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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 444 RESPUESTAREQUE Folia: 404

Trámite : 011
Evento : 379
Actuación : 444

Referencia : Expediente No. 06047181
Asunto : Solicitud de patente para: "Derivados de pirazol".
Solicitante : AVENTIS PHARMA S.A.
Fecha de solicitud : Mayo 17 de 2006.

1. Yo, Luz Clemencia de PAÉZ, mayor de edad, domiciliada en Bogotá, D.C., identificada con la Cédula de ciudadanía N° 35.456.344 de Usaquén, obrando como apoderada del solicitante en el asunto antes identificado, me refiero al Oficio No. 14421 notificado por fijación en lista del 11 de Diciembre de 2009. Mediante memorial radicado el 5 de Marzo de 2010 solicité un plazo de treinta (30) días para dar respuesta a este oficio.

2. Mediante el Oficio No. 14427 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la siguiente manera:

3. De la solicitud de patente:

Su Despacho enuncia:

- Se recomienda ajustar el título a lo que se desea proteger a través del capítulo reivindicatorio; ya que con base en la normatividad vigente, los usos y los métodos de tratamiento no son patentables.
- La Reivindicación 1 no es concisa, porque los radicales tienen muchos significados y sustituciones; solicitando un número grande de compuestos posibles reclamados bajo la característica esencial de la fórmula (1); de igual manera los términos arilo,

heteroarilo, no son claros por si mismos ya que no están delimitando.

- La Reivindicación 7; con base a los compuestos allí presentados, los mismos no corresponden a la estructura general del compuesto de fórmula (1); por lo tanto no presentan el mismo concepto inventivo. Por lo tanto se debe realizar los ajustes pertinentes.
- Las Reivindicaciones 1 a 3 y 9 a 11; las palabras y/o expresiones: "arilo", "heteroarilo", "al menos", "; no son concisas; por tanto no delimitan de manera inequívoca la materia a proteger.
- Las Reivindicaciones 12 a 17 reclaman uso, y de acuerdo con la legislación Colombiana, el uso reclamado no se considera para protección por patente.

1) **4. Modificación de la solicitud en trámite.**

4.1 Capítulo reivindicatorio correspondiente a la solicitud original:

Con el fin de atender las observaciones formuladas a este respecto, y de acuerdo con el artículo 34 de la Decisión 486, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, se presenta un nuevo capítulo reivindicatorio constituido por 5 reivindicaciones como sustituto del anteriormente presentado. En este nuevo capítulo reivindicatorio, se ha revisado la redacción del mismo con el fin de hacer claridad sobre la materia que se solicita proteger y sobre el alcance de la misma. De tal manera que, las objeciones formuladas a este respecto quedan superadas respectivamente con las modificaciones realizadas de la siguiente manera:

- La reivindicación 1 ha sido redactada nuevamente, limitando significativamente las definiciones de los sustituyentes de los compuestos de fórmula (I) con base en las definiciones encontradas en el capítulo descriptivo y debidamente sustentadas en los ejemplos de la presente solicitud.
- Con respecto a la objeción formulada a los términos arilo y heteroarilo, se pone de presente a su Despacho que en la nueva reivindicación 1 (i) se especifica que los radicales arilo se seleccionan del grupo que consiste de fenil, naftil o indenil, los cuales son opcionalmente sustituidos con un halógeno y adicionalmente, (ii) que los radicales heteroarilo contienen un anillo de 3 a 10 miembros, opcionalmente conteniendo uno o mas heteroátomos seleccionados de oxígeno, azufre e hidrógeno.

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Así entonces la objeción formulada a este respecto se debe tener por superada.

- La reivindicación 7 y las reivindicaciones de uso 12-17 han sido eliminadas del nuevo pliego reivindicatorio, de tal manera que las objeciones formuladas a este respecto se deben tener por superada.
- Con respecto a la objeción formulada al título de la presente solicitud, se pone de presente que el mismo ha sido modificado de la siguiente manera: "~~Derivados de pirazol~~". Así entonces, la objeción formulada a este respecto se debe tener por superada.

Así entonces, teniendo en cuenta las modificaciones efectuadas al capítulo reivindicatorio, consideramos que las objeciones que por claridad hizo su Despacho quedan superadas ya que el nuevo capítulo reivindicatorio es claro y conciso y se limitó en los términos sugeridos por su Despacho, permitiendo así determinar el alcance de la protección reivindicada y compararla frente al estado del arte, de acuerdo con las disposiciones del artículo 30 de la Decisión 486.

Sin embargo, en el evento que el Despacho considere que una modificación adicional sea necesaria, respetuosamente le solicito hacer uso de la facultad que le otorga el artículo 45 inciso 2. de la Decisión 486 de la Comisión de la Comunidad Andina a efecto de requerir nuevamente de nuestra parte cualquier complementación o aclaración.

4.2 Capítulo reivindicatorio de la nueva solicitud divisional:

De otro lado, con el fin de atender la observación realizada por el Señor Examinador a la reivindicación 7 y de acuerdo con el artículo 36 de la Decisión 486, que permite al solicitante en cualquier momento del trámite dividir su solicitud, sin ampliar el objeto de la invención inicialmente solicitado, me permito presentar una solicitud divisional, cuyo pliego reivindicatorio está constituido por 1 reivindicación en la cual se incluye la materia revelada en la reivindicación 7 de la solicitud inicial.

De esta manera, junto con el presente memorial se presentan dos (2) nuevos capítulos reivindicatorios correspondientes a la modificación de la presente solicitud y a la nueva solicitud divisional.

La solicitud divisional se beneficiaría de la fecha de prioridad, de acuerdo con lo establecido en el artículo 36 de la Decisión 486.

Con la modificación realizada al capítulo reivindicatorio de la solicitud inicial y la presentación de la nueva solicitud divisional

se deben tener por superadas las objeciones formuladas por falta de claridad de la presente solicitud.

5. Novedad.

Su Despacho concluye, que la novedad de la presente solicitud de patente, se ve afectada por el documento CO 05-49 197 (D1).

Con respecto a lo señalado por su Despacho mi representada desea señalar lo siguiente:

Con las modificaciones realizadas al capítulo reivindicatorio, la objeción formulada a este respecto se debe tener por superada debido a que ahora D1 no es relevante para el estudio de patentabilidad de las nuevas reivindicaciones bajo estudio. Lo anterior, por cuanto el pliego reivindicatorio modificado se refiere a derivados de pirazol que a diferencia de los compuestos tieno[3,2-b]piridina-6-carbonitrilos y tieno [2,3-b]piridina-5-carbonitrilos revelados en D1 no presentan en el anillo pirazol un grupo sustituyente CN.

En consecuencia, la invención reclamada en el nuevo pliego reivindicatorio es novedosa frente a D1, y la materia acá reivindicada se debe tener como novedosa porque únicamente invenciones con todas las características técnicas identificadas en el mismo documento de la anterioridad pueden afectar la novedad de invenciones reivindicadas en una solicitud presentada posteriormente, tal y como lo señala el Manual Andino de Patentes:

"Para determinar la novedad de la invención, se debe comprobar si existen anticipaciones del estado de la técnica que contengan explícitamente todas las características técnicas esenciales de la invención"¹;

En consecuencia, la invención es **novedosa** frente a D1, por lo que solicitamos tener esta objeción por superada.

6. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

7. Anexos

- Formulario para modificaciones.
- Nuevo pliego reivindicatorio de la solicitud original compuesto por cinco (5) reivindicaciones.
- Pliego reivindicatorio solicitud divisional constituido por 1 reivindicación.

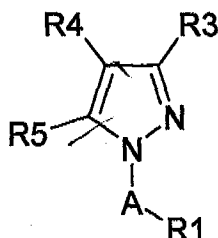
¹IEPI, BID. "MANUAL PARA EL EXAMEN DE SOLICITUDES DE PATENTES DE INVENCION EN LAS OFICINAS DE PROPIEDAD INDUSTRIAL DE LOS PAISES DE LA COMUNIDAD ANDINA". Quito, Ecuador 2004. Página 65.

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REIVINDICACIONES MODIFICADAS.

1. Compuesto de fórmula (I) en la que :



A es, si está presente, un enlace o un radical alquilo (C_1-C_6), opcionalmente sustituido por 1 o más sustituyentes alquilo (C_1-C_5).

R1 es un grupo NR6R7, azacicloalquilo (C_4-C_7), o azabicycloalquilo (C_5-C_9); opcionalmente sustituidas por 1 o más sustituyentes elegidos entre alquilo (C_1-C_5) y halógeno,

A-R1 es tal que el nitrógeno de R1 y el nitrógeno ubicado en la posición 1 del pirazol están separados obligatoriamente por al menos dos átomos de carbono,

R3 es un radical H, halógeno, OH, NH_2 , ORc, NRaRb, $NHC(O)Ra$, $NHSO_2Ra$,

R4 es un radical arilo o heteroarilo que está opcionalmente sustituido por 1 o más sustituyentes elegidos entre halógeno, NH_2 , OH, ORc, $C(O)NH_2$, NRaRb, $NHC(O)Ra$, arilo, polifluoroalquilo ^{o anillo},

en donde los radicales arilos son seleccionados de fenil, naftil o indenil, opcionalmente sustituidos por halógeno; y los radicales heteroarilo contienen un anillo de 3 a 10 miembros, opcionalmente conteniendo uno o mas heteroátomos seleccionados de oxígeno, azufre y nitrógeno.

