

HUMBERTO RUBIO & CIA.

ABOGADOS

Cra. 7a # 74 - 64 Oficina 506
Tel: (571) 3132408 - 3132423 - 3132410 - 3131759
Fax: (571) 3131647 - 3132367
E-mail: mail@rubiolawyers.com
Apartado Aéreo 21848
Bogota, D.C. - Colombia

138

Doctora

Alix Carmenza CÉSPEDES DE VERGEL

Jefe División de Nuevas Creaciones

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Patente de Invención:

03-111.723

**"DERIVADOS SUSTITUIDOS DEL
1-OXA-2,8-DAZA-ESPIRO [4,5]
DEC-2-ENO"**

Titular:

GRUNENTHAL GMBH

DESTINO: 444

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17'192.062 de Bogotá, abogado graduado portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de **Apoderado** de **GRUNENTHAL GMBH**, domiciliado en Zieglerstrasse 6, 52078 Aachen, Alemania.; encontrándome dentro de la debida oportunidad procesal para dar respuesta al auto proferido por su Despacho, mediante Oficio No. 9907, notificado por fijación en lista de 17 de agosto de 2.007, me permito manifestar y anexar:

I.- Manifiesto y Anexo

Reivindicaciones

El examinador ha formulado objeciones a la claridad de la solicitud. Atendiendo las sugerencias se ha realizado una serie de modificaciones al Capítulo de Reivindicaciones, por lo tanto estamos anexando los siguientes documentos:

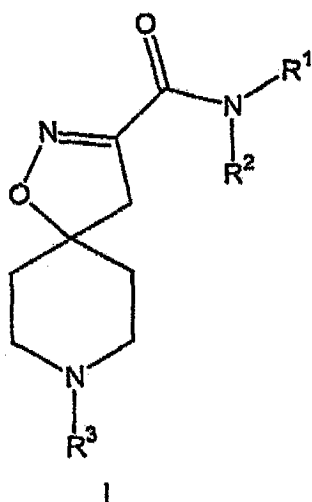
(i) Nuevo capítulo reivindicatorio.

Las reivindicaciones 3, 4, 5 y 6, no se especifica el significado de R3, como se trata de reivindicaciones dependientes no es necesario introducir el significado del radical en mención, en todas las reivindicaciones a menos que se haga alguna especificación respecto a lo indicado en la reivindicación 1, de lo contrario es suficiente y valido que esta información se encuentre en la reivindicación independiente, como ocurre con nuestra solicitud.

En el nuevo pliego también se han eliminado las reivindicaciones 12 a 17, cumpliendo así las exigencias de lo presupuestado en los artículos 14 y 21 de la Decisión 486.

Unidad de Invención

En este punto hacemos notar que se trata de nuevos compuestos donde el elemento que conforma el concepto común, que para que exista la unidad de invención debe ser nuevo e inventivo, esta dado por la estructura



donde los sustituyentes R₁, R₂ y R₃ son los que pueden tomar diferentes significados mientras que el resto de la estructura permanece constante, siendo esta estructura nueva e inventiva, proporcionando así el concepto común inventivo que configura la unidad de invención de los compuestos reivindicados. La actividad farmacológica, forma de acción, propiedades, usos y demás no son indicadores de unidad de invención, sino caracteres propios de la estructura molecular que es en realidad el producto de la invención.

No obstante lo anterior y para precisar el alcance de la invención, los dos sistemas de ensayo, NMDA/glycinB y alfa2A y los resultados mostrados en estos ensayos farmacológicos corresponden a compuestos que no poseen una característica estructural común y también presentan actividad en otros sistemas de prueba ensayados, por ejemplo.

Ejemplo 474	42% de inhibición en el ensayo de BTX
Ejemplo 202	45% de inhibición en el ensayo de BTX
Ejemplo 21	63% de inhibición en el ensayo de BTX (mostrado en esta solicitud)
Ejemplo 27	74% de inhibición en el ensayo de BTX (mostrado en esta solicitud)
Ejemplo 151	83% de inhibición en el ensayo de BTX
Ejemplo 175	30% en el ensayo de absorción de NA

Nivel Inventivo

Los documentos D1, y D2 describen compuestos que no poseen la misma estructura molecular ni tampoco la sugieren, la diferencia radica en que el grupo cetónico de los antecedentes desaparece y en su lugar se encuentra una amida ácida, donde la unión de grupo se hace a través del carbono y hay un doble enlace que está entre el C sobre el que se encuentra el grupo amina ácida y el nitrógeno del anillo a diferencia del enlace sencillo en los compuestos del arte previo. Diferencia notorias que no se hacen evidentes a partir del arte previo. Retomando lo afirmado por el examinador en el punto de unidad de invención "...se puede concluir que todas las variaciones en la molécula según la solicitud presentada, pueden poseer diferente actividad farmacológica, por lo tanto se dilucida que la materia es muy amplia y se encuentra más de un concepto común inventivo" entonces con base en esta afirmación se puede establecer que si dentro de los compuestos de la solicitud las variaciones en la molécula conducen a invenciones diferentes, más significativas resultan aún las diferencias estructurales entre los compuestos del arte anterior y los de la solicitud, donde no existe ni siquiera un elemento común en su estructura molecular, como si existe entre los compuestos de la solicitud elemento que es nuevo e inventivo como ya se expuso anteriormente.

Ahora el argumento del examinador con relación a que el problema técnico no queda plenamente definido y " podría ser solucionado por el experto en la materia con base en los compuestos divulgados en D2, realizando las siguientes modificaciones retiro de las sustituciones del nitrógeno de la posición 2 del anillo, y adición de éstas en el grupo carboxamida (posición 3) e incluye un doble enlace en 2,3(solicitud), resulta tomado muy a la ligera, y visto desde cuando ya se tiene al alcance la solución o el objeto a proteger en este caso los nuevos compuestos, pero éste análisis debe hacerse situándose en el momento en que se esta buscando la solución al problema técnico o la búsqueda de nuevos compuestos con determinada actividad farmacológica, en ese orden de ideas no existe nada en el arte previo que motive a una persona del nivel medio a realizar caprichosamente los cambios en la estructura, comenzando por quitar sin ninguna razón los sustituyentes del nitrógeno de la posición 2 del anillo y adición de éstas en el grupo carboxamida, grupo que no es propiamente una carboxamida en D2, sino un grupo cetónico(posición 3), entonces no es como pretende hacer ver el examinador que resulta tan simple llegar a los nuevos compuestos de nuestra invención, con propiedades mejoradas, conservando su actividad farmacológica. La persona del nivel medio no podría derivar evidentemente de los documentos los nuevos compuestos, que difieren notoriamente de los del arte previo.

De manera atenta solicito a su Despacho, tener en cuenta todas y cada una de las consideraciones expuestas anteriormente, al momento de estudiar el presente caso.

II.- ANEXO:

Conforme a lo indicado en el punto I, se anexan los siguientes documentos:

- (i) Nuevo capítulo reivindicatorio.

III.- PETICIÓN:

Conforme a lo anterior, una vez atendidos los requerimientos y exigencias del examinador y al tener en cuenta el nuevo capítulo descriptivo y de reivindicaciones presentado, así como los argumentos expuesto, solicito muy respetuosamente a su Despacho, continuar el trámite de rigor y de ser el caso se hagan las correspondientes observaciones con al ánimo de hacer lo pertinente dentro del presente trámite.

Atentamente,

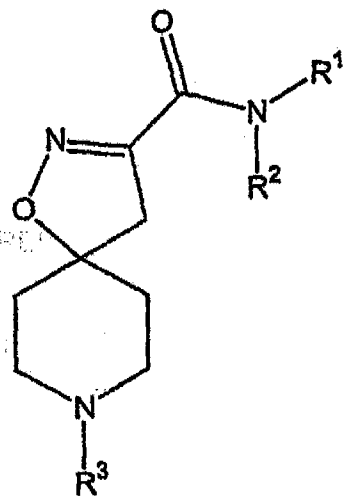


HUMBERTO RUBIO CAMACHO
C.C. 17'192.062 de Bogotá
T.P. 50.007 Consejo Superior
de la Judicatura
COD. 4134

03/1249/P000279

REIVINDICACIONES

1. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno con la fórmula general (I)



en forma de sus racematos, sus estereoisómeros puros, en especial enantiómeros o diastereómeros, o en forma de mezclas de estereoisómeros, en especial de enantiómeros o diastereómeros, en cualquier relación de mezcla; en forma aislada o en forma de sus ácidos o sus bases, o en forma de sus sales, en especial de las sales fisiológicamente admisibles, y muy en especial se prefiere en forma de sus clorhidratos o en forma de sus solvatos, en especial de los hidratos;

caracterizado porque

R^1 y R^2 son independientes entre sí y representan H, alquilo C_{1-8} , cicloalquilo C_{3-8} , (alquilo C_{1-4})-cicloalquilo C_{3-8} , arilo, (alquilo C_{1-4})-arilo, heterociclilo, (alquilo C_{1-4})-heterociclilo o $NH-C(=O)$ -arilo, en donde al menos uno de los grupos R^1 y R^2 no representa H,

o bien

los dos juntos representan $-(CR^4R^5)_m-(CR^6R^7)_n-Y-(CR^8R^9)_p-(CR^{10}R^{11})_q-$ con cada uno de $m = 1$, $n = 0$ o 1 , $p = 1$ o 2 , y $q = 1$ o 2 , o bien representan $-CH_2-CH_2-C(arilo)=CH-CH_2$;

R^3 representa SO_2R^{12} o COR^{13} ;

$R^4, R^5, R^6, R^7, R^8, R^9, R^{10}$ y R^{11} son independientes entre sí y representan H, alquilo C_{1-8} , cicloalquilo C_{3-8} o $C(=O)R^{14}$;

Y representa $CR^{15}R^{16}$ o NR^{17} ;

R^{12} representa alquilo C_{1-4} , (alquilo C_{1-4})-cicloalquilo C_{3-8} , arilo, (alquilo C_{1-4})-arilo, heterociclilo o $NR^{18}R^{19}$;

R^{13} representa alquilo C_{1-6} , cicloalquilo C_{3-10} , arilo, (alquilo C_{1-4})-arilo o

heterociclilo;

R¹⁴ representa OR²⁰;

R¹⁵ y R¹⁶ son independientes entre sí y representan H, arilo o (alquilo C₁₋₄)-arilo;

R¹⁷ representa H, cicloalquilo C₃₋₈, arilo, (alquilo C₁₋₄)-arilo, heterociclilo o C(=O)R²²;

R¹⁸ y R¹⁹ son independientes entre sí y representan H, alquilo C₁₋₆;

R²⁰ representa alquilo C₁₋₆;

R²² representa arilo, (alquilo C₁₋₄)-arilo, heterociclilo u OR²⁴; y

R²⁴ representa alquilo C₁₋₆ o (alquilo C₁₋₄)-arilo.

2. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno de acuerdo con la reivindicación 1 o 2, caracterizados porque

R¹ representa alquilo C₁₋₆, cicloalquilo C₃₋₈, (alquilo C₁₋₃)-cicloalquilo C₃₋₈, arilo, (alquilo C₁₋₃)-arilo, heterociclilo, (alquilo C₁₋₃)-heterociclilo o NH-C(=O)-arilo, y

R² representa H, alquilo C₁₋₄, (alquilo C₁₋₃)-arilo o (alquilo C₁₋₃)-heterociclilo;

3. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno de acuerdo con la reivindicación 3, caracterizados porque

R¹ representa metilo, etilo, n-propilo, isopropilo, 2-metilpropilo, n-butilo, ter-butilo, n-pentilo, 3-metilbutilo o CH₂-C(CH₃)=CH₂, no sustituido o sustituido con F, Cl, Br, I, -CN, N-alquilo-N-arilamino, N,N-dialquilamino, amida, carboxialquilo, carboxibencilo; en especial metilo, etilo, CH₂-C(CH₃)=CH₂, CH(C(=O)OCH₂CH=CH₂)-CH₂C(=O)O-ter-butilo, 2-cianoetilo, CH₂-CH₂-NH-C(=O)CH₃, 2-(N-etil-N-(3-metilpentil)-amino)-etil, 2-(N,N-dimetilamino)-etilo, 2-(C(=O)-NH-(β-naftilo)-etilo, 1,2-(di-(C(=O)O-ter-butil)-etilo, 3-(N-metil-N-fenilamino)-propilo, 1-(C(=O)O-bencilo)-3-metil-butilo, 1-(C(=O)O-butilo)-3-metil-butilo, CH₂CO₂-etilo, CH₂CH₂CO₂-etilo, CH₂-CH₂-O-fenilo, CH₂-CH₂-S-CH₂-CH₃;

ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, biciclo[3.1.1]heptano-3-ilo, en especial fenilciclopropilo, 2-(O-bencilo)-ciclopentilo, 2-(carboxietilo)-ciclohexilo, 7,7-dimetil-2-(carboxietil)-ciclohexilo, 7,7-dimetil-2-metilbiciclo[3.1.1]heptano-3-ilo, no sustituido o sustituido con F, Cl, Br, I, -CN, alquilo, arilo, carboxialquilo, carboxibencilo, O-alquilo, O-bencilo;

ciclopropilmetilo, 7,7-dimetil-2-oxo-biciclo[2.2.1]hept-1-ilometilo;

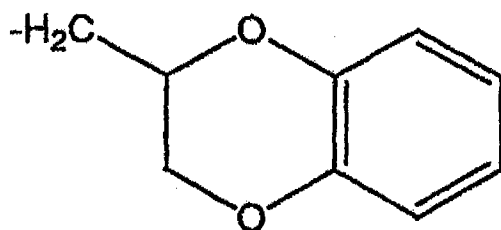
fenilo, 1-naftilo o 2-naftilo no sustituido o sustituido con fenoxi, -CH₂-P(=O)(O-etilo)₂;

CH₂-arilo, CH₂-CH₂-arilo, CH₂-CH₂-CH₂-arilo, CH₂-CH₂-CH₂-CH₂-arilo, CH(CH₃)-arilo, CH(CH₃)-CH₂-arilo, CH₂-CH-(arilo)₂, CH(CO₂-alquilo)-CH₂-

