C_6; o R^2 y R^3 junto con el átomo de carbono al que están unidos forman un anillo heterocíclico o cicloalquilo de 3 a 6 miembros;

R^4 es hidrógeno o metilo;

R^5 es arilo o heteroarilo cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 sustituido opcionalmente con 1 a 3 átomos de halógeno o con un grupo heterocíclico, alcoxi C_1-C_6 opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C_3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C_1-C_4, fenilo opcionalmente sustituido con 1 a 2 átomos de halógeno o alquilo C_1-C_4 opcionalmente sustituido con halógeno, tienilo opcionalmente sustituido con 1 a 2 átomos de halógeno o alquilo C_1-C_4 opcionalmente sustituido con halógeno y piridinilo opcionalmente sustituido con 1 a 2 alquilo C_1-C_4 opcionalmente sustituido con halógeno;

o un tautómero o una sal farmacéuticamente aceptable de los mismos.

2. El compuesto de acuerdo con la reivindicación 1, en el que

R^1 es metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, tetrahidropiranilo, biciclo(3.3.0)octanilo, biciclo[4.3.0]nonilo, bencilo o fenetilo, cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de metilo, etilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, tetrahidrofuranilo, tetrahidropiranilo, pirrolidinilo (sustituido opcionalmente con acilo, oxo o metilsulfonilo), piperidinilo (sustituido opcionalmente con acilo, oxo o metilsulfona, acilo, ciano, fenilo, oxo, fluoro, cloro, bromo e hidroxilo ;

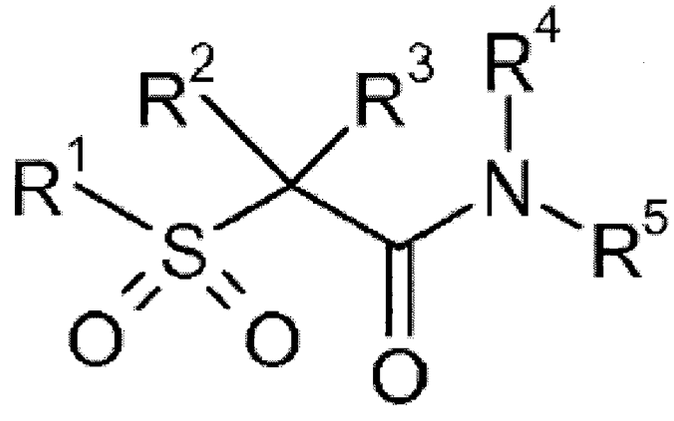
R^2 y R^3 son independientemente hidrógeno, metilo, etilo, n-propilo, isopropilo, isobutilo, terc-butilo, o R^2 y R^3 junto con el carbono al que están unidos forman un anillo de ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o tetrahidropiranilo;

R^4 es hidrógeno;

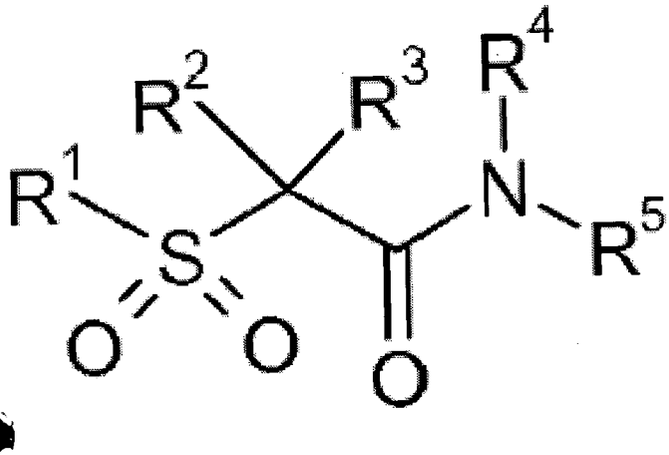
R^5 es fenilo, naftilo, piridinilo, quinolinilo, isoquinolinilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, triazolilo, oxadiazolilo, tiadiazolilo, indolilo, benzoxazolilo, benzopirazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzimidazolilo, tetrahidrobenzoxazolilo, tetrahidrobenzotiazolilo, o tetrahidrobenzimidazolilo, cada uno opcionalmente sustituido independientemente con 1 a 3 sustituyentes elegidos de alquilo C_1-C_6 que está sustituido opcionalmente con 1 a 3 átomos de halógeno, alcoxi C_1-C_6 que está opcionalmente sustituido con 1 a 3 átomos de halógeno, cicloalquilo C_3-C_6, fenoxi, halógeno, ciano, dimetilaminoalquilo C_1-C_4, fenilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno, tienilo que está sustituido opcionalmente con 1 a 2 átomos de halógeno, o alquilo C_1-C_4 sustituido opcionalmente con halógeno y piridinilo que está sustituido opcionalmente con 1 a 2 alquilo C_1-C_4 sustituido opcionalmente con halógeno.

3. El compuesto de acuerdo con la reivindicación 2, en el que

R^1 es metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, terc-butilo, n-pentilo, n-hexilo, n-heptilo, n-octilo, n-nonilo, n-decilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, tetrahidropiranilo, biciclo(3.3.0)octanilo, o biciclo[4.3.0]nonilo, cada uno opcionalmente sustituido de forma independiente con 1 a 3 sustituyentes elegidos de metilo, etilo, pivaloilo, ciclopropilo, ciclobutilo, ciclohexilo, tetrahidropiranilo, tetrahidrofuranilo, pirrolidinilo opcionalmente sustituido con metilsulfona, fluoro, cloro, bromo, oxo e hidroxi;



(I)



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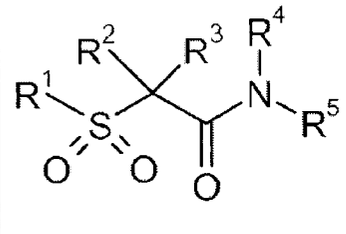

(I)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-030062- -00000-0000

Fecha: 2009-03-24 17:19:12 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 267

RECIBO OFICIAL DE CAJA : 09 - 18,933
FECHA : MARZO 9 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19779071	09/03/2009	49,854,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-06 REGISTRO DE CESION, CAMBIO NOM	13 NOMBRES Y ENSENAS COMERCIALES,MAR	273,000.00
		TOTAL : $	273,000.00

SON: DOSCIENTOS SETENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 09255-841-129-1.

267

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 18,934
FECHA : MARZO 9 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-030062- -00000-0000
Fecha: 2009-03-24 17:19:12
Tra. 11 PATENTEIYII Dep. 2020 NUECREACIONI
Act. 411 PRESENTACION Eve: 378 FASENACIONALI
Folios: 267

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19779071	09/03/2009	49,854,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-06 REGISTRO DE CESION, CAMBIO NOM	13 NOMBRES Y ENSENAS COMERCIALES,MAR	273,000.00
		TOTAL : $	273,000.00

SON: DOSCIENTOS SETENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO:09255-841-129-1.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-030062- -00000-0000

Fecha: 2009-03-24 17:19:12 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 267

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

REFERENCIA	Radicación No.	9 30062
	Solicitud internacional	PCT/US2007/078341
	Fecha inicio fase nacional	25/04/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	-5115

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 08 MAYO 2009
adpa11

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 09-030062

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **616** DE

FECHA **20** DE **MAYO DE 2010** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **19** DE **AGOSTO** DEL **2010**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ___ NO_ _____ **X** _ _