R5 es un radical H, halógeno, CF_3 , CHF_2 , CH_2F , alquilo (C_1-C_6) lineal o ramificado,

Ra es (1-6C) alquilo lineal o ramificado,

Rb es, independientemente de Ra, un hidrógeno, (1-6C) alquilo lineal o ramificado,

Rc es un radical, alquilo lineal o ramificado (C_1-C_6), (poli)fluoroalquilo, (hetero)arilalquilo

R6 y R7 son, independientemente entre sí, un hidrógeno, alquilo (C_1-C_6),

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R6 y R7 pueden formar un anillo saturado o insaturado de 5, 6 ó 7 enlaces que tiene o no un heteroátomo como O, S, N y que está sustituido en su caso por uno o varios alquilos, halógenos,

R8 es un radical Ra o NRaRb,

sus racémicos, enantiómeros, diastereoisómeros y mezclas de los mismos, sus tautómeros y sus sales farmacéuticamente aceptables

2. Compuesto según la reivindicación 1 caracterizado porque se elige entre:

1-[2-(3-metoxi-4-fenil-pirazol-1-il)-etil]-piperidina

1-(1-aza-biciclo[2.2.2]oct-3-ilmetil)-4-fenil-1H-pirazol-1-ol

3-(3-benciloxi-4-fenil-pirazol-1-ilmetil)-1-aza-biciclo[2.2.2]octano

3-(3-metoxi-4-fenil-pirazol-1-ilmetil)-1-aza-biciclo[2.2.2]octano

1-(1-aza-biciclo[2.2.2]oct-3-il)-4-fenil-1H-pirazol-3-ol

1-(2-perhidro-azepin-1-il-etil)-4-fenil-1H-pirazol-3-ol

1-[2-(2-metil-piperidin-1-il)-etil]-4-fenil-1H-pirazol-3-ol

1-[2-(4-fluoro-piperidin-1-il)-etil]-4-fenil-1H-pirazol-3-ol

1-[2-(3-metil-piperidin-1-il)-etil]-4-fenil-1H-pirazol-3-ol

10 1-[2-(3,6-dihidro-2H-piridin-1-il)-etil]-4-fenil-1H-pirazol-3-ol

1-[2-(7-aza-biciclo[2.2.1]hept-7-il)-etil]-4-fenil-1H-pirazol-3-ol

1-[2-(2-aza-biciclo[2.2.2]oct-2-il)-etil]-4-fenil-1H-pirazol-3-ol

1-[2-(2-aza-biciclo[2.2.1]hept-2-il)-etil]-4-fenil-1H-pirazol-3-ol

1-[2-dimetilamino-etil]-4-fenil-1H-pirazol-3-ol

1-[3-dimetilamino-propil]-4-fenil-1H-pirazol-3-ol

1-[2-((2S,6R)-2,6-dimetil-piperidin-1-il)-etil]-4-fenil-1H-pirazol-3-ol

1-[2-dietilamino-etil]-4-fenil-1H-pirazol-3-ol

1-(2-diisopropilamino-etil)-4-fenil-1H-pirazol-3-ol

4-fenil-1-(2-pirrolidin-1-il-etil)-1H-pirazol-3-ol

1 3-(3-metoxi-4-fenil-pirazol-1-il)-1-aza-biciclo[2.2.2]octano OK

1-[2-(3-difluorometoxi-4-fenil-pirazol-1-il)-etil]-piperidina OK

5erente
4
4-fenil-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ilamina OK
4-fenil-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ilamina OK } igual

N-[4-fenil-1-(2-piperidin-1-il-etil)-1H-pirazol-3-il]-acetamida

N-[4-fenil-1-(2-piperidin-1-il-etil)-1H-pirazol-3-il]-
metanosulfonamida

1-(2-dimetilamino-propil)-4-fenil-1H-pirazol-3-ol

1-(1-metil-piperidin-3-il-metil)-4-fenil-1H-pirazol-3-ol

5-metil-4-fenil-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol

4-(3-amino-fenil)-1-(2-dimetilamino-etil)-1H-pirazol-3-ol

N-{3-[3-hidroxi-1-(2-dimetilamino-etil)-1H-pirazol-4-il]-fenil}-
acetamida

4-(4-amino-fenil)-1-(2-dimetilamino-etil)-1H-pirazol-3-ol

1-(2-dimetilamino-etil)-4-(4'-fluoro-bifenil-3-il)-1H-pirazol-3-ol

4-bifenil-3-il-1-(2-dimetilamino-etil)-1H-pirazol-3-ol

1-(2-dimetilamino-etil)-4-(4'-fluoro-bifenil-4-il)-1H-pirazol-3-ol

1-(2-piperidin-1-il-etil)-4-piridin-2-il-1H-pirazol-3-ol

1-(2-piperidin-1-il-etil)-4-piridin-4-il-1H-pirazol-3-ol

4-(4-fluoro-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol

4-(4-trifluorometoxi-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-
3-ol

4-fenil-1-(2-piperidin-1-il-propil)-1H-pirazol-3-ol

3-(4-fenil-pirazol-1-il-metil)-1-aza-biciclo[2.2.2]octano

4-(5-cloro-tiofen-2-il)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol

4-(3-metoxi-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol

4-(2-metoxi-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol

4-(3-hidroxi-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol

4-(4-hidroxi-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(4-metoksi-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(3-fluoro-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
1-(2-piperidin-1-il-etil)-4-(3-trifluorometil-fenil)-1H-pirazol-3-ol
1-(2-piperidin-1-il-etil)-4-piridin-3-il-1H-pirazol-3-ol
4-(4-cloro-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(3-cloro-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(2-fluoro-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(2-cloro-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(4-cloro-fenil)-1H-pirazol-3-ol
1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(3-cloro-fenil)-1H-pirazol-3-ol
1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(3-fluoro-fenil)-1H-pirazol-3-ol
1-(1-metil-pirrolidin-3-il)-4-fenil-1H-pirazol-3-ol
1-[2-(1-metil-pirrolidin-2-il)-etil]-4-fenil-1H-pirazol-3-ol
1-(pirrolidin-3-il)-4-fenil-1H-pirazol-3-ol
1-[(1-metil-pirrolidin-2-(S)-il)-metil]-4-fenil-1H-pirazol-3-ol
4-fenil-1-pirrolidin-3-il-metil-1H-pirazol-3-ol
1-((2R) 1-metil-pirrolidin-2-ilmetil)-4-fenil-1H-pirazol-3-ol
4-fenil-1-(piperidin-3-il)-1H-pirazol-3-ol
1-(1-metil-piperidin-2-ilmetil)-4-fenil-1H-pirazol-3-ol
1-(1-metil-azepan-3-il)-4-fenil-1H-pirazol-3-ol
4-fenil-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(tiofen-2-il)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(3,4-dicloro-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(4-Bromo-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
4-(1H-Indol-5-il)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol

4-(5-Bromo-tiofen-2-il)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
2-[1-(2-Piperidin-1-il-etil)-1H-pirazol-4-il] benzamida
4-(2-hidroxi-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol
4-(1H-Indol-5-il)-1-(2-piperidin-1-il-etil)-1H-pirazol
4-(4-metil-fenil)-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
1-(1-Aza-biciclo[2.2.2]oct-3-il)-4-(1H-indol-5-il)-1H-pirazol
(+) 1-(1-Aza-biciclo[2.2.2]oct-3-il)-4-(1H-indol-5-il)-1H-pirazol
(-) 1-(1-Aza-biciclo[2.2.2]oct-3-il)-4-(1H-indol-5-il)-1H-pirazol
1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(5-cloro-tiofen-2-il)-1H-pirazol-3-ol
1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(5-cloro-tiofen-2-il)-1H-pirazol-3-ol
1-(1-aza-biciclo[2.2.2]oct-2-ilmetil)-4-fenil-1H-pirazol-3-ol
3-[4-(3,5-difluoro-fenil)-pirazol-1-il]-1-aza-biciclo[2.2.2]octano
4-benzo[b]tiofen-2-il-1-(2-piperidin-1-il-etil)-1H-pirazol-3-ol
1-(2-piperidin-1-il-etil)-4-tiofen-3-il-1H-pirazol-3-ol
4-[3-hidroxi-1-(2-piperidin-1-il-etil)-1H-pirazol-4-il]-benzamida
3-[3-hidroxi-1-(2-piperidin-1-il-etil)-1H-pirazol-4-il]-benzamida
(-)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-fenil-1H-pirazol-3-ol
(+)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-fenil-1H-pirazol-3-ol
(-)-1-(1-aza-biciclo[2.2.2]oct-3-ilmetil)-4-fenil-1H-pirazol-1-ol
(+)-1-(1-aza-biciclo[2.2.2]oct-3-ilmetil)-4-fenil-1H-pirazol-1-ol
1-(1-aza-biciclo[2.2.2]oct-3-ilmetil)-4-(4-cloro-fenil)-1H-pirazol-3-ol
(-)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(4-cloro-fenil)-1H-pirazol-3-ol
(+)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(4-cloro-fenil)-1H-pirazol-3-ol