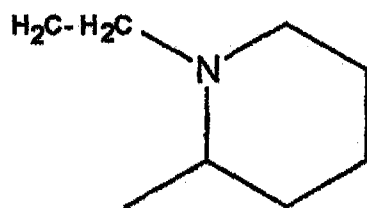
arilo, $\text{CH}_2\text{-CH}_2\text{-CH-(arilo)}_2$, en donde arilo representa fenilo no sustituido, 1-naftilo o 2-naftilo, o fenilo sustituido con F, Cl, Br, I, -CN, NO_2 , alquilo, CF_3 , alcoxi, o alquilendioxi, en especial bencilo, $\text{-CH}_2\text{-naft-1-ilo}$, 2-fluorobencilo, 3-fluorobencilo, 3-clorobencilo, 3-metoxibencilo, 2-etoxibencilo, 2,4-difluorobencilo, 3,5-diclorobencilo, 3-fluoro-5-trifluorometilbencilo, 3-fluoro-4-trifluorometilbencilo, 2-cloro-6-fluorobencilo, 2,5-dimetoxibencilo, 2-cloro-6-metil-bencilo, 3,4-dimetoxibencilo, 3,4-dioximetilbencilo, $\text{CH(CH}_3\text{)-fenilo}$, $\text{CH(CH}_3\text{)-4-CH}_3\text{-fenilo}$, $\text{CH(CH}_3\text{)-(4-nitrofenilo)}$, $\text{CH(CH}_3\text{)-(2,3-dioxietilen-fenilo)}$, $\text{CH}_2\text{-CH}_2\text{-fenilo}$, $\text{CH}_2\text{-CH}_2\text{-(2-fluorofenilo)}$, $\text{CH}_2\text{-CH}_2\text{-fenilo}$, $\text{CH}_2\text{-CH}_2\text{-(4-fluorofenilo)}$, $\text{CH}_2\text{-CH}_2\text{-(4-clorofenilo)}$, $\text{CH}_2\text{-CH}_2\text{-(3,4-diclorofenilo)}$, $\text{CH}_2\text{-CH}_2\text{-(3-metoxifenilo)}$, $\text{CH}_2\text{-CH}_2\text{-(2,5-dimetoxifenilo)}$, $\text{CH(CO}_2\text{-ter-butilo)-CH}_2\text{-fenilo}$, $\text{CH(CO}_2\text{-metilo)-CH}_2\text{-4-clorofenilo}$, $\text{CH}_2\text{-CH(fenilo)}_2$, $\text{CH(CH}_3\text{)-CH}_2\text{-(4-clorofenilo)}$, $\text{CH}_2\text{-CH}_2\text{-CH(fenilo)}_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{-fenilo}$;

pirrolidin o piperidin no sustituido o sustituido con arilo, alquilarilo o carboxietilo, en especial pirrolidin-3-ilo, N-(4-trifluorobencil)-pirrolidin-3-ilo, N-(3-metoxibencil)-pirrolidin-3-ilo, N($\text{CH}_2\text{-(}\beta\text{-naftil)}$)-pirrolidin-3-ilo o N-(carboxietil)-piperidin-4-ilo;

$(\text{CH}_2)_{1-3}$ -heterociclilo no sustituido, o sustituido con alquilo, F, Cl, Br, I, -CN, arilo, alquilarilo, donde el heterociclilo es furanilo, benzofuranilo, 1,4-dioxanilo, benzo-1,4-dioxanilo, tienilo, piridinilo, pirrolidinilo, 1H-indolilo, imidazolilo, piperidinilo, tetrahidrofuranilo, en especial $\text{CH}_2\text{-furanilo}$, 5-metilfuran-2-ilo, $\text{CH}_2\text{-benzofuran-2-ilo}$,



$\text{CH}_2\text{-tien-2-ilo}$, $\text{CH}_2\text{-piridin-3-ilo}$, $\text{CH}_2\text{-piridin-4-ilo}$, $\text{CH}_2\text{-CH}_2\text{-piridin-2-ilo}$, $\text{CH}_2\text{-CH}_2\text{-(1H-indol-3-ilo)}$, $\text{CH}_2\text{-CH}_2\text{-pirrolidin-1-ilo}$, $\text{CH}_2\text{(N-2,5-diclorobencil-pirrolidin-3-ilo)}$, $\text{(CH}_2\text{-CH}_2\text{-(N-metil-pirrolidin-2-ilo))}$, $\text{-(CH}_2\text{)}_3\text{-imidazol-1-ilo}$, $\text{CH}_2\text{-(tetrahidrofuran-2-ilo)}$ o



o $\text{CH(CO}_2\text{-metil)-CH}_2\text{-(1H-indol-3-ilo)}$;

$\text{NH-C(=O)-(4-dimetilaminofenil)}$, y

R^2 representa H;

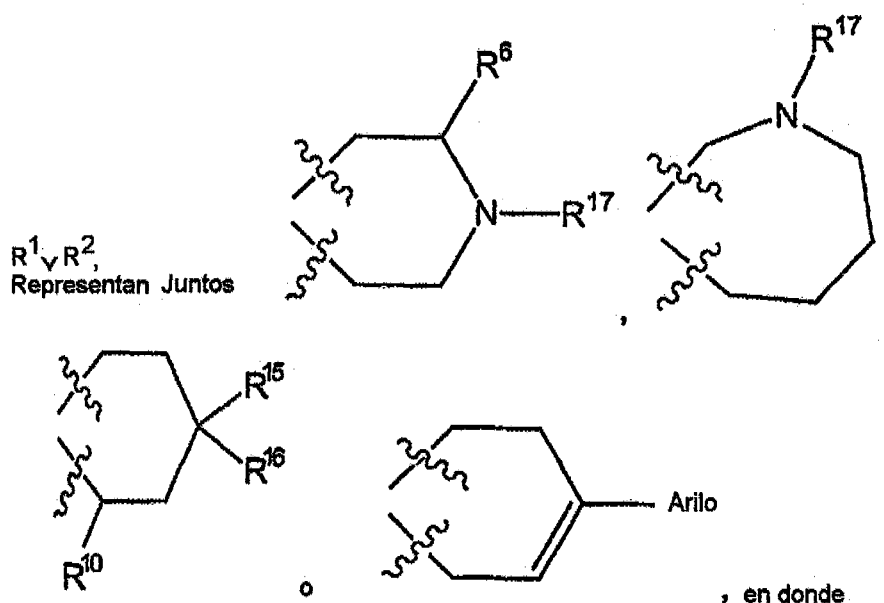
metilo, etilo o $\text{CH}_2\text{-C(CH}_3\text{)}$ sustituido con F, Cl, Br, I, -CN, en especial

metilo, etilo, 2-cianoetilo, $\text{CH}_2\text{-C}(\text{CH}_3)=\text{CH}_2$;

bencilo o fenetilo no sustituido o sustituido con F, Cl, Br, I, -CN, metoxi o etoxi, en especial bencilo, 4-fluorobencilo, 2-cloro-6-fluorobencilo, 2,5-dimetoxibencilo, fenetilo, o bien

5 CH_2 -furanilo, en especial CH_2 -furano-2-ilo, CH_2 -benzofuranilo, en especial CH_2 -benzofuran-2-ilo, CH_2 -piridinilo, en especial CH_2 -piridin-3-ilo, CH_2 -tetrahydrofuranilo, en especial CH_2 -tetrahydrofuran-2-ilo, $\text{CH}_2\text{-CH}_2$ -piridinilo, en especial $\text{CH}_2\text{-CH}_2$ -piridin-2-ilo.

10 4. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno de acuerdo con la reivindicación 1 o 2, caracterizado porque



15 arilo representa fenilo o fenilo sustituido con F, Cl, Br, I, en especial 4-fluorofenilo;

R^6 representa H o alquilo C_{1-4} , en especial metilo;

R^{10} representa H, $\text{C}(=\text{O})\text{O}$ -metilo, $\text{C}(=\text{O})\text{O}$ -etilo, $\text{C}(=\text{O})\text{O}$ -n-propilo, $\text{C}(=\text{O})\text{O}$ -isopropilo, $\text{C}(=\text{O})\text{O}$ -n-butilo, $\text{C}(=\text{O})\text{O}$ -ter-butilo;

R^{15} representa H o CH_2 -arilo;

20 R^{16} representa H

R^{17} representa H;

cicloalquilo C_{3-8} , en especial cicloheptilo;

fenilo o naftilo, sustituido con arilo, en especial no sustituido o sustituido con metilo, etilo, n-propilo, iso-propilo, n-butilo, ter-butilo, CF_3 , F, Cl, Br, I, -CN, metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, ter-butoxi;

25 (alquilo $(\text{CH}_2)_{1-3}$)-arilo o $\text{CH}(\text{CH}_3)$ -arilo, donde el arilo no está sustituido o está sustituido con alquilo, CF_3 , F, Cl, Br, I, -CN, fenilo o naftilo sustituido con alcoxi;

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representa piridinilo, pirazinilo o tieno[2,3-d]pirimidinilo no sustituido o sustituido con alquilo, CF_3 , F, Cl, Br, I, -CN o alcoxi; o bien representa $\text{C}(=\text{O})\text{R}^{22}$; y

R^{22} representa fenilo, O-metilo, O-etilo, O-n-propilo, O-isopropilo, O-n-butilo, O-ter-butilo, O-bencilo, bencilo no sustituido, bencilo sustituido con F, pirazinilo no sustituido o sustituido con alquilo, todos ellos sustituidos con fenilo o con alcoxi;

5. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno de acuerdo con la reivindicación 5, caracterizados porque

R^6 representa H o metilo;

R^{10} representa H o $\text{C}(=\text{O})\text{O}$ -etilo;

R^{15} representa H o bencilo;

R^{16} representa H, y

R^{17} representa H; cicloheptilo;

fenilo, 2-metilfenilo, 3-metilfenilo, 2,4-dimetilfenilo, 2-etilfenilo, 3-trifluorometilo, 4-fluorofenilo, 4-clorofenilo, 2-metoxifenilo, 3,5-dimetoxifenilo, 3-cloro-6-metilfenilo;

bencilo, CH_2 -(4-ter-butilfenilo), CH_2 -(β -naftilo), $\text{CH}(\text{CH}_3)$ -fenilo, $(\text{CH}_2)_3$ -fenilo; piridin-2-ilo, (4-trifluorometil)-piridin-2-ilo, tieno[2,3-d]pirimidin-4-ilo, o bien $\text{C}(=\text{O})$ -(4-metoxifenilo), $\text{C}(=\text{O})$ -bencilo, $\text{C}(=\text{O})$ - CH_2 -(3,4-difluorofenilo), $\text{C}(=\text{O})$ -(2-metilpirazin-5-ilo), $\text{C}(=\text{O})\text{O}$ -ter-butilo u O-bencilo.

6. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno de acuerdo con cualquiera de las reivindicaciones 1 a 6, caracterizados porque

R^3 representa SO_2R^{12} ;

R^{12} represente metilo, etilo, n-propilo, isopropilo, en especial n-propilo;

7,7-dimetil-2-oxo-biciclo[2.2.1]hept-1-ilometilo, fenilo o fenilo sustituido con metilo, etilo, n-propilo, isopropilo, n-butilo, ter-butilo, CF_3 , F, Cl, Br, I, -CN, NO_2 , metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, ter-butoxi, OCF_3 o CO_2 -metilo, en especial 4-metilfenilo, 3-trifluorometil-fenilo, 4-fluorofenilo, 2-clorofenilo, 3-clorofenilo, 4-clorofenilo, 4-metoxifenilo, 4-trifluorometoxi-fenilo, 4-nitrofenilo, 2- CO_2 -metil-fenilo, 2,5-diclorofenilo, 3-fluoro-6-metilfenilo, 3-bromo-6-metoxifenilo, 2-metilo-5-nitrofenilo, 2,4,6-trimetilfenilo;

bencilo no sustituido o sustituido con metilo, etilo, n-propilo, isopropilo, n-butilo, ter-butilo, CF_3 , F, Cl, Br, I, -CN, NO_2 , metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, ter-butoxi u OCF_3 ;

furanilo o tienilo, no sustituido o sustituido con metilo, etilo, n-propilo,



isopropilo, n-butilo, ter-butilo, CF_3 , Cl, Br, I, -CN, NO_2 , metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi o ter-butoxi; en especial tien-2-ilo, 5-clorotien-2-ilo o $\text{NR}^{18}\text{R}^{19}$; y

R^{18} y R^{19} son independientes entre sí y representan H, metilo o etilo.

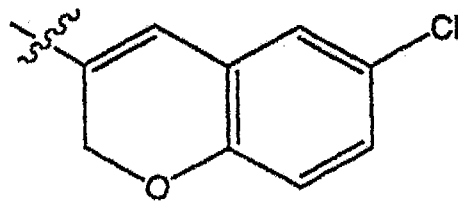
- 5
7. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno de acuerdo con cualquiera de las reivindicaciones 1 a 6, caracterizado porque

R^3 representa COR^{13} y

10
 R^{13} sea no sustituido o sustituido con O-metilo, O-etilo, $\text{O}-(\text{CH}_2)_2\text{OCH}_3$, O-bencilo, O-fenilo, en donde el fenilo no está sustituido, o está sustituido con F, Cl, Br, I, -CN, metilo sustituido con $\text{O}-\text{C}(=\text{O})$ -metilo, $\text{O}-\text{C}(=\text{O})$ -etilo, etilo, $\text{C}(=\text{O})\text{O}$ -metilo, n-propilo, isopropilo, 2-metilpropilo, n-butilo, ter-butilo, n-pentilo o 3-metilbutilo, en especial metilo, etilo, n-propilo, n-butilo, ter-butilo, n-pentilo, $\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}(\text{CH}_3)\text{-O-fenilo}$, $\text{CH}_2\text{-CH}_2\text{-C}(=\text{O})\text{OCH}_3$, $\text{C}(\text{CH}_3)_2\text{-OC}(=\text{O})\text{CH}_3$, $\text{CH}_2\text{-O-bencilo}$, $\text{CH}_2\text{-O-(3-clorofenilo)}$, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-O-fenilo}$, $\text{CH}(\text{OC}(=\text{O})\text{metilo})\text{CH}_3$; ciclopropilo, 2-fenilciclopropilo, 1-adamantilo;

15
fenilo o naftilo no sustituido o sustituido con F, Cl, Br, I, -CN, fenilo, metilo, etilo, n-propilo, isopropilo, n-butilo, ter-butilo, CF_3 , F, Cl, Br, I, -CN, NO_2 , metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, ter-butoxi, OCF_3 , OCHF_2 , OCH_2F , SCF_3 , SCHF_2 , SCH_2F , $\text{SCH}_3\text{CH}_2\text{OC}(=\text{O})\text{fenilo}$ o $-\text{N}(\text{CH}_3)$; en especial 4-fluorofenilo, 2-clorofenilo, 3-clorofenilo, 4-bromofenilo, 4-fenilfenilo (4-bifenilo), 4-etilfenilo, 4- CF_3 -fenilo, 4-metoxifenilo, 2-etoxifenilo, 4-ter-butilo, 3- OCF_3 -fenilo, 4- OCF_3 -fenilo, 4- SCF_3 -fenilo, 3- SCF_2 -fenilo, 2- $\text{CH}_2\text{-OC}(=\text{O})\text{fenilo}$, 3-dimetilaminofenilo, 2,3-diclorofenilo, 2,4-difluorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-2-fluorofenilo, 4- CF_3 -3-fluorofenilo, 3- CF_3 -6-fluorofenilo, 4-bromo-3-metilfenilo, 2-cloro-4-nitrofenilo, 2,3,4,5,6-pentafluorofenilo, 2,6-difluoro-3-metilfenilo, 2,3-difluoro-4-metilfenilo, 2-cloro-5-metil-6-fluorofenilo, 1-naftilo, 2-naftilo;

20
30
(alquilo C_{1-2})-arilo, no sustituido o sustituido, en especial bencilo, fenetilo, $\text{CH}(\text{C}_2\text{H}_5)\text{-fenilo}$, $\text{CH}(\text{NH-SO}_2\text{-(4-metilfenilo)})\text{-CH}_2\text{-fenilo}$, $\text{CH}=\text{CH-fenilo}$, $\text{CH}=\text{CH}_3\text{-(3-trifluorofenilo)}$ o furanilo, benzofuranilo; tienilo, piridinilo, pirazolilo, benzodihidropiranilo, isoxazolilo no sustituido o sustituido con alquilo, no sustituido o sustituido con alquilo, CF_3 , arilo, O-fenilo, cloro, S-metilo, S-etilo; en especial 1,5-dimetilfuran-3-ilo, 2-metil-5-ter-butil-furan-3-ilo, 3-clorotien-2-ilo, 1-(4-clorofenil)-5-trifluorometil-pirazol-4-ilo, 1-metil-3-ter-butil-pirazol-5-ilo,



5

piridin-4-ilo, 2-metiltiopiridin-3-ilo, 2-etiltiopiridin-3-ilo, 2-fenoxipiridin-3-ilo, 2-cloropiridin-3-ilo, 5-metil-3-(2,6-diclorofenil)-isoxazol-4-ilo, 5-metil-3-(2-cloro-6-fluorofenil)-isoxazol-4-ilo no sustituido o sustituido con alquilo, CF_3 , arilo, O-fenilo, cloro, S-metilo o S-etilo.