(-)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(4-fluoro-fenil)-1H-pirazol-3-ol

(+)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(4-fluoro-fenil)-1H-pirazol-3-ol

3-[4-(4-cloro-fenil)-pirazol-1-il]-1-aza-biciclo[2.2.2]octano

3-[4-(4-cloro-fenil)-pirazol-1-ilmetil]-1-aza-biciclo[2.2.2]octano

3-[4-(3-Cloro-4-metoxi-fenil)-pirazol-1-ilmetil]-1-aza-biciclo[2.2.2]octano

4-[1-(1-aza-biciclo[2.2.2]oct-3-ilmetil)-1H-pirazol-4-il]-2-cloro-fenol

4-[1-(1-Aza-biciclo[2.2.2]oct-3-il)-1H-pirazol-4-il]-2-cloro-fenol

(-)-4-[1-(1-Aza-biciclo[2.2.2]oct-3-il)-1H-pirazol-4-il]-2-cloro-fenol

(+)-4-[1-(1-Aza-biciclo[2.2.2]oct-3-il)-1H-pirazol-4-il]-2-cloro-fenol

(+)-1-(1-Aza-biciclo[2.2.2]oct-3-il)-4-piridin-2-il-1H-pirazol-3-ol

(-)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-piridin-2-il-1H-pirazol-3-ol

(+)-1-(1-Aza-biciclo[2.2.2]oct-3-il)-4-fenil-1H-pirazol-3-ilamina

(-)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-fenil-1H-pirazol-3-ilamina

(+)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(1H-indol-4-il)-1H-pirazol

(-)-1-(1-aza-biciclo[2.2.2]oct-3-il)-4-(1H-indol-4-il)-1H-pirazol,

sus racémicos, enantiómeros, diastereoisómeros y mezclas de los mismos, sus tautómeros y sus sales farmacéuticamente aceptables.

3. Procedimiento de preparación de un compuesto de fórmula (I) tal como se define en la reivindicación 1 o de un compuesto elegido entre la 3-(3-piridinil)-1H-pirazol-1-butanamina y la 4-(3-piridinil)-1H-pirazol-1-butanamina y la N-(dietil)-4-fenil-1H-pirazol-1-etilamina y para el que R3 es OH partir del compuesto (II).

No es
congruente
con la
reiv 1.

United States Patent [19]

Carting et al.

US00539436A

[31] Patent Number: 5,939,436

[45] Date of Patent: Aug. 17, 1999

[54] FIVE-MEMBERED HETEROAROMATIC COMPOUNDS AS DOPAMINE RECEPTOR SUBTYPE LIGANDS

[75] Inventors: William Robert Carting, Bishops Stortford, United Kingdom; Paul David Leeson, Princeton, N.J.; Kevin William Moore, Buntingford, United Kingdom

[73] Assignee: Merck Sharp & Dohme Ltd., Hoddesdon, United Kingdom

[21] Appl. No.: 08/875,059

[22] PCT Filed: Feb. 13, 1997

[86] PCT No.: PCT/EP97/00678

§ 371 Date: Jun. 25, 1997

§ 102(e) Date: Jun. 25, 1997

[87] PCT Pub. No.: WO96/21660

PCT Pub. Date: Jul. 18, 1996

[30] Foreign Application Priority Data

Jan. 12, 1995 [GB] United Kingdom 9500580

[51] Int. Cl.⁶ A61K 31/445; C07D 401/04

[52] U.S. Cl. 514/326; 514/318; 546/193; 546/194; 546/208; 546/209; 546/211

[58] Field of Search 546/211; 514/326

[56] References Cited

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WO 93/10742 6/1993 WIPO
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WO 94/27994 12/1994 WIPO
WO 95/02591 1/1995 WIPO
WO 95/07904 3/1995 WIPO

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Cram and Hammond, "Organic Chemistry", McGraw-Hill Book Co., NY (1964) 2nd Ed. pp. 565-567.

Primary Examiner—Patricia L. Morris

Attorney, Agent, or Firm—Philippe L. Durette; Melvin Winokur

[57] ABSTRACT

A class of heteroaromatic compounds incorporating a substituted five-membered heteroaromatic nucleus which contains at least two nitrogen atoms are ligands for dopamine receptor subtypes within the body and are therefore useful in the treatment and/or prevention of disorders of the dopamine system, in particular schizophrenia and depression.

7 Claims, No Drawings

11

white solid which was triturated with 1:1 diethyl ether and hexane (30 ml) to give the required product, Mp. 92-94° C. c) N-Butyloxycarbonyl-4-(1-(3-methyl-4-phenyl)pyrazolyl)piperidine and N-Butyloxycarbonyl-4-(1-(5-methyl-4-phenyl)pyrazolyl)piperidine

To a solution of N-Butyloxycarbonyl-4-methylsulphonyloxypiperidine (1 g, 0.004 Mol) in N,N-dimethylformamide (20 ml), under nitrogen at room temperature, was added the preformed sodium salt of 3-methyl-4-phenylpyrazole (2.1 g, 0.012 Mol) (formed by addition of sodium hydride to a solution of 3-methyl-4-phenylpyrazole in N,N-dimethylformamide and the resultant solid filtered and dried). The solution was heated to reflux for 2 hrs., left to cool, concentrated under vacuum and the residue was partitioned between dichloromethane (2x50 ml) and water (50 ml). The combined organic layers were washed with brine (2x50 ml), dried (MgSO₄), filtered and concentrated under vacuum. The residue was purified by flash silica chromatography using ethyl acetate-hexane (0-40%) as the eluent to give the less polar (0.29 g) and more polar (0.37 g) products. Less polar ¹H NMR (DMSO) δ 1.43 (9H,s), 1.85 (4H,m), 2.39 (3H,s), 2.94 (2H,m), 4.04 (2H,m), 4.41 (1H,m), 7.23 (1H,m), 7.38 (4H,m), 7.60 (1H,s). More polar ¹H NMR (DMSO) δ 1.42 (9H,s), 1.75 (2H,m), 1.99 (2H,m), 2.29 (3H,s), 2.90 (2H,m), 4.02 (2H,m), 4.26 (1H,m), 7.21 (1H,m), 7.38 (4H,m), 7.98 (1H,s). d) 4-((5-Methyl-4-phenyl)pyrazol-1-yl)piperidine hydrochloride

To a solution of the less polar product from Example 1 part c (0.28 g) in diethyl ether (20 ml) was added a solution of hydrogen chloride in ether (30 ml of ~5 Mol). After 2 hrs the solid was filtered and dried to give the title compound (0.22 g). ¹H NMR (DMSO) δ 2.02 (2H,m), 2.75 (2H,m), 2.41 (3H,s), 3.08 (2H,m), 3.40 (2H,m), 4.58 (1H,m), 7.26 (1H,m), 7.38 (4H,m), 7.64 (1H,s), 9.02 (1H,bs), 9.38 (1H,bs). The structure was confirmed by N.O.E.'s between the 5-methyl protons and the 4-piperidine proton.

e) 1-Benzyl-4-((5-methyl-4-phenyl)pyrazol-1-yl)-piperidine dihydrochloride

To a solution of 1-((5-Methyl-4-phenyl)pyrazol-1-yl)-piperidine hydrochloride (0.21 g, 0.76 mmol) in N,N-dimethylformamide (10 ml) was added benzyl bromide (0.108 ml, 0.91 mmol) and ethyldiisopropylamine (0.46 ml, 2.57 mmol) and the reaction mixture was stirred at 45° C. for 18 hrs. The reaction mixture was concentrated under vacuum and the residue was partitioned between dichloromethane (2x50 ml) and water (50 ml). The combined organic layers were washed with brine (2x50 ml), dried (MgSO₄), filtered and concentrated under vacuum. The residue was dissolved in a mixture of diethyl ether and methanol (10 ml, 1:1) and a solution of hydrogen chloride in ether (3 ml ~5 mol) added, after 5 mins. concentrated under vacuum. The residue was recrystallised from ethyl acetate-methanol to give the required compound as a white solid (0.11 g). Mp 198-201° C. ¹H NMR (DMSO+NaOD) δ 1.82 (2H,m), 2.12 (4H,m), 2.37 (3H,m), 2.91 (2H,m), 3.53 (2H,s), 4.17 (1H,m), 7.34 (10H,m), 7.59 (1H,s). MS (CI) m/e 332 [MH]⁺. Anal. Found C, 64.83; H, 6.71; N, 10.17. C₂₂H₂₅N₃·2HCl·0.2H₂O requires C, 64.77; H, 6.77; N, 10.17%.

EXAMPLE 2

1-(3-Cyanobenzyl)-4-((5-methyl-4-phenyl)pyrazol-1-yl)piperidine

This compound was prepared using the procedure described in Example 1 part e, using 3-cyanobenzyl bromide

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instead of benzyl bromide, and the free base was recrystallised from ethyl acetate and hexane to give the required compound as a white solid. Mp 145-147° C. dec. ¹H NMR (DMSO) δ 1.83 (2H,m), 2.1 (2H,m), 2.19 (2H,m), 2.38 (3H,s), 2.90 (2H,m), 3.60 (2H,s), 4.18 (1H,m), 7.24 (1H,m), 7.30 (4H,m), 7.55 (2H,m), 7.59 (2H,m), 7.77 (1H,s). MS (CI) m/e 357 [MH]⁺. Anal. Found C, 77.36; H, 6.83; N, 15.52. C₂₃H₂₄N₄ requires C, 77.50; H, 6.79; N, 15.72%.

EXAMPLE 3

1-(3-Chlorobenzyl)-4-((5-methyl-4-phenyl)pyrazol-1-yl)piperidine

This compound was prepared using the procedure described in Example 1 part e, using 3-chlorobenzyl bromide instead of benzyl bromide, and the free base was recrystallised from ethyl acetate and hexane to give the required compound as a white solid. Mp 126-127° C. ¹H NMR (DMSO) δ 1.83 (2H,m), 2.10 (4H,m), 2.37 (3H,s), 2.91 (2H,m), 3.55 (2H,s), 4.18 (1H,m), 7.21-7.39 (9H,m), 7.59 (1H,s). MS (CI) m/e 366.5 [MH]⁺. Anal. Found C, 71.73; H, 6.45; N, 11.55. C₂₂H₂₄ClN₃·0.1H₂O requires C, 71.86; H, 6.63; N, 11.43%.

EXAMPLE 4

1-Benzyl-4-((3-methyl-4-phenyl)pyrazol-1-yl)piperidine dihydrochloride

a) 4-((3-Methyl-4-phenyl)pyrazol-1-yl)piperidine hydrochloride

To a solution of the more polar product from Example 1 part c (0.36 g) in diethyl ether (20 ml) was added a solution of hydrogen chloride in ether (30 ml of ~5 Mol). After 2 hrs the solid was filtered and dried to give the title compound (0.33 g). ¹H NMR (DMSO) δ 2.19 (4H,m), 2.31 (3H,s), 3.06 (2H,m), 3.39 (2H,m), 4.42 (1H,m), 7.23 (1H,m), 7.40 (4H,m), 7.96 (1H,s), 9.09 (1H,bs), 9.34 (1H,bs). The structure was confirmed by N.O.E.'s between the pyrazole-5-proton and the piperidine-4-proton.

b) 1-Benzyl-4-((3-methyl-4-phenyl)pyrazol-1-yl)piperidine dihydrochloride

To a solution of 4-((3-Methyl-4-phenyl)pyrazol-1-yl)piperidine hydrochloride (0.33 g, 1.19 mmol) in N,N-dimethylformamide (10 ml) was added benzyl bromide (0.17 ml, 1.43 mmol) and ethyldiisopropylamine (0.70 ml, 4.05 mmol) and the reaction mixture was stirred at 45° C. for 18 hrs. The reaction mixture was concentrated under vacuum and the residue was partitioned between dichloromethane (2x50 ml) and water (50 ml). The combined organic layers were washed with brine (2x50 ml), dried (MgSO₄), filtered and concentrated under vacuum. The residue was dissolved in a mixture of diethyl ether and methanol (10 ml, 1:1) and a solution of hydrogen chloride in ether (3 ml ~5 mol) added, after 5 mins. concentrated under vacuum. The residue was recrystallised from ethyl acetate-methanol to give the required compound as a white solid (0.22 g). Mp 194-195° C. ¹H NMR (DMSO+NaOD) δ 1.98 (4H,m), 2.09 (2H,m), 2.30 (3H,s), 2.91 (2H,m), 3.73 (2H,s), 4.07 (1H,m), 7.21-7.44 (10H,m), 7.96 (1H,s). MS (CI) m/e 332 [MH]⁺. Anal. Found C, 64.98; H, 6.84; N, 10.24. C₂₂H₂₅N₃·2HCl·0.2H₂O requires C, 64.77; H, 6.77; N, 10.17%.

EXAMPLE 5

1-(3-Cyanobenzyl)-4-((3-methyl-4-phenyl)pyrazol-1-yl)piperidine oxalate

This compound was prepared using the procedure described in Example 4, using 3-cyanobenzyl bromide



US00664398B2

D3
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(12) **United States Patent**
Denis

(10) Patent No.: **US 6,664,398 B2**
(45) Date of Patent: **Dec. 16, 2003**

(54) **DERIVATIVES OF ERYTHROMYCIN, THEIR PREPARATION PROCESS AND THEIR USE AS MEDICAMENTS**

(75) Inventor: **Alexis Denis, Paris (FR)**

(73) Assignee: **Aventis Pharma S.A. (FR)**

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

(21) Appl. No.: **10/188,394**

(22) Filed: **Jul. 2, 2002**

(65) **Prior Publication Data**

US 2003/0050254 A1 Mar. 13, 2003

Related U.S. Application Data

(62) Division of application No. 09/442,681, filed on Nov. 18, 1999, now Pat. No. 6,440,941.

(51) Int. Cl.⁷ **C07D 293/00**

(52) U.S. Cl. **544/100; 544/1; 544/184**

(58) Field of Search **546/183; 1, 184; 548/100**

(56) **References Cited**

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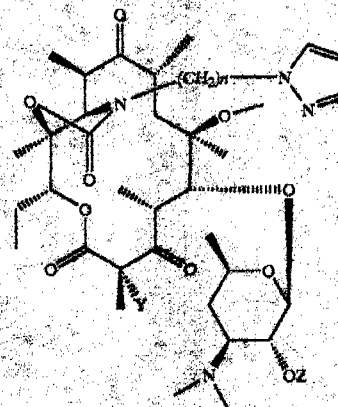
Primary Examiner—Elli Pescelev

(74) Attorney, Agent, or Firm—Muserlian, Lucas and Mercanti

(57) **ABSTRACT**

A subject of the invention is the compounds of formula

(I)



in which

Y represents a hydrogen atom or a fluorine atom,

n represents an integer comprised between 1 and 8,

Z represents a hydrogen atom or the remainder of a carboxylic acid, optionally substituted on the heterocycle by one or more alkyl, alkenyl, alkynyl, O-alkyl, O-alkenyl, O-alkynyl, S-alkyl, S-alkenyl, S-alkynyl radicals containing up to 8 carbon atoms, one or more OH, NH₂, O=N, NO₂, CF₃ radicals or one or more aryl radicals containing up to 14 carbon atoms or heteroaryl radicals containing one or more nitrogen oxygen or sulphur atoms, the aryl or heteroaryl radicals themselves being able to be substituted as well as their addition salts with acids,

The products of formula (I) have antibiotic properties.

3 Claims, No Drawings

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Stage B: 3-(3-pyridinyl)-1H-pyrazole-1-butanamine

7 ml of hydrazine hydrate is added to a suspension containing 450 ml of ethanol and 22.33 g of the product of Stage A. The reaction medium is taken to reflux for 15 hours. The ethanol is evaporated off, the reaction mixture is agitated with 200 ml of ethyl acetate, washed with salt water, dried, filtered and concentrated. In this way 9.60 g of sought product is obtained.

EXAMPLE 2

11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)oxy]2-fluoro-6-O-methyl-3-oxo-12,11-[oxycarbonyl][4-[3-(3-pyridinyl)-1H-pyrazol-1-yl]butyl]imino]]-erythromycin

By operating as previously, starting with the corresponding 2-fluorinated derivative of formula (II) prepared as indicated hereafter, the sought product is obtained M.p. = 117-121° C.

Preparation of the compound of formula (II) in which Y represents a fluorine atom.

2'-acetoxy 2 α -fluoro of 12-(oxycarbonylimidazol)11-deoxy 10,11-didehydro 3-de[(2,6-dideoxy 3-C-methyl 3-O-methyl α -L-ribohexopyranosyl)oxy]6-O-methyl 3-oxo erythromycin.

Stage A: 11-deoxy 10,11-didehydro 3-de[(2,6-dideoxy 3-O-methyl α -L-ribohexopyranosyl) oxy]6-O-methyl 3-oxo erythromycin.

A mixture of 8.722 g of 11-deoxy 10,11-didehydro 3-de [(2,6-dideoxy 3-O-methyl α -L-ribohexopyranosyl)oxy]6-O-methyl 3-oxo erythromycin 2'-acetate and 350 ml of anhydrous methanol (HF 596802) is agitated for 44 hours. 8.794 g of the sought product is obtained.

Stage B: 2'-trimethylsilyloxy of 11-deoxy 10,11-didehydro 3-de[(2,6-dideoxy 3-O-methyl α -L-ribohexopyranosyl)oxy]6-O-methyl 3-oxo erythromycin.

A mixture containing 3.08 g of the product of the preceding stage, 340 mg of imidazole, 32 ml of THF anhydride and 1.06 ml of hexamethyldisilylazane is agitated at ambient temperature for 4 days. The reaction medium is evaporated to dryness, then taken up in a mixture of 60 ml of methylene chloride and 60 ml of 0.5 M sodium acid phosphate. The reaction mixture is maintained under agitation for 15 minutes, decanted, extracted with methylene chloride, dried and evaporated to dryness. 3.345 g of the sought product is obtained.