8. Derivados sustituidos de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno de acuerdo con la reivindicación 1, caracterizados porque se seleccionan del grupo formado por
 - éster metílico del ácido 3-(1H-indol-3-ilo)-2-[[8-(4-trifluorometoxi-benzosulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-carbonil]-amino]-propanoico
 - éster dietílico del ácido {4-[(8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil)-amino]-bencil}-fosfónico
 - (4-cicloheptil-piperazin-1-ilo)-[8-tiofeno-2-sulfonilo]-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-ilo]-metanona
 - [8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-ilo]-(4-fenil-piperazin-1-ilo)-metanona
 - ciclopentilamida del ácido 8-(2-cloro-4-nitro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-carboxílico
 - (4-naftalen-2-ilometil-piperazin-1-ilo)-(8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-ilo)-metanona
 - fenetilamida del ácido 8-dimetil-sulfamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (1-fenil-etil)-amida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [2-(3,4-dicloro-fenil)-etil]-amida del ácido 8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - N'-[8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-carbonil]-hidrazida del ácido 4-dietilamino-benzoacético
 - (2-pirrolidin-1-ilo-etil)-amida del ácido 8-(3-cloro-4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - fenetil-amida del ácido 8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-carboxílico
 - (2-dimetilamino-etil)-amida del ácido 8-bencensulfonil-1-oxa-2,8-espiro[4.5]dec-2-eno-2-carboxílico
 - [4-(3-fenil-propil)-piperazin-1-ilo]-[8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-

en-3-ilo]metanona

- [3-(2-metil-piperidin-1-ilo)-propil]-amida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-carboxílico
- [2-(1H-indol-3-ilo)-etil]-metil-amida del ácido 8-(4-trifluorometoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-carboxílico
- (2-acetilamino-etil)-amida del ácido 8-(5-fluoro-2-metil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- bencil-fenetil-amida del ácido 8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-dimetilamino-etil)-amida del ácido 8-(2-metil-5-nitro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-en-3-carboxílico
- (2-benciloxi-ciclopentil)-amida del ácido 8-feniletanosulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2,3-dihidro-benzo[1,4]dioxin-2-ilometil)-amida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (4-fenoxi-fenil)-amida del ácido 8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (1-p-tolil-etil)-amida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 3-fluoro-bencilamida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 2-fenil-1-[4-[8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-piperazin-1-ilo]-etanona
- [1-(4-trifluorometil-bencil)-pirrolidin-3-ilo]-amida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-(4-o-tolil-piperazin-1-ilo)-metanona
- bencil-(2-ciano-etil)-amida del ácido 8-toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]4-tieno[2,3d]pirimidin-4-ilo-piperazin-1-ilo)-metanona
- (benzo[1,3]dioxol-5-ilometil)-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (3-metil-4-m-tolil-piperazin-1-ilo)-[8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
- [4-(1-fenil-etil)-piperazin-1-ilo]-[8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
- [4-(2,5-dimetil-fenil)-piperazin-1-ilo]-[8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
- ciclopentilamida del ácido 8-(2-cloro-piridin-3-carbonil)-1-oxa-2,8-diaza-

espiro[4.5]dec-2-eno-3-carboxílico

- (4-naftalen-2-ilometil-piperazin-1-ilo)-[8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
- (piridin-3-ilometil)-amida del ácido 8-[3-fenil-2-toluen-4-sulfonilamino)-propionil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-dimetilamino-etil)-amida del ácido 8-(5-fluoro-2-metil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (tiofen-2-ilometil)-amida del ácido 8-(4-nitro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 3-fluoro-5-trifluorometil-bencilamida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- benzhidril-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-ciano-etil)-amida del ácido 8-[3-fenil-2-(toluen-4-sulfonilamino)-propionil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster etílico del ácido [(6-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil)-amino]-acético
- (2-ciano-etil)-amida del ácido 8-(3-dimetilamino-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [1-(naftalen-2-ilo-carbamoilo)-etil]-amida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (1-p-tolil-etil)-amida del ácido 8-(toluen-4-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [4-(4-cloro-fenil)-piperazin-1-ilo]-(8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo)-metanona
- (2-benciloxi-ciclopentil)-amida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- encilamida del ácido 8-acetil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 2,5-difluoro-bencilamida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (1-naftalen-2-ilometil-pirrolidin-3-ilo)-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 2-etoxi-bencilamida del ácido 8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (tiofen-2-ilometil)-amida del ácido 8-(4-etil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster 1-alílico éster 4-ter-butílico del ácido 2-[[8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-succínico
- naftalen-2-ilo-amida del ácido 8-(4-trifluorometoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico

- éster etílico del ácido 4-[[8-(2-fenil-ciclopropano-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-piperidin-1-carboxílico
- éster etílico del ácido 4-[[8-(2,4-difluoro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-piperidina-1-carboxílico
- (2-dimetilamino-etil)-amida del ácido 8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [2-(4-cloro-fenil)-etil]-amida del ácido 8-dimetil-sulfamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (5-metil-furan-2-ilometil)-amida del ácido 8-(4-metoxi-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [2-(4-cloro-fenil)-etil]-amida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [2-(1-metil-pirrolidin-2-ilo)-etil]-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster etílico del ácido 4-[[8-(4-bromo-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-piperidina
- 3,5-dicloro-bencilamida del ácido 8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [1-(3-metoxi-bencil)-pirrolidin-3-ilo]-amida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- dimetilamida del ácido 3-(4-naftalen-2-ilometil-piperazin-1-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-sulfónico
- éster etílico del ácido 3-[[8-(7,7-dimetil-2-oxo-biciclo[2.2.1]hept-1-ilo-metanosulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-propanoico
- (2-benciloxi-ciclopentil)-amida del ácido-8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 3,4-dimetoxi-bencilamida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (8-fenil-metano-sulfonil-1-oxa-2,6-diaza-espiro[4.5]dec-2-en-3-ilo)-[4-(3-fenil-propil)-piperazin-1-ilo]-metanona
- dimetilamida del ácido 3-(4-tieno[2,3-d]-pirimidin-4-ilo)-piperazin-1-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-sulfónico
- [8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-[4-(3,5-dimetoxi-fenil)-piperazin-1-ilo]-metanona
- 3-fluoro-4-trifluorometil-bencilamida del ácido 8-dimetilsulfamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-benciloxi-ciclopentil)-amida del ácido 8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster etílico del ácido 4-[(8-butil-1-oxa-2,8-diaza-espiro-[4.5]dec-2-eno-3-carbonil)-amino]-piperidin-1-carboxílico

- (2-fenil-ciclopropil)-amida del ácido 8-(toluen-4-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [8-(4-fluoro-benzoilsulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-[4-(5-metil-piperazin-2-carbonil)-piperazin-1-ilo]-metanona
- 2,4-difluoro-bencilamida del ácido 8-dimetil-sulfamoi-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [2-(3-fluoro-fenil)-etil]-amida del ácido 8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-2-difenil-etil)-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- dimetilamida del ácido 3-[4-(3-fenil-propil)-piperazin-1-carbonil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-sulfónico
- éster etílico del ácido 3-[[8-(3,5-difluoro-benzoi)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-propanoico
- [4-(3-fenil-propil)-piperazin-1-ilo]-[8-(3-trifluorometil-benzoi-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
- [1-(2,3-dihidro-benzo[1,4-dioxin-5-ilo)-etil]-amida del ácido 8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- fenilamida del ácido 8-butil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- ciclooctil-amida del ácido 8-(4-trifluorometoxi-benzoi-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- bencilamida del ácido 8-[2-(2-metoxi-etoxi)-acetil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- isobutil-amida del ácido 8-(4-bromo-3-metil-benzoi)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [3-(,etil-fenil-amino)-propil]amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster etílico del ácido 4-[[8-(2-metil-5-nitro-bencen-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-piperidin-1-carboxílico
- [8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-[4-(4-fluoro-fenil)-piperazin-1-ilo]-metanona
- metil-piperidin-3-ilometil-amida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 2-(3,4-difluoro-fenil)-1-[4-[8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-piperazin-1-ilo]-etanona
- ciclopropil-metil-amida del ácido 8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster etílico del ácido 3-[[8-(2-metil-5-nitro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-propanoico
- (tiofen-2-ilometil)-amida del ácido 8-[2-(3-cloro-fenoxi)-acetil]-1-oxa-2,8-diaza-

- espiro[4.5]dec-2-eno-3-carboxílico
- bencil-fenetil-amida del ácido 8-(4-trifluoro-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - bencil-fenetil-amida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-ciano-etil)-piridin-3-ilometil-amida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-ciano-etil)-(tetrahydro-furan-2-ilometil)-amida del ácido 8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - metil-piridin-3-ilometil-amida del ácido 8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - bencilamida del ácido 8-(piridin-4-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - etil-(2-metil-alil)-amida del ácido 8-(4-trifluorometoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [2-(2-fluoro-fenil)-etil]-amida del ácido 8-(4-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - isobutil-amida del ácido 8-(5-ter-butil-2-metil-furan-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (tiofen-2-ilometil)-amida del ácido 8-(3-fenil-acrilol)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - ciclopropil-metil-amida del ácido 8-(4-trifluorometil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - ciclopropil-metil-amida del ácido 8-(4-trifluorometil-sulfanil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (5-metil-furan-2-ilometil)-amida del ácido 8-(4-bromo-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - ciclopropil-metil-amida del ácido 8-(3-fluoro-4-trifluorometil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-etil-sulfanil-etil)-amida del ácido 8-(7,7-dimetil-2-oxo-biciclo[2.2.1]hept-1-ilo-metanosulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (tetrahydro-furan-2-ilometil)-amida del ácido 8-(2,4-difluoro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster etílico del ácido {[8-(3-cloro-tiofen-2-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino}-acético
 - éster metílico del ácido 4-oxo-4-{3-[(tiofen-2-ilometil)-carbamoil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-ilo-butírico
 - bencilamida del ácido 8-(2-etil-sulfanil-piridin-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster etílico del ácido 3-[[8-(2-cloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-

eno-3-carbonil]-amino}-propanoico

- ciclopropil-metil-amida del ácido 8-(4-trifluorometoxi-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- ciclopropil-metil-amida del ácido 8-(4-fenoxi-butil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-[4-(4-trifluorometil-piridin-2-ilo)-piperazin-1-ilo]-metanona
- ciclopropil-metil-amida del ácido 8-(2-cloro-5-trifluorometil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-benciloxi-ciclopentil)-amida del ácido 8-(4-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster etílico del ácido 4-[[8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]piperidin-1-carboxílico
- ciclopropil-metil-amida del ácido 8-(2-fenoxi-propionil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [2-(3-metoxi-fenil)-etil]-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- isobutil-amida del ácido 8-(2-metilsulfanil-piridin-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- ciclopentil-amida del ácido 8-(5-ter-butil-2-metil-furan-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (tiofen-2-ilometil)-amida del ácido 8-(4-cloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (naftalen-1-ilometil)-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [2-(4-fluoro-fenil)-etil]-amida del ácido 8-(4-trifluoro-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-carboxílico
- (piridin-4-ilometil)-amida del ácido 8-(4-bromo-3-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- bencilamida del ácido 8-(4-metoxi-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- 3-cloro-bencilamida del ácido 8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo)-(4-o-tolil-piperazin-1-ilo)-metanona
- (8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo(4-piridin-2-ilo-piperazin-1-ilo)-metanona
- (tiofen-2-ilometil)-amida del ácido 8-(4-trifluorometil-sulfanil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- bencilamida del ácido 8-[tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-

carboxílico

- isobutilamida del ácido 8-(4-fluoro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster metílico del ácido 2-(3-isobutil-carbamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-sulfonil)-bencen-acético
- éster ter-butílico del ácido 2-[(8-dimetil-sulfamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil)-amino]-3-fenil-propanoico
- [1-(2,3-dihidro-benzo[1,4]dioxin-5-ilo)-etil]-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (tiofen-2-ilometil)-amida del ácido 8-(4-bromo-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (3-imidazol-1-propil)-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster bencílico del ácido 4-[8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-piperazin-1-carboxílico
- dimetilamida del ácido 3-(4-cicloheptil-piperazin-1-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-sulfónico
- éster ter-butílico del ácido 4-metil-2-[[8-(tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-pentanoico
- (tiofen-2-ilometil)-amida del ácido 8-(3-cloro-2-fluoro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster ter-butílico del ácido 2-[[8-(4-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-4-metil-pentanoico
- éster etílico del ácido 3-[[8-(6-cloro-2-fluoro-3-metil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-propanoico
- bencilamida del ácido 8-(2-fenoxi-propionil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (tiofen-2-ilometil)-amida del ácido 8-(5-fluoro-2-metil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- [8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-[4-(2-metoxi-fenil)-piperidin-1-ilo]-metanona
- (tiofen-2-ilometil)-amida del ácido 8-(2-cloro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- ciclopentil-amida del ácido 8-(2-fenoxi-piridin-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-etil-sulfanil-etil)-amida del ácido 8-(4-bromo-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- éster etílico del ácido 1-[8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-piperidin-2-carboxílico
- (tiofen-2-ilometil)-amida del ácido 8-(2-cloro-bencensulfonil)-1-oxa-2,8-diaza-