Stage C: 2'-trimethylsilyloxy 2 α -fluoro of 11-deoxy 10,11-didehydro 3-de[(2,6-dideoxy 3-O-methyl α -L-ribohexopyranosyl) oxy]6-O-methyl 3-oxo erythromycin.

1.24 ml of a 0.97M solution of potassium tertbutylate in THF is added at -12° C. under an argon atmosphere to a solution containing 668 mg of 2'-trimethylsilyloxy of 11-deoxy 10,11-didehydro 3-de[(2,6-dideoxy 3-O-methyl α -L-ribohexopyranosyl) oxy]6-O-methyl 3-oxo erythromycin and 6.7 ml of anhydrous THF. The reaction medium is agitated for 5 minutes and 378 mg of N-fluoro dibenzene-sulphonimide is added. The reaction medium is agitated for 10 minutes at -12° C. and left to return to ambient temperature for 1 hour 30 minutes. The isolation and purification operations are carried out and 695 mg of the sought product is obtained.

Stage D: 2 α -fluoro of 11-deoxy 10,11-didehydro 3-de[(2,6-dideoxy 3-O-methyl 3-O-methyl α -L-ribohexopyranosyl) oxy]6-O-methyl 3-oxo erythromycin

A mixture of 5.476 g of product of Example 2, 50 ml of THF and 11.2 ml of 1M tetrabutylammonium fluoride in

THF is agitated for 3 hours 30 minutes. The solvent is evaporated off and 37 ml of ethyl acetate, 37 ml of water and 7.5 ml of 20% ammonium hydroxide are added. The reaction medium is agitated for 10 minutes, decanted, extracted with ethyl acetate, dried, filtered and the filtrate is concentrated to dryness. The product obtained is chromatographed on silica eluting with an ammoniated CH₂Cl₂-MeOH mixture 99-1, then 98-2, 97-3, 96-4, 95-5. 2.452 g of sought product is obtained.

Stage E: 2'-acetoxy 2 α -fluoro of 11-deoxy 10,11-didehydro 3-de [(2,6-dideoxy 3-O-methyl α -L-ribohexopyranosyl) oxy]6-O-methyl 3-oxo erythromycin

1.02 g of the product of Stage A, 10 ml of methylene chloride and 241 μ l of acetic anhydride are maintained under agitation for 3 hours. After evaporation 10 ml of water and 10 ml of ethyl acetate are added. The reaction medium is left for 1 hour under agitation at an ambient temperature, decanted, dried and evaporated. 1.01 g of sought product is obtained.

Stage F: 2'-acetoxy 2 α -fluoro of 12-(oxycarbonylimidazol) 11-deoxy 10,11-didehydro 3-de[(2,6-dideoxy 3-C-methyl-3-O-methyl α -L-ribohexopyranosyl)oxy]6-O-methyl 3-oxo erythromycin

0.388 g of carbonylimidazole and 24 μ L of DBU are added at 0° C. to a solution containing 1.01 g of the product of the preceding stage and 10 ml of anhydrous THF. The THF is evaporated off and 10 ml of water and 10 ml of ethyl acetate are added. The reaction mixture is maintained under agitation for 10 minutes, extracted, dried and evaporated. 0.902 g of crude sought product is obtained which is chromatographed eluting with an ethyl acetate-triethylamine mixture 96-4. 0.573 g of sought product is obtained.

EXAMPLE 3

By operating as in Example 1 using 4-(3-pyridinyl)-1H-pyrazole-1-butanamine, 11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl- α -L-ribohexopyranosyl)oxy]-6-O-methyl-3-oxo-12,11-[oxycarbonyl][4-[4-(3-pyridinyl)-1H-pyrazol-1-yl]butyl]-imino]]-erythromycin is obtained.

Mass spectrum MH⁺ = 812⁺

NMR spectrum (300MHz in CDCl₃)

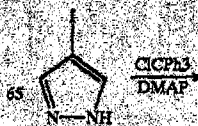
H2: 3.84 ppm; H4: 3.006 ppm; H5: 4.22 ppm; H7: 1.58 1.83 ppm; H8: 2.58 ppm; H10: 3.12 ppm; H11: 3.56 ppm; H13: 4.92 ppm; H14: 1.55 1.94; H15: 0.81 ppm; 2Me: 1.35 ppm; 4Me 1.29 ppm; 6 Me: 1.32 or 1.46 ppm; 8 Me 1.16 ppm; 10 Me: 1.01 ppm; 12 Me: 1.32 or 1.46 ppm; 60 Me: 2.6 ppm; 1': 4.27 ppm; 2': 3.17 ppm; 3': 2.44 ppm; 4': 1.67 and 1.24 ppm; 5': 3.55 ppm; Nme₂: 2.26 ppm; NCH₂: 3.69 ppm; CH₂: 1.64 1.94 ppm; CH₂N: 4.19 ppm; pyrazole: 7.77 ppm; pyridine: 8.76 7.75 7.27 8.44 ppm.

Mass spectrum

812⁺: MH⁺

850⁺: MK⁺

The starting amine was prepared as in Preparation 1 starting with the product prepared as indicated in the following diagram.





Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: AVENTIS PHARMA S.A. Sociedad constituida y existente bajo las leyes de Francia. Dirección: 20 Avenue Raymond Aron, Antony 92160, Francia Domicilio: Antony, Francia Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: LUZ CLEMENCIA DE PÁEZ Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax: 211 86 50 E-mail: clientes@cavelier.com Domicilio: Bogotá, Colombia.	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>35.456.344</u> T. P. <u>23.555</u>
4	Número de expediente: <u>06.047.181</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 3 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.	
6	Comprobante de pago No. _____ Fecha: _____	
7	Anexos ☐ Comprobante de pago de la tasa por \$114.000, por concepto de modificaciones. ☐ Comprobante de pago por reivindicaciones adicionales después de la décima reivindicación por ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
LUZ CLEMENCIA DE PÁEZ.

ASUNTO

Radicación 06 047181
Trámite 011
Evento 379
Actuación 519
Oficio
Folios 7

17926

Patente de Invención



Patente de Modelo de Utilidad



Vía Nacional



Vía PCT (fase nacional)



Cap. I



Cap. II



No. Sol. Internacional

PCT/FR2004/002968

Fecha de Presentación Internal.

22/Noviembre/2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados

Descripción:

Folios: 150 a 390 17/Mayo/2006

Reivindicaciones:

Folios: 391 a 420 17/Mayo/2006
Folios: 520 a 549 19/Noviembre/2008
Folios: 575 a 581 20/Abril/2010.

Prioridad:

Folio 2 FR03-13775 25/Noviembre/2003

Respuesta del solicitante:

Folios 570 a 574 20/04/2010

Se acepta para estudio el capítulo reivindicatorio de los folios 575 a 581.

Objeto de la invención

Título original: Derivados de pirazol como medicamentos para el tratamiento de degeneraciones neuronales agudas o crónicas.

Título modificado: Derivados de pirazol.

El objeto de la presente solicitud de patente de invención consiste en:
Compuestos derivados 4-aril/heteroaril- pirazol.

El problema planteado en esta solicitud consiste en la necesidad proporcionar compuestos ligandos de los receptores nicotínicos $\alpha 7$, para el tratamiento de problemas o enfermedades psiquiátricas o neurológicas.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos derivados 4-aril/heteroaril- pirazol, su procedimiento de preparación y composiciones farmacéuticas que los contienen.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): **A61K31/41, A61K31/435.**

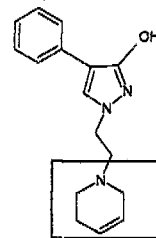
De la solicitud de Patente

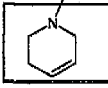
Reivindicaciones (artículo 30 D 486)

- La reivindicación 1 no es concisa cuando se encuentran términos como Polifluoroalquilo, (hetero)arilalquilo, alquilos: No se define el número de átomos de carbono que conforman la parte alquílica.

Se requiere al solicitante definir los números de átomos de carbono que definen la parte alquílica.

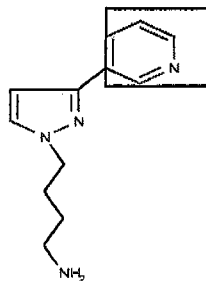
- En el folio 575 para la reivindicación 1, cuando se define a Rb, como (1-6C)alquilo se sugiere al solicitante corregirlo por alquilo (C₁-C₆).
- La reivindicación 2 no es clara, cuando se encuentra el compuesto número 10 del folio 576 denominado como 1-[2-(3,6-dihidro-2H-piridin-1-il)-etil]-4-

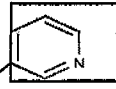


fenil-1H-pirazol-3-ol y el cual corresponde a la estructura  ya que el grupo resaltado (3,6-dihidro-2H-piridin-1-il) no se encuentra dentro del alcance del la reivindicación 1, porque R1 no se define como azacicloalqueno.

Se requiere al solicitante realizar la aclaración o corrección respectiva

- En el folio 576 reivindicación 2, los compuestos nombrados como 3 y 4 corresponden a la misma fórmula química. Se requiere al solicitante realizar la corrección respectiva.
- La reivindicación 3 no es clara cuando se habla del compuesto 3-(3-piridinil)-

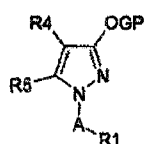


1H-pirazol-1-butanamina de estructura  ya que el grupo resaltado (3-piridinilo) no se encuentra dentro del alcance de la reivindicación 1, porque R3 no se define como un grupo heteroarilo. Además de este

compuesto, los otros allí nombrados como la 4-(3-piridinil)-1H-pirazol-1-butanamina y la N-(dietil)-4-fenil-1H-pirazol-1-etil-amina, no estarían tampoco dentro del alcance de la reivindicación 3, porque según lo establecido en la descripción (Ver folio 185) y lo presentado en el capítulo reivindicatorio original en el folio 409, la condición que deben tener los compuestos que se preparan con dicho procedimiento es que R3 sea -OH, lo que no acontece con los compuestos aquí objetados.

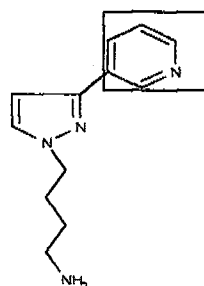
Por lo tanto se sugiere al solicitante redactar la reivindicación 3 de la siguiente manera:

Un procedimiento para la preparación de compuestos de fórmula (I) como los definidos en la reivindicación 1 y para la cual R3 es OH a partir del compuesto (II)



(II) en el que GP es una agrupación protectora de la función hidroxilo caracterizada porque el compuesto (II) se desprotege y luego se transforma en su caso en sal farmacéuticamente aceptable.

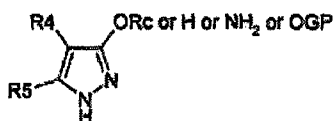
- La reivindicación 4 no es clara cuando se habla del compuesto 3-(3-piridinil)-



1H-pirazol-1-butanamina de estructura ya que el grupo resaltado (3-piridinilo) no se encuentra dentro del alcance de la reivindicación 1, porque R3 no se define como un grupo heteroarilo.

Por lo tanto se sugiere al solicitante redactar la reivindicación 4 de la siguiente manera :

Un procedimiento para la preparación de compuestos de fórmula (I) como los definidos en la reivindicación 1 y para la cual R3 es ORc, H, NH2 por alquilación de



pirazoles de fórmula (III) en el que GP es una agrupación protectora de la función OH con un compuesto de fórmula (IV) R1-A-X en el cual X es Cl, Br, I, OTs, OMs, OTf en medio básico en un disolvente aprótico y en su caso desprotege y en su caso transforma el producto obtenido en sal farmacéuticamente aceptable.

En este caso no se considera necesario nombrar específicamente el compuesto N-(dietil)-4-fenil-1H-pirazol-1-etil-amina, porque este ya se encuentra dentro del alcance de la reivindicación 1, para cuando se define a R3 y R5 como hidrógeno, R4 como fenilo, A como alquilo de 4 átomos de carbono (butilo) y R1 como NR6R7, donde R6 y R7 son alquilo de dos átomos de carbono (etilo).

- Para la reivindicación 5 que se refiere a una composición farmacéutica, se debe eliminar el compuesto 3-(3-piridinil)-1H-pirazol-1-butanamina porque como ya se explicó, este no se encuentra dentro del alcance de la reivindicación 1 porque R3 no es heteroarilo. Además depende incorrectamente de las reivindicaciones 3 y 4 que se refieren a un procedimiento de preparación

Por lo tanto se sugiere al solicitante redactar la reivindicación 5 de la siguiente manera:

Una composición farmacéutica que comprende en un medio farmacéuticamente aceptable, al menos un compuesto definido en las reivindicaciones 1 y 2.

Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 25-11-2003, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación.
D2	US5939436	Five-membered heteroaromatic compounds as dopamine receptor subtype ligands	10-04-2003
D3	US6664398	Derivatives of erythromycin, their preparation process and their use as medicaments	12-04-2001

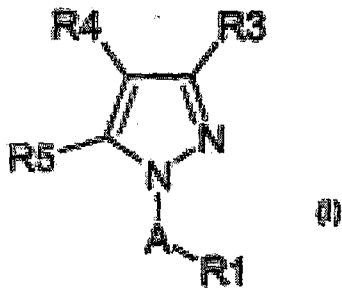
D2 (folios 585 a 586) divulga compuestos los cuales son ligandos de la dopamina y sus intermediarios

D3 (folios 587 a 588) divulga compuestos derivados de eritromicina y sus intermediarios, los cuales posee actividad antibiótica.

Análisis de patentabilidad (artículo 14 D486)

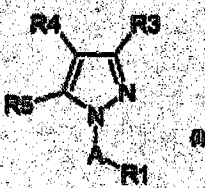
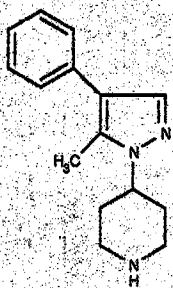
Novedad (artículo 16 D486)

La reivindicación 1 dice: compuesto de fórmula (I) en la que :

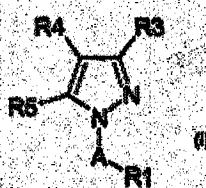


(Ver folios 575 y 576).

Al comparar elemento por elemento el objeto de la presente solicitud con el estado de la técnica esta oficina encuentra que D2 divulga compuestos derivados de anillos de 5 miembros, los cuales son ligandos de la dopamina y sus intermediarios.

SOLICITUD		D2
		 4-(5-metil-4-fenil-1H-pirazol-1-il) piperidina
A es un enlace	✓	
R1 es azacicloalquilo de 6 átomos de carbono, 4-piperidina)	✓	
R3 es hidrógeno.	✓	
R4 es arilo (fenilo	✓	
R5 es alquilo de un átomo de carbono (metilo)	✓	

D3 divulga compuestos derivados de eritromicina y sus intermediarios, los cuales poseen actividad como antibióticos.

SOLICITUD		D3
		 4-(3-piridinil)-1H-pirazol-1-butanamina
A es un grupo alquilo de 4 átomos de carbono.	✓	
R1 es un grupo NR6R7, en donde R6 y R7 son alquilo de 2 átomos de carbono.	✓	
R3 es hidrógeno.	✓	
R4 es heteroarilo (3- piridinilo)	✓	
R5 es hidrógeno	✓	

Por lo tanto, D2 (en el Folio 586, columna 11, líneas 40-41 y D3 en el folio 558, columna 6, líneas 36-37, ejemplo 3) divulga de manera específica compuestos reclamados bajo la fórmula (I) de la actual solicitud, tal como se expone en el cuadro comparativo. En consecuencia, la reivindicación 1 carece de novedad frente a D2 y D3, al igual que la composición farmacéutica que los contiene según la reivindicación 5.

Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D2	US5939436	1,5	Novedad
D3	US6664398	1,5	Novedad.

Respuesta a los argumentos del solicitante.

Modificación de la solicitud en trámite.

Capítulo reivindicatorio correspondiente a la solicitud original:

[...]La reivindicación 1 ha sido redactada nuevamente, limitando significativamente las definiciones de los sustituyentes de los compuestos de fórmula (1) con base en las definiciones encontradas en el capítulo descriptivo y debidamente sustentadas en los ejemplos de la presente solicitud.

Con respecto a la objeción formulada a los términos arilo y heteroarilo, se pone de presente a su Despacho que en la nueva reivindicación 1 (i) se especifica que los radicales arilo se seleccionan del grupo que consiste de fenil, naftil o indenil, los cuales son opcionalmente sustituidos con un halógeno y adicionalmente, (ii) que los radicales heteroarilo contienen un anillo de 3 a 10 miembros, opcionalmente conteniendo uno o mas heteroátomos seleccionados de oxígeno, azufre e hidrógeno.

Se aclara al solicitante que si bien es cierto que el capítulo reivindicatorio se ha delimitado de manera considerable y se han definido los términos arilo y heteroarilo de acuerdo a lo sustentado en la descripción, la reivindicación 1 aún presenta problemas de concisión en la definición de algunos términos tal como se estableció en el análisis de dicha reclamación en el folio 590.

Por lo tanto se le recomienda al solicitante definir las expresiones allí objetadas, con el fin de dar concisión al capítulo reivindicatorio. Asimismo, deben tenerse en cuenta las observaciones realizadas para las reivindicaciones 2 a 5, las cuales se encuentran afectadas en su claridad de acuerdo a lo establecido en los folios 590 a 592.

- *La reivindicación 7 y las reivindicaciones de uso 12-17 han sido eliminadas del nuevo pliego reivindicatorio, de tal manera que las objeciones formuladas a este respecto se deben tener por superada.*

Se le aclara al solicitante, que este Despacho acepta sus argumentos, porque las reivindicaciones 7 y 12-17, presentadas anteriormente ya no hacen parte del capítulo reivindicatorio presentado en los folios 575 a 581.