- espiro[4.5]dec-2-eno-3-carboxílico
- ciclopropil-metil-amida del ácido 8-(2,3-dicloro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - ciclopropil-metil-amida del ácido 8-hexanoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - ciclopropil-,etil-amida del ácido 8-(2,3-difluoro-4-metil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2,5-dimetoxi-bencil)-furan-2-ilometil-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-acético
 - (2-etilsulfanil-etil)-amida del ácido 8-dimetil-sulfamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - 3-metoxi-bencilamida del ácido 8-(4-trifluorometoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-benciloxi-ciclopentil)-amida del ácido 8-dimetil-sulfamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [2-(4-cloro-fenil)-1-metil-etil]-amida del ácido 8-(4-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [2-(3,4-dicloro-fenil)-etil]-amida del ácido 8-(4-trifluoro-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - bencilamida del ácido 8-[2-(3-cloro-fenoxi-acetil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-ciano-etil)-(2-piridin-2-ilo-etil)-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [2-(4-cloro-fenil)-1-metil-etil]-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-benciloxi-ciclopentil)-amida del ácido 8-(4-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (tiofen-2-ilometil)-amida del ácido 8-(2,6-difluoro-3-metil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - bencilamida del ácido 8-(2-benciloxi-acetil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - fenilamida del ácido 8-(2,3-dicloro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - ciclopentil-amida del ácido 8-(5-bromo-2-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster 2-(3-bencil-carbamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-ilo)-1,1-dimetil-2-oxo-acético
 - (2-etil-sulfanil-etil)-amida del ácido 8-[3-(2-cloro-6-fluoro-fenil)-5-metil-isoxazol-4-carbonil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [4-(3-fenil-propil)-piperazin-1-ilo]-[8-(4-trifluoro-metoxi-bencensulfonil)-1-oxa-2,8-diaza-

- espiro[4.5]dec-2-eno-3-ilo]-metanona
- bencilamida del ácido 8-3-(2-cloro-6-fluoro-fenil)-5-metil-isoxazol-4-carbonil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - isobutil-amida del ácido 8-(naftalen-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster etílico del ácido 1-[8-(5-ter-butil-2-metil-furan-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-piperidin-2-carboxílico
 - bencilamida del ácido 8-(3-difluoro-metil-sulfanil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - fenilamida del ácido 8-(4-bromo-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-fenil-ciclopropil)-amida del ácido 8-(4-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (tiofen-2-ilometil)-amida del ácido 8-(4-fenoxi-butiril)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (tiofen-2-ilometil)-amida del ácido 8-(3-cloro-4-fluoro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-etil-sulfanil-etil)-amida del ácido 8-(5-ter-butil-2-metil-2H-pirazol-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-[4-(3-fenil-propil)-piperazin-1-ilo]-metanona
 - (piridin-4-ilometil)-amida del ácido 8-(4-trifluoro-metoxi-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster bencílico del ácido 2-(3-ciclopentil-carbamoil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-carbonil)-benzoico
 - dimetilamida del ácido 3-[4-(4-ter-butil-bencil)-piperazin-1-carbonil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-8-sulfónico
 - éster etílico del ácido {[8-(2-etoxi-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino}-acético
 - (2-benciloxi-ciclopentil)-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (tiofen-2-ilometil)-amida del ácido 8-(naftalen-1-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (3-metil-propil)-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2,3-dihidro-benzo[1,4]-dioxin-2-ilometil)-amida del ácido 8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster etílico del ácido 1-[8-(4-ter-butil-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-piperidin-2-carboxílico
 - [2-(3-trifluorometil-fenil)-etil]-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-

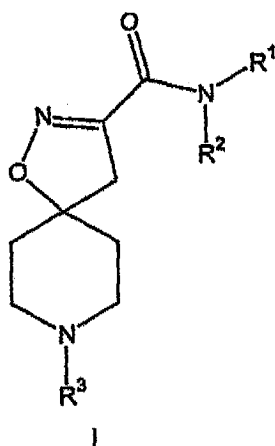
- diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (tiofen-2-ilometil)-amida del ácido 8-[3-(2,6-dicloro-fenil)-5-metil-isoxazol-4-carbonil]-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [1-(naftalen-2-ilo-carbamóilo)-etil]-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-benciloxi-ciclopentil)-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster metílico del ácido 3-(4-cloro-fenil)-2-[[8-(4-metoxi-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-propanoico
 - (2-benciloxi-ciclopentil)-amida del ácido 8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-fenoxi-etil)-amida del ácido 8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - bencilamida del ácido 8-(2-fenoxi-piridin-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - ciclopropil-metil-amida del ácido 8-(naftalen-2-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - bencilamida del ácido 8-(3-cloro-4-fluoro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (2-ciano-etil)-amida del ácido 8-(fenil-butiril)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - 2-fluoro-bencilamida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (tiofen-2-ilometil)-amida del ácido 8-(3-cloro-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (4-bencil-piperazin-1-ilo)-[8-(2,5-dicloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
 - bencilamida del ácido 8-(3-cloro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - (4-bencil-piperidin-1-ilo)-[8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
 - bencilamida del ácido 8-(4-bromo-benzoil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - [1-(4-nitro-fenil)-etil]-amida del ácido 8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
 - éster ter-butílico del ácido 4-metil-2-[[8-(3-trifluorometil-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carbonil]-amino]-pentanoico
 - [4-(4-fluoro-fenil)-3,6-dihidro-2H-piridin-1-ilo]-(8-fenil-metano-sulfonil-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo)-metanona
 - [2-(etil-m-tolil-amino)-etil]-amida del ácido 8-dimetil-sulfamóil-1-oxa-2,8-diaza-

espiro[4.5]dec-2-eno-3-carboxílico

- bencilamida del ácido 8-(2,5-dimetil-furan-3-carbonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (4-cicloheptil-piperazin-1-ilo)-[8-(4-fluoro-bencensulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-ilo]-metanona
- bencilamida del ácido 8-(2-benciloxi-acetil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico
- (2-benciloxi-ciclopentil)-amida del ácido *R,R*-8-(5-cloro-tiofen-2-sulfonil)-1-oxa-2,8-diaza-espiro[4.5]dec-2-eno-3-carboxílico;

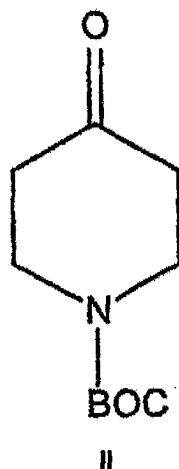
así como sus clorhidratos.

9. Procedimiento de preparación de un derivado sustituido de 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno con la fórmula general (I)

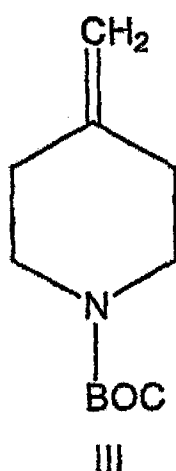


en donde R^1 , R^2 y R^3 son como se definieron arriba, caracterizado porque

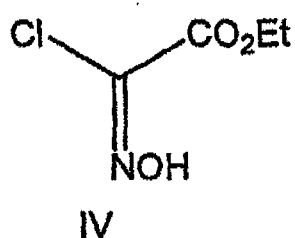
(a) el compuesto con la fórmula (II)



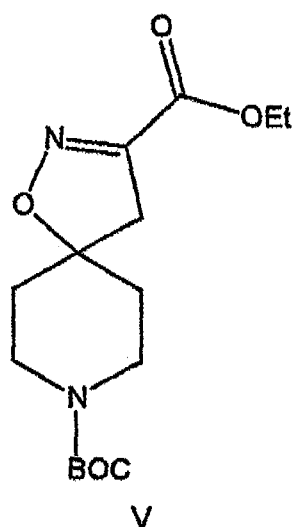
se transforma en el compuesto (III), mediante un agente metilador, de preferencia Pb_3PCH_3Br en presencia de ter-butilato de potasio en THF



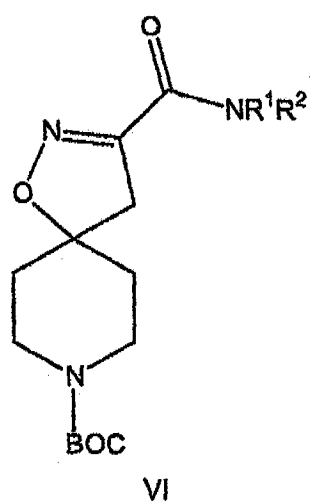
(b) El compuesto (III) se transforma con acetato de etil-cloroimida (IV)



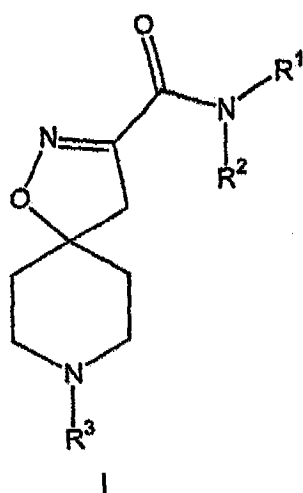
5 en presencia de una base, de preferencia carbonato de sodio e hidrógeno, o hidróxido de litio, de preferencia en un solvente orgánico, en especial metanol, diclorometano o THF, formando el derivado del 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno con la fórmula (V)



10 (c) El compuesto (V) se convierte en el derivado del 1-oxa-2,8-diaza-espiro[4.5]dec-2-eno con la fórmula (VI), ya sea en forma directa o con previa saponificación de la función éster etílico de ácido carboxílico del compuesto (V) y según el caso activando la función ácido carboxílico así obtenida, con una amina de la fórmula HNR^1R^2 , donde R^1 y R^2 se definen como arriba,



(d) el compuesto con la fórmula (I), con $R^3 = H$, se obtiene apartando el grupo protector BOC del compuesto (VI), y



(e) según el caso, el compuesto (I) con $R^3 = H$ se transforma en un compuesto (I) con SO_2R^{12} , con un cloruro de ácido de la fórmula $R^{12}SO_2Cl$, estando R^{12} definido en cualquiera de las reivindicaciones 1 a 8, o con cloruro de ácido carboxílico con la fórmula $R^{13}COCl$, en un compuesto (I) con $R^{13} = COR^{13}$, donde R^{13} está definido como en alguna de las reivindicaciones 1 a 7.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : C07D 221/20, A61K 31/435, C07D 498/10, 471/10, 401/06, 263/52, A61K 31/42 // (C07D 498/10, 263:00, 221:00) (C07D 498/10, 261:00, 221:00) (C07D 498/10, 265:00, 221:00) (C07D 471/10, 235:00, 221:00) (C07D 471/10, 221:00, 221:00)	A1	(11) International Publication Number: WO 97/11940 (43) International Publication Date: 3 April 1997 (03.04.97)
(21) International Application Number: PCT/US96/15703 (22) International Filing Date: 27 September 1996 (27.09.96) (30) Priority Data: 60/004,557 29 September 1995 (29.09.95) US (71) Applicants (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). COR THERAPEUTICS, INC. [US/US]; 256 East Grand Avenue, South San Francisco, CA 94080 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): FISHER, Matthew, J. [US/US]; 4106 Armon Court, Carmel, IN 46033 (US). JAKUBOWSKI, Joseph, A. [US/US]; 3740 Governors Road, Indianapolis, IN 46208 (US). MASTERS, John, J. [US/US]; 8338 Crystal Pointe Lane, Indianapolis, IN 46236 (US). MULLANEY, Jeffrey, T. [US/US]; 6153 Welker Drive, Indianapolis, IN 46236 (US). PAAL, Michael	[DE/DE]; Hummelsbütteler Kirchenweg 11, D-22335 Hamburg (DE). RÜHTER, Gerd [DE/DE]; Vierzigstücken 53 a, D-21129 Hamburg (DE). RUTERBORIES, Kenneth, J. [US/US]; 6747 Bluffridge Court, Indianapolis, IN 46278 (US). SCARBOROUGH, Robert, M. [US/US]; 2544 Belmont Canyon Road, Belmont, CA 94002 (US). SCHOTTEN, Theo [DE/DE]; Hintern Bach 34, D-21444 Vierhöfen (DE). STENZEL, Wolfgang [DE/DE]; Lerchenweg 8, D-21465 Reinbek (DE). (74) Agents: LEEDS, James, P. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: SPIRO COMPOUNDS AS INHIBITORS OF FIBRINOGEN-DEPENDENT PLATELET AGGREGATION (57) Abstract This invention relates to certain spirocyclic compounds substituted with both basic and acidic functionality, which are useful in inhibition of platelet aggregation.		



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(12) **United States Patent**
Fisher et al.

(10) **Patent No.: US 6,291,469 B1**
(45) **Date of Patent: Sep. 18, 2001**

(54) **SPIRO COMPOUNDS AS INHIBITORS OF
FIBRINOGEN-DEPENDENT PLATELET
AGGREGATION**

5,817,756 * 10/1998 Kyle et al. 530/331
5,849,736 * 12/1998 Wityak et al. 514/227.8

FOREIGN PATENT DOCUMENTS

(75) **Inventors:** **Matthew J. Fisher**, Carmel; **Joseph A. Jakubowski**, Indianapolis; **John J. Masters**, Indianapolis; **Jeffrey T. Mullaney**, Indianapolis; **Kenneth J. Ruterbories**, Indianapolis, all of IN (US); **Michael Paal**, Gerd Ruhter, both of Hamburg (DE); **Robert M. Scarborough**, Belmont, CA (US); **Theo Schotten**, Vierhoeven (DE); **Wolfgang Stenzel**, Reinbek (DE)

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0 655 439 5/1995 (EP) .
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94 12181 6/1994 (WO) .
94 18981 9/1994 (WO) .
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(73) **Assignees:** **Eli Lilly and Company**, Indianapolis, IN (US); **COR Therapeutics Inc.**, San Francisco, CA (US)

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(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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§ 371 **Date:** **Oct. 5, 1998**
§ 102(e) **Date:** **Oct. 5, 1998**
(87) **PCT Pub. No.:** **WO97/11940**
PCT Pub. Date: **Apr. 3, 1997**

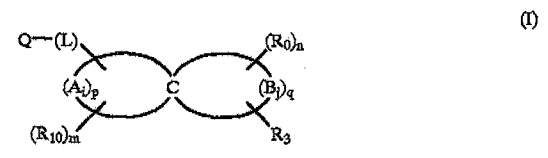
* cited by examiner

Primary Examiner—Richard L. Raymond
Assistant Examiner—Deepak R. Rao
(74) **Attorney, Agent, or Firm**—Knobbe, Martens Olson & Bear, LLP

Related U.S. Application Data
(60) Provisional application No. 60/004,557, filed on Sep. 29, 1995.
(51) **Int. Cl.⁷** **C07D 221/20; A61K 31/4747**
(52) **U.S. Cl.** **514/278; 546/15; 546/16; 546/19; 546/20**
(58) **Field of Search** **514/278; 546/15, 546/16, 19, 20**

(57) **ABSTRACT**

This invention relates to certain spirocyclic compounds substituted with both basic and acidic functionality, as shown by formula (I):



wherein Q, L, A₁, B₁, R₀, R₃, R₁₀, m, n, p and q are as defined in the disclosure, which are useful in inhibiting of platelet aggregation.

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41 Claims, No Drawings

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another two days. The solvent was removed in vacuo, and the remaining solid title compound was purified by stirring with ethyl acetate, filtration, and chromatography on silica gel with dichloromethane/methanol 4:1.

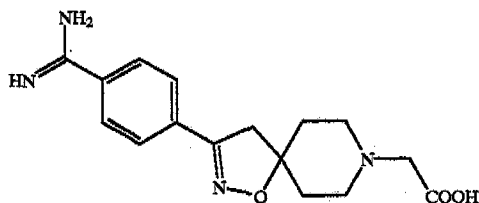
yield: 0.23 g (40%), white powder, m.p. >254° C. (dec.)