- *Con respecto a la objeción formulada al título de la presente solicitud, se pone de presente que el mismo ha sido modificado de la siguiente manera: "Derivados de pirazol". Así entonces, la objeción formulada a este respecto se debe tener por superada.*

Se le aclara al solicitante que este Despacho acepta la modificación del título presentada como respuesta al requerimiento realizado.

- *Así entonces, teniendo en cuenta las modificaciones efectuadas al capítulo reivindicatorio, consideramos que las objeciones que por claridad hizo su Despacho quedan superadas ya que el nuevo capítulo reivindicatorio es claro y conciso y se limitó en los términos sugeridos por su Despacho, permitiendo así determinar el alcance de la protección reivindicada y compararla frente al estado del arte, de acuerdo con las disposiciones del artículo 30 de la Decisión 486.*

Se le aclara al solicitante que este Despacho emite un nuevo oficio, con el fin de que se corrijan las deficiencias de claridad y concisión que presenta aún el nuevo pliego reivindicatorio.

Capítulo reivindicatorio de la nueva solicitud divisional:

De otro lado, con el fin de atender la observación realizada por el Señor Examinador a la reivindicación 7 y de acuerdo con el artículo 36 de la Decisión 486 [...] junto con el presente memorial se presentan dos (2) nuevos capítulos reivindicatorios correspondientes a la modificación de la presente solicitud y a la nueva solicitud divisional.

La solicitud divisional se beneficiaría de la fecha de prioridad, de acuerdo con lo establecido en el artículo 36 de la Decisión 486.

Con la modificación realizada al capítulo reivindicatorio de la solicitud inicial y la presentación de la nueva solicitud divisional se deben tener por superadas las objeciones formuladas por falta de claridad de la presente solicitud.

Se le aclara al solicitante que la divisional presentada ha sido aceptada, porque no amplía la materia inicialmente reclamada y adicionalmente no se encuentra comprendida dentro de la solicitud original.

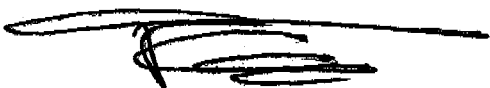
Novedad

Su Despacho concluye, que la novedad de la presente solicitud de patente se ve afectada por el documento CO 05-49 197 (D1).

Con las modificaciones realizadas al capítulo reivindicatorio, la objeción formulada a este respecto se debe tener por superada debido a que ahora D1 no es relevante para el estudio de patentabilidad de las nuevas reivindicaciones bajo estudio. Lo anterior, por cuanto el pliego reivindicatorio modificado se refiere a derivados de pirazol que a diferencia de los compuestos tieno[3,2-b]piridina-6-carbonitrilos y tieno [2,3-b]piridina-5-carbonitrilos revelados en D1 no presentan en el anillo pirazol un grupo sustituyente CN[...] En consecuencia, la invención es novedosa frente a D1, por lo que solicitamos tener esta objeción por superada.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


JOSE LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C).

El anterior requerimiento fue notificado por fijación en lista, de fecha
19 8 NOV. 2011

Elaborado por : Jacqueline Alfonso 
Revisado por. Consuelo Leguizamón 

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Abstract: 1979849 Reference: *J. Heterocyclic Chem.* 16, 849 (1979)

Mol Weight: 144.16 Formula: C₈H₇N




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Abstracts: 1979, Volume 16, pp. 849-853

Study of Some Reactions of Ethyl 4-Phenyl-3-benzoyl-2-pyrazoline-5-carboxylate

Ibrahim El-Sayed El-Kholi, Marcos Michael Mishakey, Hassan Mostafa Foad, Abla, Mary Amis Nashed

Chemistry Department, Faculty of Science, Alexandria University, Maharama Bay, Alexandria, Egypt

Several reactions of the pyrazoline 1a were investigated. With bromine water, potassium permanganate, hydrogen peroxide, or potassium hydroxide, different pyrazole derivatives were formed. While the reaction with hydroxylamine or some hydrazines gave the corresponding pyrazoline Schiff bases, with arylhydrazines, pyrazole Schiff bases were formed.

DOI: 10.1002/jhet.19795370160505

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US00772333B2

(2) **United States Patent**
Broo et al.(10) **Patent No.:** **US 7,723,333 B2**
(45) **Date of Patent:** ***May 25, 2010**(54) **NON-ANILINIC DERIVATIVES OF
ISOTHAZOL-3(2H)-ONE 1,1-DIOXIDES AS
LIVER X RECEPTOR MODULATORS**(75) **Inventors:** **Anders Broo, Mölndal (SE); Robert
Judkins, Mölndal (SE); Lanna Li,
Mölndal (SE); Eva-Lotte
Lindstedt-Alstermark, Mölndal (SE);
Pernilla Sandberg, Mölndal (SE);
Marianne Swanson, Mölndal (SE);
Lars Weddolf, Mölndal (SE); Kay
Brickmann, Mölndal (SE); Patrik
Holm, Pargas (FI)**(73) **Assignee:** **AstraZeneca AB, Sodertälje (SE)**(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-
claimer.(21) **Appl. No.:** **11/813,470**(22) **PCT Filed:** **Jan. 9, 2006**(86) **PCT No.:** **PCT/SE2006/000029**§ 371 (c)(1).
(2): (4) **Date:** **May 8, 2008**(87) **PCT Pub. No.:** **WO2006/073366****PCT Pub. Date:** **Jul. 13, 2006**(65) **Prior Publication Data**

US 2009/0005353 A1 Jan. 1, 2009

(30) **Foreign Application Priority Data**

Jan. 10, 2005 (SE) 0500055

(41) **Int. Cl.**
A61K 31/5355 (2006.01)
A61K 31/501 (2006.01)
A61K 31/4523 (2006.01)
A61K 31/4427 (2006.01)
A61K 31/427 (2006.01)
A61K 31/4155 (2006.01)
C07D 275/02 (2006.01)
C07D 233/54 (2006.01)
C07D 413/02 (2006.01)
C07D 401/02 (2006.01)
C07D 239/02 (2006.01)
C07D 211/00 (2006.01)
C07D 417/02 (2006.01)(52) **U.S. Cl. 514/236.8; 514/252.05;
514/256; 514/326; 514/342; 514/372; 514/397;
544/133; 544/238; 544/242; 546/184; 546/269.7;
548/213; 548/311.1**(58) **Field of Classification Search** 514/236.8,
514/252.05, 256, 326, 342, 372, 397; 544/133,
544/238, 242; 546/184, 269.7; 548/213,
548/311.1

See application file for complete search history.

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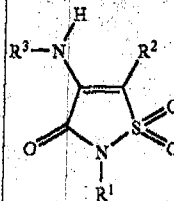
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(Continued)

Primary Examiner—Kamal A Saeed**Assistant Examiner**—Samantha L Shterengarts(74) **Attorney, Agent, or Firm**—Pepper Hamilton LLP(57) **ABSTRACT**The present invention relates to certain novel compounds of
the formula (I)

formula (I)

to processes for preparing such compounds, to their the utility
in modulation of nuclear hormone receptors Liver X Receptor
(LXR) α (NR1H3) and/or β (NR1H2) and in treating and/or
preventing clinical conditions including cardiovascular dis-
eases such as atherosclerosis; inflammatory diseases, Alzhe-
imer's disease, lipid disorders (dyslipidemias) whether or not
associated with insulin resistance, type 2 diabetes and other
manifestations of the metabolic syndrome, to methods for
their therapeutic use and to pharmaceutical compositions
containing them.**26 Claims, No Drawings**

D2
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Information

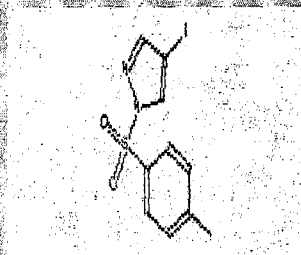
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Abstract: 19950189 Reference: *J. Heterocyclic Chem.*, 32, 189 (1995)

Mol. Weight: 348.16 Formula: C₁₀H₉ClN₂O₂S



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Abstracts: 1995, Volume 32, pp. 189-194

Synthesis and ¹³C NMR Study of Some N-Substituted 4-Iodo- and 3,4-Diiodopyrazoles

Wolfgang Holzer, Ingrid Pocher

Institute of Pharmaceutical Chemistry, University of Vienna, Pharmazienzentrum, Althanstrasse 14, A-1090 Vienna, Austria

The synthesis of some novel N-1 substituted 4-iodo- and 3,4-diiodopyrazoles starting from the corresponding NH-pyrazoles is described. On basis of their ¹³C nmr data and those of already known related congeners the influence of iodo- as well as N-1 substituents on pyrazole ¹³C chemical shifts and ¹³C-¹H spin coupling constants is investigated.