ELISA: not tested

PRP (ADP): not tested

EXAMPLE 6

Preparation of (3-(4-(Aminoiminomethyl)phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)acetic Acid



0.12 g (0.315 mmol) of the ester from Example 5 were dissolved in 2 ml ethanol, and after addition of 0.4 ml 2 N aqueous sodium hydroxide solution the mixture was stirred overnight at room temperature. It was adjusted to pH 4 with diluted acetic acid. The solvent was removed from the clear solution under reduced pressure to leave a brown oil, which solidified by stirring with a mixture of ethanol and water. It was filtered, stirred in a small amount of hot ethanol, filtered again, and dried in vacuo.

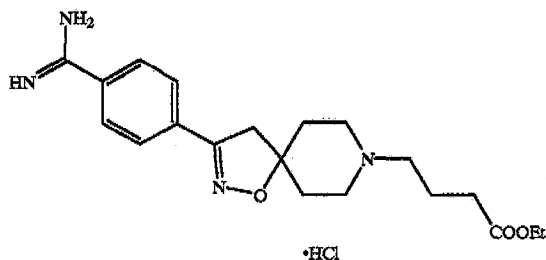
yield: 88 mg (88%) colorless amorphous solid, m.p. >265° C.

ELISA: not tested

PRP (ADP): IC₅₀ = 4 μM

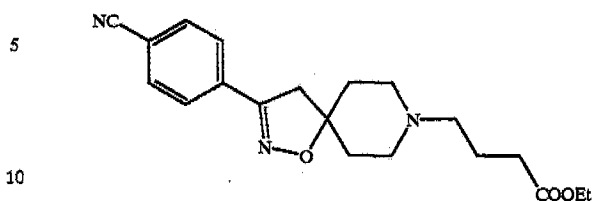
EXAMPLE 7

Preparation of Ethyl 4-(3-(4-(Aminoiminomethyl)phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)butanoate Hydrochloride



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Step A: Preparation of ethyl 4-(3-(4-cyanophenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)butanoate



1.2 g (5.0 mmol) of the piperidine from Example 5, Step B, 1.37 g (9.9 mmol) potassium carbonate, and a catalytic amount of potassium iodide were suspended in 30 ml dry acetone followed by addition of 0.99 g (5.1 mmol) ethyl 4-bromobutanoate. The mixture was heated with reflux overnight, cooled to room temperature, diluted with water, and extracted three times with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The title compound was purified by chromatography on silica gel with dichloromethane containing 5% ethanol and recrystallized from ether.

yield: 0.59 g (33%) white powder, m.p. 85–88° C.

Step B: Preparation of ethyl 4-(3-(4-(aminoiminomethyl)phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)butanoate hydrochloride

0.58 g (1.63 mmol) of the nitrile from Step A were dissolved in 35 ml dry ethanol and converted to the title amidine as described for Example 5, Step D. It was purified by chromatography on silica gel with dichloromethane/methanol 7:3.

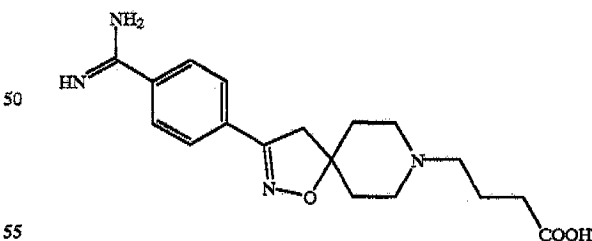
yield: 0.4 g (60%) colorless foam

ELISA: not tested

PRP (ADP): IC₅₀ = 2.8 μM

EXAMPLE 8

Preparation of 4-(3-(4-(Aminoiminomethyl)phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)butanoic Acid



0.28 g (0.685 mmol) of the ethyl ester from Example 7 were hydrolyzed in a mixture of 4 ml ethanol and 0.9 ml 2 N aqueous sodium hydroxide solution according to the procedure from Example 6. The title acid crystallized from water/ethanol 1:2, and it was filtered and dried in vacuo.

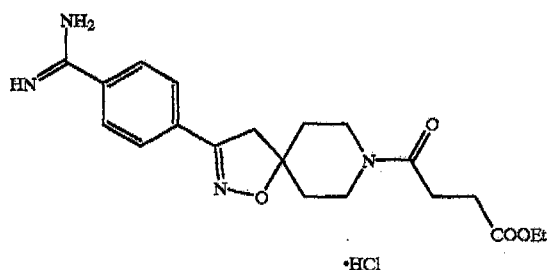
yield: 0.09 g (38%), colorless crystals, m.p. >185° C. (dec.)

ELISA: not tested

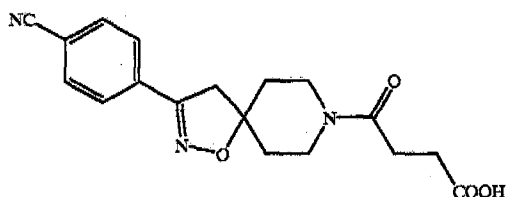
PRP (ADP) : IC₅₀ = 0.32 μM

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EXAMPLE 9

Ethyl 4-(3-(4-(Aminoiminomethyl)phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)-4-oxobutanoate Hydrochloride



Step A: Preparation of 4-(3-(4-cyanophenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)-4-oxobutanoic acid



To a suspension of 1.2 g (5.0 mmol) of the intermediate from Example 5, Step B in 30 ml dry THF were added 0.5 g (5.0 mmol) succinic anhydride and 60 mg 4-N,N-dimethylaminopyridine (DMAP). After 30 min. heating with reflux another 0.15 g (1.5 mmol) succinic anhydride were added and refluxing was continued from 1.5 hours. The solvent was removed under reduced pressure, and the title compound was obtained by chromatography on silica gel with dichloromethane/ethanol 9:1. It was recrystallized from ether, filtered, and dried in vacuo.

yield: 0.98 g (58%) white powder, m.p. 167–170° C.

Step B: Preparation of ethyl 4-(3-(4-(aminoiminomethyl)phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)-4-oxobutanoate hydrochloride

A solution of 0.98 g (2.87 mmol) of the nitrile from Step A in 65 ml dry ethanol was converted to the amidine with by saturation with hydrogen chloride followed by addition of 65 ml saturated ethanolic ammonia solution as described for Example 5, Step D. It was purified by chromatography on silica gel with dichloromethane/ethanol 4:1.

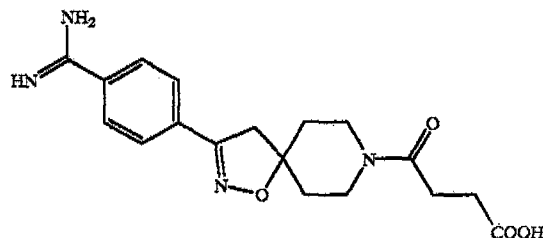
yield: 0.48 g (40%), oil which solidified upon standing

ELISA: not tested

PRP (ADP): not tested

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EXAMPLE 10

Preparation of 4-(3-(4-(Aminoiminomethyl)phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-en-8-yl)-4-oxobutanoic Acid



0.34 g (0.8 mmol) of the ethyl ester from Example 9 were hydrolyzed in a mixture of 5 ml ethanol and 1 ml 2 N aqueous sodium hydroxide solution according to the procedure from Example 6. A first crop (200 mg) of the title acid crystallized from water/ethanol 1:2. The mother liquid was concentrated, and a second crop (60 mg) was obtained by stirring with a mixture of ethyl acetate and ether. The crystals were filtered and dried in vacuo.

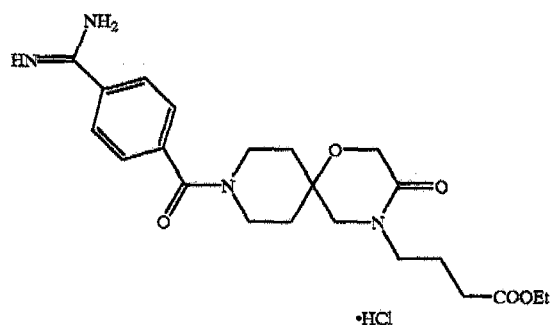
total yield: 0.26 g (90%) white powder, m.p. >255° C. (dec.)

ELISA: not tested

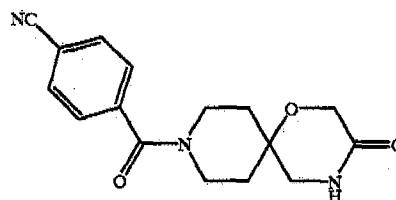
PRP (ADP): IC₅₀=1 μm

EXAMPLE 11

Preparation of Ethyl 4-(9-(4-(Aminoiminomethyl)benzoyl)-3-oxo-1-oxa-4,9-diaza-spiro[5.5]undec-4-yl)butanoate Hydrochloride



Step A: Preparation of 9-(4-cyanobenzoyl)-3-oxo-1-oxa-4,9-diaza-spiro[5.5]undecane



18.0 g (71.7 mmol) 3-oxo-1-oxa-4,9-diaza-spiro[5.5]undecane hydrobromide (prepared according to J. Med. Chem. 1983, 26, 855) were dissolved in 300 ml dry pyridine,

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PAIs prevent platelet aggregation, embolization, or consumption associated with intravascular devices, and administration results in improved utility of intraaortic balloon pumps, ventricular assist devices, and arterial catheters.

The PAIs will also be useful in treatment or prevention of venous thrombosis as in deep venous thrombosis, IVC, renal vein or portal vein thrombosis, and pulmonary venous thrombosis.

Various disorders involving platelet consumption, such as thrombotic thrombocytopenic purpura are also treatable.

In addition, the PAIs of the present invention may be used in numerous nontherapeutic applications where inhibiting platelet aggregation is desired. For example, improved platelet and whole blood storage can be obtained by adding sufficient quantities of the compounds, the amount of which will vary depending upon the length of proposed storage time, the conditions of storage, the ultimate use of the stored material, etc.

Preferably, the compounds of this invention are administered in the form of a pharmaceutical formulation. Thus, the compounds of this invention may be administered orally, parenterally, topically, rectally and etc., in appropriate dosage units, as desired.

The term parenteral as used herein includes subcutaneous, intravenous, intraarterial, injection or infusion techniques, without limitation. The term, "topically" encompasses administration rectally and by inhalation spray, as well as the more common routes of the skin and the mucous membranes of the mouth and nose.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to administer an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient.

The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g., two to four separate doses per day. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the body weight, general health, diet, time and route of administration, combination with other drugs and the severity of the particular disease being treated.

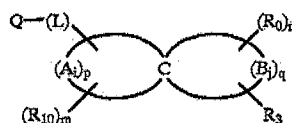
The range of therapeutic dosages is from about 0.01 to about 10,000 milligrams per day, with from 1 to 300 milligrams being preferred.

Many modifications and variations of this invention may be made without departing from its scope, as is apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims.

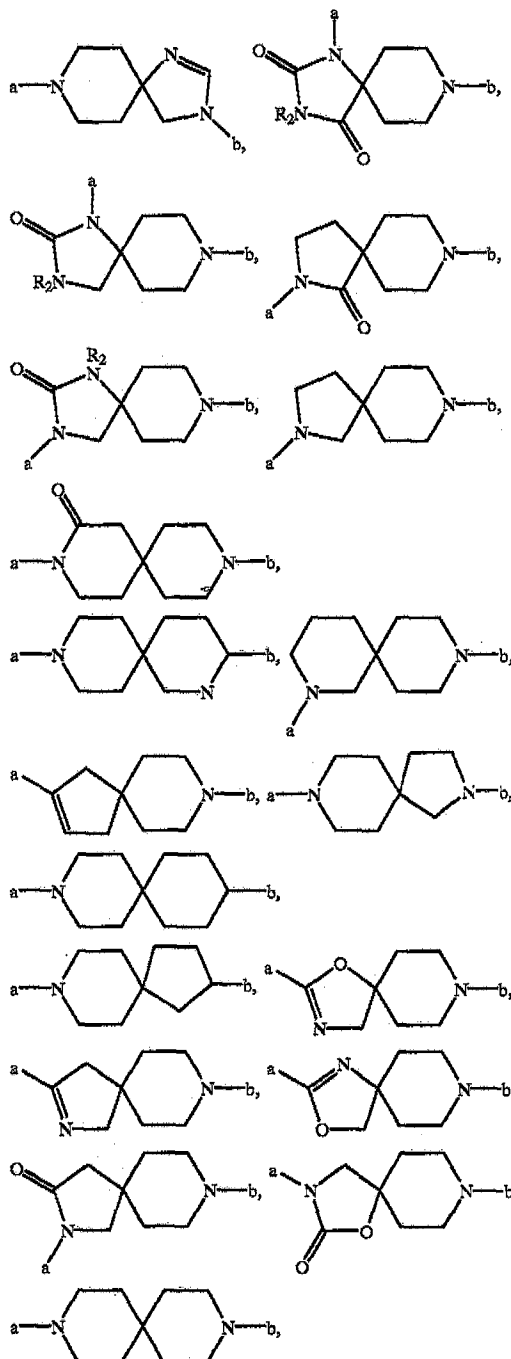
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What is claimed is:

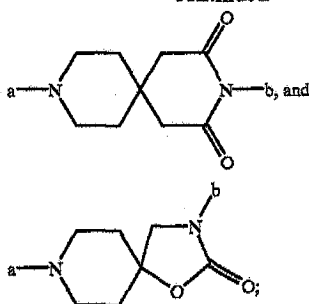
1. A compound of formula (I):



wherein;
the spirocycle comprising (A)_p, C, and (B)_q is selected from the formulae:



-continued



m is a number from zero to 6;

R_{10} is the same or different and is a non-interfering substituent independently selected from alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, arylalkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, or sulfo;

n is a number from zero to 6;

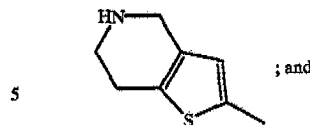
R_0 is the same or different and is a non-interfering substituent independently selected from alkyl, halosubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, hydroxy, alkoxy, arylalkoxy, amino, substituted amino, carbamoyl, carboxy, acyl, cyano, halo, nitro, or sulfo;

where Q—(L) is attached at a, and R_3 is attached at b;

the linking group —(L)— is a bond or a substituted or unsubstituted chain selected from the group consisting of CO, CO(C_1 – C_6 alkyl), O(C_1 – C_6 alkyl), NHCO, and C_1 – C_6 alkyl;

R_2 is hydrogen, C_1 – C_6 alkyl, aryl, substituted aryl, or arylalkyl;

Q is a basic group selected from the group consisting of amino, imino, amidino, hydroxyamidino, N-alkylamidino, N,N'-dialkylamidino, N-arylamidino, aminomethyleneamino, iminomethylamino, guanidino, aminoguanidino, alkylamino, dialkylamino, trialkylamino, alkylideneamino, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indoliziny, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxaliny, quinazolinyl, cinnolinyl, amido, thioamido, benzamidino, pteridinyl, 4aH-carbozoyl, carbozoyl, beta-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, any of the foregoing radicals substituted on a benzene ring, and any of the foregoing radicals substituted by amino, imino, amidino, hydroxyamidino, aminomethyleneamino, iminomethylamino, guanidino, alkylamino, dialkylamino, trialkylamino, tetrahydroisoquinoliny, dihydroisoindolyl, alkylideneamino or

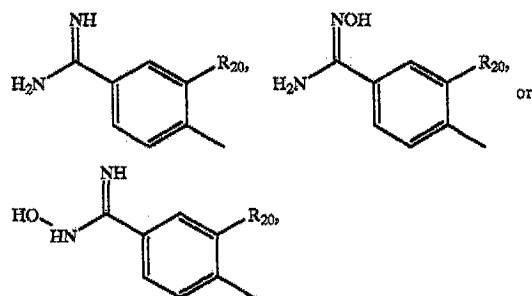


R_3 is an acidic group selected from the group consisting of CO_2R_5 , (C_1 – C_6 alkyl) CO_2R_5 , CO(C_1 – C_6 alkyl) CO_2R_5 , CONH(C_1 – C_6 alkyl) CO_2R_5 , (C_1 – C_6 alkyl)CH(NHR_4) CO_2R_5 , CO(C_1 – C_6 alkyl)CH(NHR_4) CO_2R_5 , or CONH(C_1 – C_6 alkyl)CH(NHR_4) CO_2R_5 , wherein

R_4 is SO_2 (C_1 – C_6 alkyl), SO_2 aryl, or SO_2 (substituted aryl); and

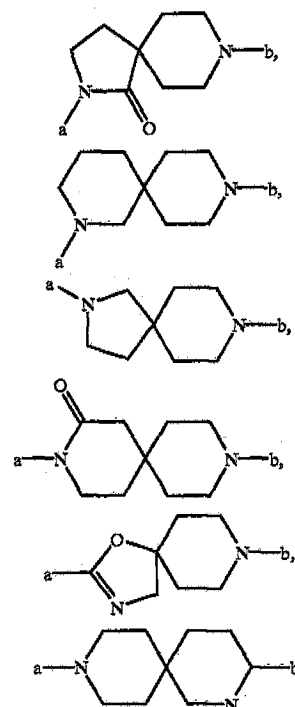
R_5 is hydrogen, C_1 – C_6 alkyl, aryl, or substituted aryl; or a pharmaceutically-acceptable salt, solvate or prodrug thereof.

2. The compound of claim 1 wherein Q is pyridin-4-yl, piperidin-4-yl, amidino, hydroxyamidino, guanidinyl, or a group of the formula:



wherein R_{20} is hydrogen or halogen.

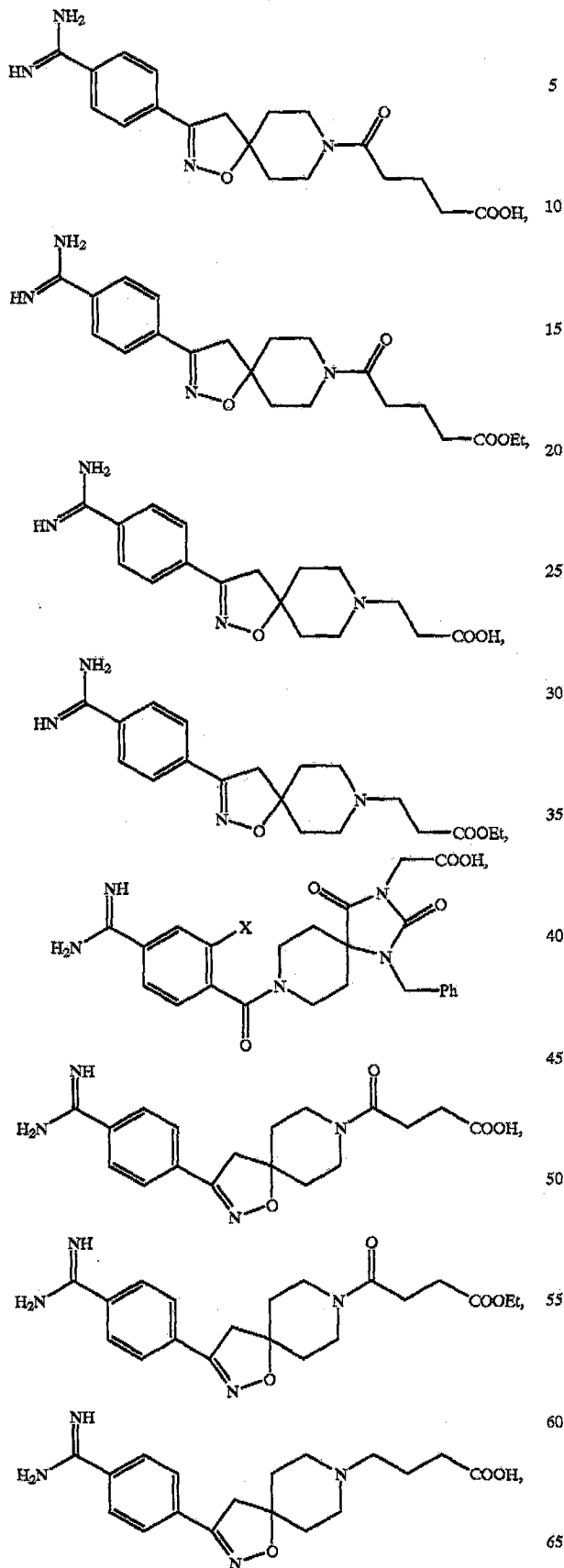
3. The compound of claim 2 wherein the spirocycle is selected from the formulae:



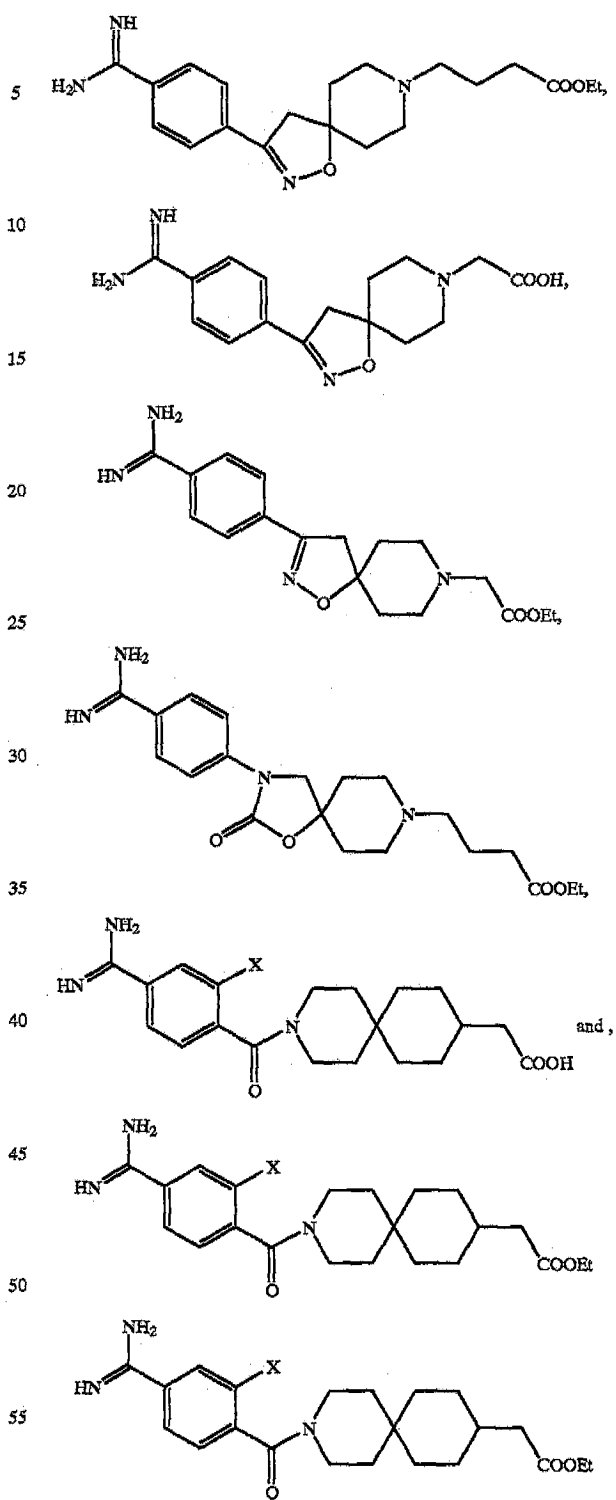
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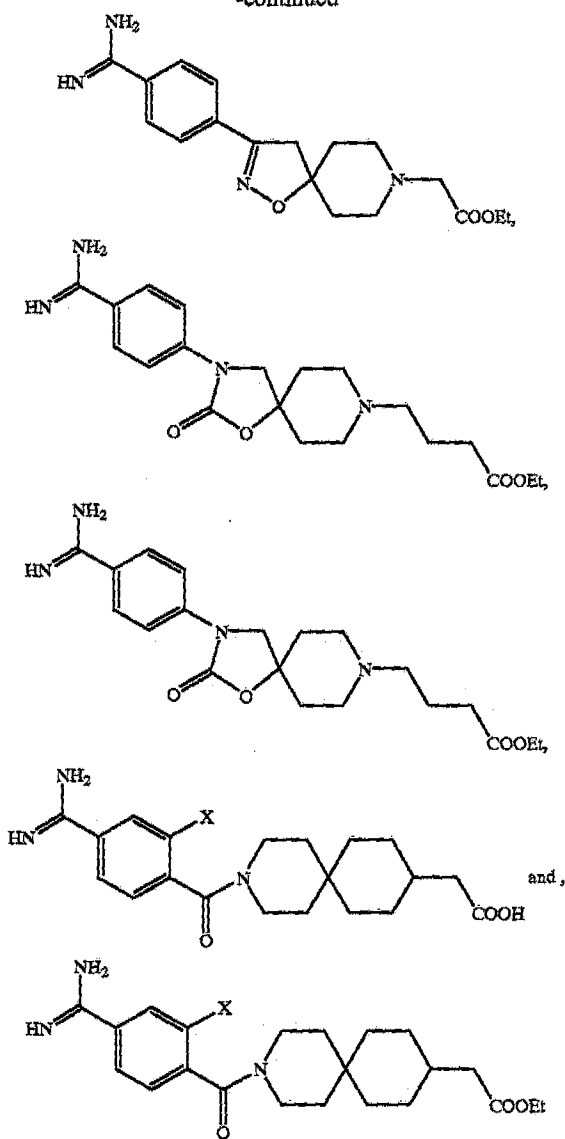
wherein X is F or H, or a pharmaceutically-acceptable salt, solvate, or prodrug thereof.

15. A compound of claim 12 selected from the group consisting of:

122
168

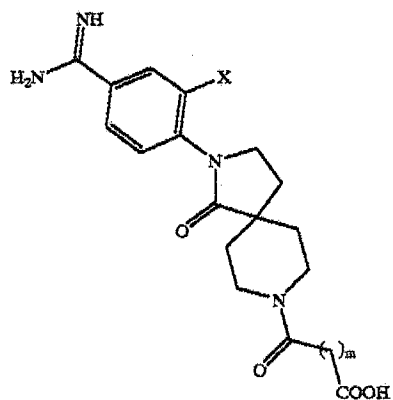
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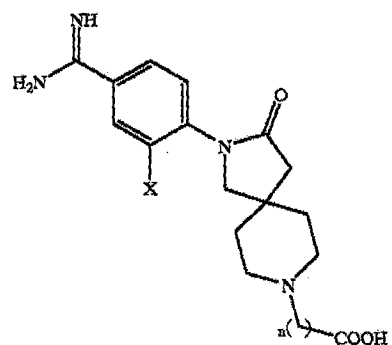
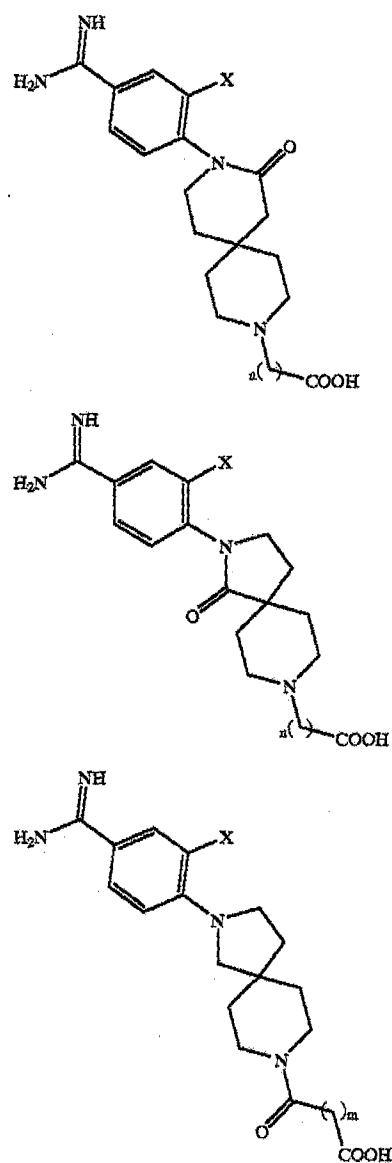
wherein X is F or H, or a pharmaceutically-acceptable salt, solvate, or prodrug thereof.

16. A compound of claim 12 selected from the group consisting of:



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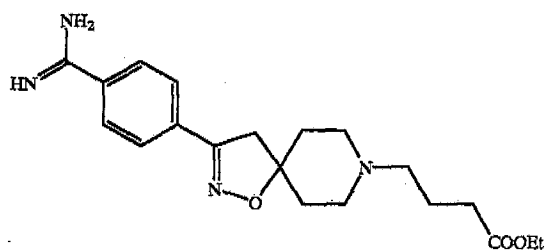
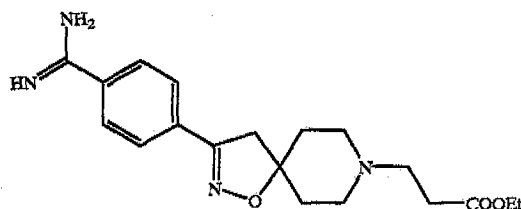
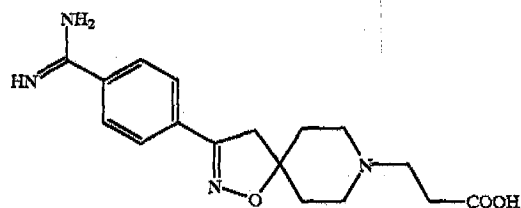
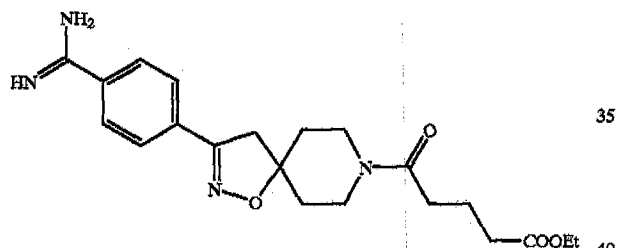
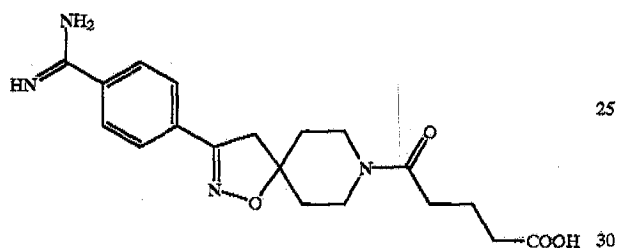
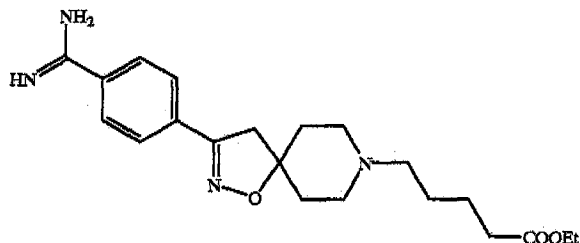
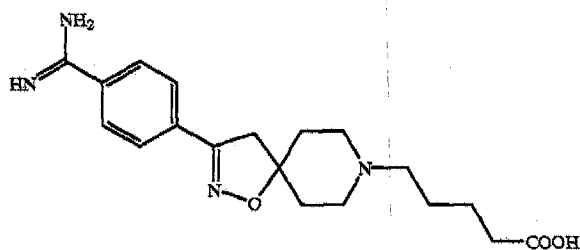


wherein X is F or H, m is zero to four, and n is one to four, or a pharmaceutically-acceptable salt, solvate, or prodrug thereof.

17. A compound of claim 12 selected from the group consisting of:

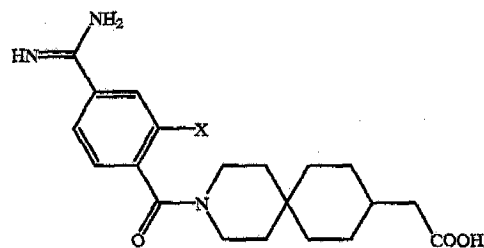
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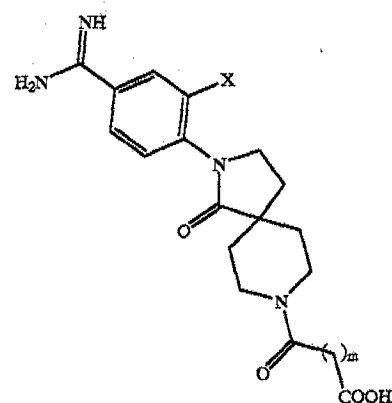
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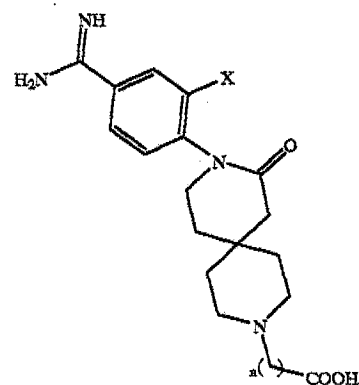
wherein X is F or H, or a pharmaceutically-acceptable salt, solvate, or prodrug thereof.

18. A compound having the formula:



wherein X is F or H and m is zero to four, or a pharmaceutically-acceptable salt, solvate, or prodrug thereof.

19. A compound having the formula:



wherein X is F or H and n is one to four, or a pharmaceutically-acceptable salt, solvate, or prodrug thereof.



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United States Patent [19]

Weinhardt et al.

[11] Patent Number: 5,739,336

[45] Date of Patent: Apr. 14, 1998

[54] 1,3,8-TRIAZA- AND 3,8-DIAZA-1-OXASPIRO
[4,5] DECANE DERIVATIVES1815450 12/1967 Germany 260/293.4
48-34597 10/1973 Japan .[75] Inventors: Klaus K. Weinhardt, Palo Alto; Jacob
Berger, Los Altos Hills; David S.
Carter, Costa Mesa; Lee A. Flippin,
Woodside, all of Calif.

[73] Assignee: Syntex (U.S.A.) Inc., Palo Alto, Calif.

[21] Appl. No.: 667,247

[22] Filed: Jun. 20, 1996

Related U.S. Application Data

[60] Provisional application No. 60/035,193 Jun. 23, 1995.

[51] Int. Cl.⁶ A61K 31/395; C07D 471/10[52] U.S. Cl. 546/20; 546/19; 514/278;
549/430

[58] Field of Search 546/20, 19

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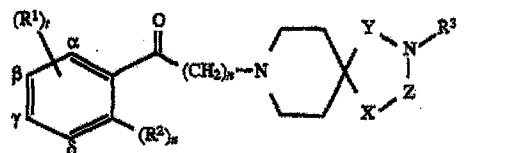
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2502-2507 (1978).G. Winters et al., "Sintesi di spiroidantoini da chetoni
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(1970).Primary Examiner—Robert T. Bond
Attorney, Agent, or Firm—Heller Ehrman White &
McAuliffe**[57] ABSTRACT**

Heterocyclic compounds of Formula I:



in which n is 2, 3, 4, 5 or 6; t is 1, 2, 3 or 4; u is 0 or 1 (provided that t is not 1 when u is 0); X is O or N(R⁴); Y and Z are independently C(O), C(S) or CH₂ (provided that Y and Z are not both CH₂); R¹, R², R³, and R⁴ are as defined in the specification; and their pharmaceutically acceptable salts and N-oxides, formulations containing them, their uses as therapeutic agents, and their synthesis.

17 Claims, No Drawings

A mixture of 8-[5-(5-ethylenedioxy-5-(5-chloro-2-methoxyphenyl)pentyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (1-1.1 g, 2.3-2.6 mmol), prepared as in Example 23, 10% hydrochloric acid (approximately 1 mL) and methanol (approximately 30 mL) was heated to a boil and then allowed to cool and stand approximately 4 hour at 25° C. The solids were collected and dried under vacuum at 70° C. to give 8-[5-(5-chloro-2-methoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione hydrochloride (0.37 g, 0.57 mmol), m.p. 260°-262° C.

Proceeding similarly as in Example 24 with different starting materials gave the following compounds of Formula I:

N-[3-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-4,5-ethylenedioxyphenyl]-4-(3-trifluoromethylbenzenesulfonamide hydrochloride, m.p. 261°-262° C.; and

8-[4-(5-chloro-2-methoxyphenyl)-4-oxobutyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione.

EXAMPLE 25

8-[5-(5-amino-2,4-dimethoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione

The following is the preparation of a compound of Formula I in which n is 4, t is 2, u is 1, X is NH, Y is C(O), Z is C(O), R¹ is amino and methoxy at the β- and γ-positions, respectively, R² is methoxy and R³ is hydro.

A mixture of 8-[5-(2,4-dimethoxy-5-nitrophenyl)-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione (0.33 g, 0.76 mmol), prepared as in Example 23, 10% palladium on carbon (140 mg in 5 mL of water), THF (50 mL) and ethanol (50 mL) was stirred 2 hours under a hydrogen atmosphere (15 psi). The mixture was filtered and concentrated to give 8-[5-(5-amino-2,4-dimethoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione hydrochloride, m.p. 245° C. (dec).

Proceeding similarly as in Example 25 with different starting materials gave the following compounds of Formula I:

8-[5-(5-amino-2-methoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione, m.p. 211°-213° C.; and

N-[5-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-2,4-dimethoxyphenyl]-4-aminobenzenesulfonamide hydrochloride, m.p. 206°-208° C.

EXAMPLE 26

1-[5-[5-(2,4-Dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-2,4-dimethoxyphenyl]-3-(3-trifluoromethylphenyl)thiourea

The following is the preparation of a compound of Formula I in which n is 4, t is 2, u is 1, X is NH, Y is C(O), Z is C(O), R¹ is 3-trifluoromethylthiourea and methoxy at the β- and γ-positions, respectively, R² is methoxy and R³ is hydro.

A mixture of 8-[5-(5-amino-2,4-dimethoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione (62 mg, 0.15 mmol), prepared as in Example 21, α,α,α-trifluoro-m-tolyl isothiocyanate (1.335 g/mL, 0.03 mL, 0.17 mmol) and N-methyl-2-pyrrolidinone was stirred 10 minutes. The mixture was added to water (50 mL) and the solids were collected, washed with water, dried and recrystallized from a solution of hydrogen chloride in ethanol/ether to give

1-[5-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-2,4-dimethoxyphenyl]-3-(3-trifluoromethylphenyl)thiourea hydrochloride (40 mg, 0.06 mmol), m.p. 159°-168° C.

EXAMPLE 27

N-[5-[5-(2,4-Dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-2,4-dimethoxyphenyl]-3-(5-trifluoromethyl-1-methylpyrazol-3-yl)-2-thiophenesulfonamide

The following is the preparation of a compound of Formula I in which n is 4, t is 2, u is 1, X is NH, Y is C(O), Z is C(O), R¹ is 3-(5-trifluoromethyl-1-methylpyrazol-3-yl)thien-2-ylsulfonamino and methoxy at the β- and γ-positions, respectively, R² is methoxy and R³ is hydro.

A mixture of 8-[5-(5-amino-2,4-dimethoxyphenyl)-5-oxopentyl]-1,3,8-triazaspiro[4.5]decane-2,4-dione (202 mg, 0.5 mmol), prepared as in Example 21, 3-(5-trifluoromethyl-1-methylpyrazol-3-yl)-2-thiophenesulfonyl chloride (200 mg, 0.6 mmol) and THF (1 mL) and N-methyl-2-pyrrolidinone (1 mL) was stirred 16 hours at approximately 25° C. The mixture was purified by flash chromatography eluting first with methylene chloride and then with methylene chloride/methanol-ammonium hydroxide (9:1). The purified product was recrystallized from ethanol and then from a solution of hydrogen chloride in ethanol/ether to give N-[5-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-2,4-dimethoxyphenyl]-3-(5-trifluoromethyl-1-methylpyrazol-3-yl)-2-thiophenesulfonamide hydrochloride (94 mg, 0.13 mmol), m.p. 162°-170° C.

Proceeding similarly as in Example 27 with different starting materials the following compounds of Formula I were prepared:

N-[3-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-4-methoxyphenyl]-1-pyrrolidinesulfonamide hydrochloride, m.p. 227°-229° C.;

N-[3-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-4-methoxyphenyl]benzenesulfonamide hydrochloride, m.p. 170°-182° C.;

N-[3-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-4-methoxyphenyl]-3,4-dimethoxybenzenesulfonamide hydrochloride, m.p. 150°-167° C.; and

4-[5-[5-(2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)pentanoyl]-2,4-dimethoxyphenyl]benzenesulfonamide, m.p. 270°-272° C.

EXAMPLE 28

8-[5-(5-Chloro-2-methoxyphenyl)-5-oxopentyl]-1-oxa-3,8-diazaspiro[4.5]decane-2-one

The following is the preparation of a compound of Formula I in which n is 1, t is 1, u is 1, X is O, Y is CH, Z is C(O), R¹ is chloro at the β-position, R² is methoxy and R³ is hydro.

A mixture of 3-tert-butyl-8-[5-(5-chloro-2-methoxyphenyl)-5-oxopentyl]-1-oxa-3,8-triazaspiro[4.5]decane-2-one (200 mg, 0.46 mmol), prepared as in Example 23, trifluoroacetic acid (5 mL) and water (2 mL) was stirred 6 days at reflux and then concentrated to 2 mL. The residue was combined with water and the mixture was stirred with sodium bicarbonate and then extracted with methylene chloride. The product was purified by column chromatography eluting with methylene chloride/methanol.

hydroxide (20:1) to give 8-[5-(5-chloro-2-methoxyphenyl)-5-oxopentyl]-1-oxa-3,8-triazaspiro[4.5]decane-2-one (50 mg, 0.13 mmol). The free base was recrystallized from a solution of hydrogen chloride in ethanol/ether to give 8-[5-(5-chloro-2-methoxyphenyl)-5-oxopentyl]-1-oxa-3,8-triazaspiro[4.5]decane-2-one hydrochloride, m.p. 130°–134° C.

EXAMPLE 29

The following are representative pharmaceutical formulations containing a compound of Formula I.

ORAL FORMULATION

A representative solution for oral administration contains:

Compound of Formula I	100–1000 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

A representative solution for intravenous administration contains:

Compound of Formula I	10–100 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

A representative tablet form of a compound of Formula I may contain:

Compound of Formula I	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%

EXAMPLE 30

Cloned Rat 5-HT_{2C} Receptor Binding Assay

The following describes an in vitro binding assay utilizing cloned 5-HT_{2C} receptors radiolabelled with [³H] mesulergine.

Mouse NIH3T3 fibroblasts expressing a cloned rat 5-HT_{2C} receptor were maintained in Dulbecco's Modified Eagle medium with 10% Fetal Calf Serum and g/mL G418 in 95/5% O₂/CO₂. The cells were harvested using 2 mM EDTA in phosphate buffered saline (calcium/magnesium free) and centrifuged (500 g). The cell pellet was homogenized using a Polytron P10 disrupter (setting 5, 5 sec) in homogenization buffer (Tris, 50 mM; Na₂EDTA, 5 mM) and the homogenate was centrifuged at 19,500 rpm using a Sorvall/Dupont RC5C centrifuge with an SS34 rotor (30,000–48,000 g, 15 minutes). The pellet was homogenized (setting 5, 5 sec) in homogenization buffer and the homogenate was centrifuged (30,000–48,000 g, 15 minutes). The pellet was homogenized (setting 5, 5 sec) in resuspension buffer (Tris, 50 mM; EDTA 0.5 mM) and the homogenate

was centrifuged (30,000–48,000 g, 15 minutes). The pellet was homogenized (setting 5, 5 sec) in a small volume of resuspension buffer to give approximately 1×10⁷ cells/mL. The membranes were separated into 1 mL aliquots and stored at –70° C.

The membranes were thawed at room temperature and diluted with assay buffer (NaCl, 118 mM; KCl, 4.5 mM; KH₂PO₄, 1.2 mM; CaCl₂·2H₂O, 2.5 mM; MgCl₂, 1 mM; D-glucosol 10 mM; Tris, 25 mM). An optimal dilution ratio was predetermined for each batch of membranes to ensure that less than 10% of 5×10^{–10} M [³H]mesulergine binds, specific binding is at least 10 times greater than a machine background of 23 dpm and the best ratio of specific binding to total binding is achieved. The membranes were homogenized (setting 5, 5 sec) and then added to assay tubes containing mesulergine (5×10^{–10} M), test compound (1×10^{–10}–1×10^{–4} M) and assay buffer (q.s. to 500 µL). The assay mixture was incubated at 32° C. for 60 minutes and then filtered over 0.1% polyethyleneimine pretreated glass fiber filtermats using a Brandel cell harvester. The assay tubes were rinsed with cold 0.1M sodium chloride (3×3 sec) and dried by drawing air over the filter for 10 seconds. Radioactivity retained on the filters was determined by liquid scintillation counting. In a similar fashion, total binding was measured with methysergide (1×10^{–5} M) in the absence of test compound. For each compound tested the concentration producing 50% inhibition of binding (IC₅₀) was determined using iterative curve fitting techniques.

Proceeding as in Example 30, compounds of the invention were tested and found to have affinity for the 5-HT_{2C} receptor.

EXAMPLE 31

Cloned Rat 5-HT_{2C} Receptor Functional Assay

The following describes an in vitro functional assay utilizing 5-HT induced, 5-HT_{2C} mediated increases in NIH3T3 cellular metabolic activity.

Mouse NIH3T3 fibroblasts expressing cloned 5-HT_{2C} receptor were maintained in high glucose Dulbecco's Minimal Essential Medium (DMEM) further comprising glutamine, sodium pyruvate and 10% Fetal Bovine. The cells were harvested using 2 mM EDTA in phosphate buffered saline and transferred to 6.5 mm transwell capsule plates (3 micron pore size) to give approximately 1×10⁵ cells/capsule. The cells were allowed to adhere overnight and then transwell spacers and inserts were added to each transwell capsule. The capsules were placed into sensor chambers and the sensor chambers were loaded onto a microphysiometer.

The 5-HT_{2C} receptor antagonist properties of test compounds were appraised by determining their effect on 5-HT induced increases in cellular metabolic activity, expressed as percent increase in acidification rate. Microphysiometer Running Medium (high glucose, sodium bicarbonate free DMEM) was pump through the transwell capsules for 1.5 minutes, 30 seconds of which 5-HT was present in the medium, followed by a 45 minute washout and recovery period. In this manner, cells were exposed to 5-HT in a non-cumulative concentration fashion, increasing in concentration until maximal or near maximal effect was observed.

Concentration-effect curves were constructed for 5-HT with and without the test compound present. Data was analyzed by iterative curve fitting techniques and the concentration ratio (CR) of 5-HT necessary to produce equi-active responses in the absence and presence of the test

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compound was determined. Relying on the concentration ratio, the molar concentration of the test compound, and the relationship:

$$pK_d = -\log \frac{[\text{test compound}]}{CR - 1}$$

the negative log of the dissociation constant (pK_d) for each test compound was determined.

Proceeding as in Example 31, compounds of the invention were tested and found to be antagonists at the 5-HT_{2c} receptor.

EXAMPLE 32

Anxiolytic Behavior Assay

The following describes an *in vivo* method for determining anxiolytic activity by measuring the extent the drug affects the natural anxiety of mice when exposed to a novel, brightly lighted environment.

Naive male C57BL/6J mice, 18–20 g, are kept in groups of 10 mice in quarters controlled for sound, temperature and humidity. Food and water are available *ad libitum*. The mice are kept on a 12 hour light and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

The automated apparatus for detecting changes in exploration is obtained from Omni-Tech Electronics Columbus Ohio and is similar to that of Crawley and Goodwin (1980), as described in Kilfoil et al., cited previously. Briefly, the chamber consists of a plexiglass box (44×21×21 cm), divided into two chambers by a black plexiglass partition. The partition dividing the two chambers contains a 13×5 cm opening through which the mouse can easily pass. The dark chamber has clear sides and a white floor. A fluorescent tube light (40 watt) placed above the chambers provides the only illumination. The Digiscan Animal Activity Monitor System RXYZCM16 (Omni-Tech Electronics) records the exploratory activity of the mice within the test chambers.

Prior to commencement of the study the mice are given 60 min to acclimatize to the laboratory environment. After a mouse receives an intraperitoneal (i.p.) injection of either test compound or vehicle it is returned to its home cage for a 15 min post-treatment period. The mouse is then placed in the center of the light chamber and monitored for 10 minutes.

Anxiolytic behavior is seen as a general increase in exploratory activity in the lighted area. An increase in exploratory activity is reflected by increased latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), increase in shuttle activity, increased or unaltered locomotor activity (number of grid lines crossed) and decreased time spent in the dark compartment.

EXAMPLE 33

Withdrawal Anxiety Assay

The following describes an *in vivo* procedure for determining amelioration of the symptoms caused by withdrawal from addictive substances by measuring the extent the drug affects the anxiety that occurs in mice after chronically treating with an addictive substance and then abruptly ceasing the treatments.

Naive male B6W mice (25–30 g) are caged in groups of ten in quarters controlled for sound, temperature and humid-

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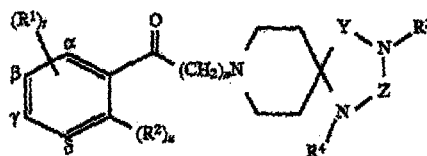
ity. Food and water are available *ad libitum*. The mice are kept on a 12 hour light cycle and 12 hour dark cycle, with lights on at 6:00 a.m. and off at 6:00 p.m. All experiments begin at least 7 days after arrival on site.

Levels of anxiety are determined by the two-compartment exploratory model of Crawley and Goodwin (see Example 14). Anxiolysis is seen as a general increase in exploratory activity in the lighted area. An increase in exploratory activity is reflected by increased latency (the time for the mouse to move to the dark chamber when first placed in the center of the lighted area), increased or unaltered locomotor activity (number of grid lines crossed), increased number of rears and decreased time spent in the dark compartment.

Increased exploratory activity in the lighted area is induced by treating the mice for 14 days with ethanol (8.0 % w/v in drinking water), nicotine (0.1 mg/kg, i.p., twice daily) or cocaine (1.0 mg/kg; i.p., twice daily). Anxiolysis is assessed 1, 3, 7 and 14 days after commencement of the drug regime. The treatment is abruptly ceased and exploratory activity in the lighted area is determined 8, 24 and 48 hours thereafter. Vehicle or test compounds are administered during the withdrawal phase by intraperitoneal injection. Responses are represented as inhibition of the decrease in anxiolytic behavior after the ethanol, cocaine or nicotine treatment is ceased.

We claim:

1. A compound of the formula:



in which:

n is 2, 3, 4, 5 or 6;

t is 1, 2, 3 or 4;

u is 0 or 1 (provided that t is not 1 when u is 0);

Y and Z are independently C(O), C(S) or CH₂ (provided that Y and Z are not both CH₂);

each R¹ is independently: amino, carbamoyl, cyano, halo, nitro, thiocarbamoyl, thioureido, ureido, a group selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, or (C₁₋₄)alkylthio (optionally further substituted with one to three halo atoms), a group selected from aryloxy, aryl(C₁₋₄)alkoxy, arylsulfonyl, or arylthio, a group selected from —NHSO₂R⁵, —NHC(O)R⁵, —NHC(O)NHR⁵, —NHC(S)NHR⁵ and —SO₂NHR⁵ (which R⁵ is (C₁₋₄)alkyl (optionally further substituted with one to three halo atoms) or a group selected from aryl, aryl(C₁₋₄)alkyl, heteroaryl and heteroaryl(C₁₋₄)alkyl (optionally further substituted with one to two radicals independently selected from amino, carbamoyl, cyano, halo, nitro, a group selected from (C₁₋₄)alkyl, (C₁₋₄)alkylsulfonylamino, (C₁₋₄)alkanoylamino, (C₁₋₄)alkyl and (C₁₋₄)alkoxy, optionally further substituted with one to three halo atoms, and a group selected from aryl, arylsulfonyl, heteroaryl and heteroarylsulfonyl, optionally further substituted with one to two radicals independently selected from amino, cyano, halo, nitro and a group selected from (C₁₋₄)alkyl and (C₁₋₄)alkoxy, optionally further substituted with one to three halo atoms)} or with an adjacent R⁴ radical form ethylenedioxy, methylenedioxy or butadienyleno (the butadienyleno being optionally substituted with one or two radicals selected from halo and (C₁₋₄)alkoxy);

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Grauert et al.

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[45] Date of Patent: Aug. 31, 1999

[54] METHOD OF PREPARING NORBENZOMORPHANES

5,731,318 3/1998 Carter et al. 546/97

[75] Inventors: Matthias Grauert; Herbert Merz,
both of Ingelheim; Hanfried Baltes,
Wöllstein, all of Germany

[73] Assignee: Boehringer Ingelheim KG, Ingelheim,
Germany

[21] Appl. No.: 08/982,000

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[52] U.S. Cl. 546/97; 546/242

[58] Field of Search 546/97

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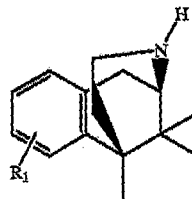
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Primary Examiner—Donald G. Daus

Attorney, Agent, or Firm—Robert P. Raymond; Alan R.
Stempel; Mary-Ellen Devlin

[57] ABSTRACT

The present invention relates to a new process for preparing norbenzomorphan, the central intermediate step in the preparation of pharmaceutically useful benzomorphan derivatives of general formula 1



especially (-)-(1R,5S,2'R)-3'-hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan or [(-)-(2R,6S,2'R)-3-(2-methoxypropyl)-6,11,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-benzo[α]oxacin-9-ol] (BIII 277).

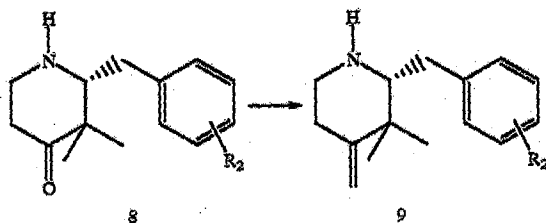
6 Claims, No Drawings

In this way, the reaction with D-(-)-tartaric acid yields the corresponding enantiomerically pure 3,3-dimethyl-4-piperidone derivative of type 8aA or 8B in the form of the hydrogen tartrate thereof, and in the case of BIII 277, for example, (+)-2-(3-methoxyphenyl)-methyl-3,3-dimethyl-4-piperidonium hydrogen tartrate (R_2 =meta-methoxy).

In order to separate the isomers, for example via the corresponding tartrates, the piperidone derivative 7 in the form of its acid addition salt, e.g. the hydrochloride, is dissolved in water and mixed with a basically reacting compound or, preferably the aqueous solution thereof; it is particularly preferable to use concentrated aqueous ammonia solution. The aqueous phase is extracted with an organic, water-immiscible solvent, preferably with a haloalkane, most preferably dichloromethane. After drying and evaporation in vacuo, the residue is dissolved in a reaction medium which is inert under the reaction conditions used for salt formation, preferably in a branched or unbranched C_{1-4} -alkanol, most preferably in ethanol, and mixed with the appropriate stereoisomer of one of the above-mentioned acids, such as D-(-)-tartaric acid. If desired, a sufficient quantity of a nonsolvent—preferably a branched or unbranched C_{3-8} -alkanol, most preferably isopropanol—with regard to the desired salt—preferably the corresponding hydrogen tartrate, is added, whereupon the enantiomerically pure isomer of the piperidone crystallises out as the piperidonium hydrogen tartrate; i.e. in the preparation of BIII 277, the corresponding (+)-2-(3-methoxyphenyl)-methyl-3,3-dimethyl-4-piperidonium hydrogen tartrate (R_2 =meta-methoxy).

It has now, surprisingly, been found that after heating the mother liquor which predominantly contains the other enantiomer, a fresh attempt at crystallisation under analogous conditions will again yield a large amount of the desired enantiomer, e.g. in the form of its hydrogen tartrate. Thermal racemisation of the unwanted enantiomer and subsequent recovery of the desired stereoisomer can certainly be carried out several times. In this way, in the case of (+)-2-(3-methoxyphenyl)-methyl-3,3-dimethyl-4-piperidonium hydrogen tartrate, the total yield of desired isomer can be increased to more than 75%.

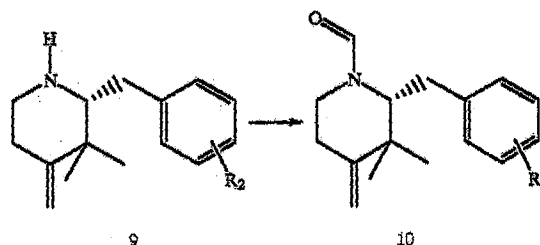
The subsequent Wittig reaction with methyltriphenylphosphonium bromide leads, in the next step, to the corresponding 4-methylene-piperidine derivative 9—in the case of BIII 277, (+)-2-(3-methoxyphenyl)methyl-3,3-dimethyl-4-methylene-piperidine (R_2 =meta-methoxy)—which may be isolated in the form of its acid addition salt, preferably in the form of a hydrohalide, most preferably in the form of its hydrochloride.



In order to carry out the Wittig reaction the 3,3-dimethylpiperidone derivative 8 is dissolved in water in the form of its acid addition salt, e.g. the hydrochloride, and mixed with a basically reacting compound or, preferably, an

aqueous solution thereof; it is particularly preferable to use concentrated aqueous ammonia solution. The aqueous phase is extracted with an organic, water-immiscible solvent, preferably a haloalkane, most preferably dichloromethane. After drying and evaporation in vacuo, the residue is taken up in a reaction medium which is inert under the reaction conditions used for the Wittig reaction, preferably a cyclic ether, most preferably tetrahydrofuran, and mixed with a Wittig reagent which generates a methylene group—preferably a methyltriphenylphosphonium halide, most preferably methyltriphenylphosphonium bromide—in the presence of a basically reacting compound, preferably an alkali metal alkoxide, most preferably potassium tert-butoxide, and reacted at a temperature in the range from 0 to 80° C.—depending on the reactivity of the educts used—preferably in the range from 20 to 60° C. and most preferably at about 40° C. After the reaction has ended the reaction mixture is mixed with water and a water-immiscible organic solvent, preferably a haloalkane, most preferably dichloromethane, and the organic phase is separated. After the aqueous phase has been extracted exhaustively and the combined extracts have been dried, the extracting agent is eliminated, the residue is dissolved with a solvent suitable for forming an acid addition salt, preferably in a branched or unbranched C_{1-4} -alkanol, most preferably isopropanol, and mixed with a suitable acid, preferably an inorganic acid, such as a hydrohalic acid, most preferably concentrated hydrochloric acid, and the acid addition salt of the Wittig product 9 which crystallises out is isolated.

In the subsequent 7th stage of the reaction the piperidine nitrogen is formylated, e.g. with n-butylformate, resulting in the corresponding enantiomerically pure N-formyl-3,3-dimethyl-4-methylene-piperidine derivative of type 10—in the manufacture of BIII 277, the corresponding (+)-N-formyl-2-(3-methoxyphenyl)methyl-3,3-dimethyl-4-methylene-piperidine (R_2 =meta-methoxy):



To do this, the piperidine derivative of type 9 which was isolated as the hydrohalide in the proceeding stage, is first converted into the corresponding free base, for example by dissolving the piperidine derivative 9 in the form of its hydrohalide in water and mixing it with a basically reacting compound, preferably with the aqueous solution of a basically reacting compound and most preferably with concentrated ammonia solution, and extracting the free piperidine with an organic solvent, preferably a halogenated hydrocarbon and most preferably with dichloromethane. After the extract has been dried and the extracting agent distilled off, the free base is taken up in an organic solvent such as a hydrocarbon, preferably in an alkyl aromatic compound, most preferably in toluene, and reacted with a formylating agent, preferably an alkylformate, most preferably n-butylformate, and the reaction product is isolated.