DOI: 10.1002/jhet.5570320131

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US006599904B2

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

(10) **Patent No.: US 6,599,904 B2**
(45) **Date of Patent: *Jul. 29, 2003**

(54) **SULFONAMIDE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS MEDICAMENTS**

(75) **Inventors:** Steven Mark Bromidge, Sawbridgeworth (GB); Francis David King, Bishops Stortford (GB); Paul Adrian Wyman, Epping (GB)

(73) **Assignee:** SmithKline Beecham p.l.c., Brentford (GB)

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

This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** 10/157,258

(22) **Filed:** May 29, 2002

(65) **Prior Publication Data**

US 2003/0069233 A1 Apr. 10, 2003

Related U.S. Application Data

(62) Division of application No. 09/643,200, filed on Aug. 21, 2000, now Pat. No. 6,423,717, which is a continuation of application No. 09/331,378, filed as application No. PCT/EP97/07159 on Dec. 15, 1997, now abandoned.

(30) **Foreign Application Priority Data**

Dec. 19, 1996 (GB) 9626377
Jan. 17, 1997 (GB) 9700901
Oct. 27, 1997 (GB) 9722757

(51) **Int. Cl.⁷** A61K 31/496

(52) **U.S. Cl.** 514/252.13; 514/253.06; 514/254.03; 514/254.09; 514/254.11

(58) **Field of Search** 514/253.06, 254.11, 514/252.13, 254.03, 254.09

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Primary Examiner—Emily Bernhardt

(74) **Attorney, Agent, or Firm**—Soma G. Simon; Mary E. McCarthy; Charles M. Kinzig

(57) **ABSTRACT**

Novel sulphonamide derivatives having CNS activity, processes for their preparation and their use as medicaments are disclosed. The present compounds are of formula (I) or a salt thereof:



wherein:

P is benzothiophene, benzothiadiazole, quinoline, benzofuran or indole;

A is a single bond, a C₁₋₆alkylene or a C₂₋₆alkenylene group;

R¹ is halogen, C₁₋₆alkyl optionally substituted by one or more halogen atoms, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, OCF₃, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, nitro, amino, C₁₋₆alkylamino or C₁₋₆dialkylamino, cyano or R² is phenyl, naphthyl;

n is 0, 1, 2, 3, 4, 5 or 6;

R² is hydrogen, C₁₋₆alkyl or aryl C₁₋₆alkyl or R² is linked to R³ to form a group (CH₂)₂ or (CH₂)₃;

R³ is a group R⁵ or together with R⁵ forms a group (CH₂)₂O or (CH₂)₃O or R³ is linked to R² to form a group (CH₂)₂ or (CH₂)₃;

R⁴ is an N-piperazine ring optionally substituted by C₁₋₆alkyl; and

R⁵ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, nitro, trifluoromethyl, cyano or aryl.

1 Claim, No Drawings

11

mixture was concentrated and the residue recrystallised from chloroform to yield the title compound (D15) as a yellow solid (43 g, 61%). Found MH⁺ 382/384.

Description 16

1-(5-Amino-2-methoxyphenyl)-4-trichloroacetyl piperazine (D16)

A solution of stannous chloride dihydrate (27 g) in concentrated HCl (60 ml) was slowly added to a stirred suspension of 1-(2-methoxy-5-nitrophenyl)-4-trichloroacetyl piperazine (D15) (15 g) in concentrated HCl/ethanol (1:2, 120 ml). After 24 hrs, the mixture was filtered, diluted with dichloromethane (600 ml) and basified with Na₂CO₃ solution. The layers were separated, the organic phase dried, concentrated to 1/3 the volume and acidified with 1M ethereal HCl solution to afford the title compound (D16) as a green solid (2.5 g, 15%). Found MH⁺ 352.

Description 17

Cyclopropyl-[4-(2-methoxy-5-nitrophenyl)-piperazin-1-yl]methanone (D17)

To a solution of 1-(2-methoxy-5-nitrophenyl)-piperazine (500 mg, 2.1 mmol) in dichloromethane (50 ml) at 0° C. under argon was added triethylamine (0.59 ml, 4.2 mmol) and cyclopropane carbonyl chloride (2.1 mmol). Stirring was continued for 12 hrs. The reaction mixture was concentrated in vacuo and partitioned between saturated aqueous NaHCO₃ and dichloromethane. The organic layer was dried over sodium sulphate and concentrated in vacuo to give the title compound (D17) in 90% yield. Found MH⁺ 306.

Description 18

[4-(2-Methoxy-5-nitrophenyl)-piperazin-1-yl]phenyl methanone (D18)

The title compound was prepared in 85% yield using the procedure outlined in D17 using benzoyl chloride. Found MH⁺ 342.

Description 19

[4-(5-Amino-2-methoxy-phenyl)-piperazin-1-yl]cyclopropyl methanone (D19)

A solution of the cyclopropyl-[4-(2-methoxy-5-nitrophenyl)-piperazin-1-yl]methanone (D17) (1.8 mmol) in ethanol was hydrogenated over 10% Palladium on charcoal catalyst for 2 hrs at room temperature to give the title compound in 91% yield. Found MH⁺ 276.

Description 20

[4-(5-Amino-2-methoxy-phenyl)-piperazin-1-yl]phenyl methanone (D20)

The title compound was prepared in 95% yield using the procedure outlined in D19. Found MH⁺ 312.

Description 21

3-(4-Cyclopropylmethyl-piperazin-1-yl)-4-methoxy-phenylamine (D21)

To a solution of [4-(5-amino-2-methoxy-phenyl)-piperazin-1-yl]cyclopropyl methanone (D19) (1.6 mmol) in

12

dry THF (10 ml) under argon was added LiAlH₄ (240 mg, 6.4 mmol). The resulting mixture was heated to reflux for 12 hrs and cooled before quenching with water (0.25 ml), 10% aqueous NaOH (0.25 ml) and finally water (0.75 ml). Filtration through celite and concentration in vacuo afforded the title compound (D21) in 75% yield. Found MH⁺ 262.

Description 22

3-(4-Benzyl-piperazin-1-yl)-4-methoxy-phenylamine (D22)

The title compound was prepared in 76% yield using the procedure outlined in D21. Found MH⁺ 298.

Description 23

Methane sulphonic acid 1-methyl pyrrolidin-3-yl ester (D23)

To a solution of 1-methyl-pyrrolidin-3-ol (2.0 g, 20 mmol) and triethylamine (3 ml, 22 mmol) in dichloromethane (25 ml) at 0° C. under argon was added methane sulphonyl chloride (2.4 g, 21 mmol). Stirring was continued at 0° C. to room temperature for 1 hr before partitioning between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was dried over sodium sulphate and concentrated in vacuo to afford the crude mesylate (3.6 g) which was used directly in the next step.

Description 24

3-(2-Methoxy-5-nitrophenoxy)-1-methyl-pyrrolidine (D24)

A solution of 2-methoxy-5-nitro phenol (5.1 g, 30 mmol) in DMF (10 ml) was added to sodium hydride (1.6 g, 66 mmol) under argon. After 1 hr a solution of the crude mesylate (D23, 3.6 g, 20 mmol) in DMF (10 ml) was added and the reaction mixture warmed to 50° C. for 48 hrs. The reaction was cooled, quenched with water and concentrated in vacuo before partitioning between saturated aqueous sodium bicarbonate and dichloromethane. The organic phase was dried over sodium sulphate and concentrated in vacuo. The residue was purified by chromatography on silica gel to afford the title compound (D24). Found MH⁺ 253.

Description 25

4-Methoxy-3-(1-methyl-pyrrolidin-3-yloxy)phenylamine (D25)

A solution of 3-(2-methoxy-5-nitro-phenoxy)-1-methyl-pyrrolidine (3.0 g, 0.12 mmol) in ethanol (50 ml) was hydrogenated over 10% palladium on charcoal catalyst for 2 hrs to afford the title compound (D25). Found MH⁺ 223.

Description 26

1-(4-Bromo-3-nitrophenyl)-4-methylpiperazine (D26)

A solution of 1-methyl-4-(3-nitrophenyl)piperazine (EP0533267A) (1.0 g, 4.5 mmol) in glacial acetic acid (25 ml) was treated with bromine (0.23 ml; 1 equivalent). The reaction mixture was stirred at 75° overnight, then cooled, filtered, and the yellow sticky solid was partitioned between potassium carbonate (aq) and 2% methanol in dichloromethane. The organic phase was dried (Na₂SO₄) and evaporated under reduced pressure to leave the title compound (D26) as a viscous orange oil (928 mg, 68%) MH⁺ 300/302.



US005786441A

United States Patent [19]

Lawson et al.

[11] Patent Number: 5,786,441

[45] Date of Patent: Jul. 28, 1998

[54] POLYMERS, ELASTOMERIC COMPOUNDS AND PRODUCTS THEREOF, DERIVED FROM NOVEL AMINE COMPOUNDS CONTAINING SIDE-CHAIN ORGANOLITHIUM MOIETIES

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[21] Appl. No.: 777,656

[22] Filed: Dec. 31, 1996

[51] Int. Cl.⁶ C08G 12/00; C08F 293/00

[52] U.S. Cl. 528/229; 528/392; 526/173; 526/180; 526/335; 526/336; 525/280; 525/332.8; 525/332.9; 525/333.1; 525/333.2; 525/366; 502/131; 502/157; 502/167; 152/450

[58] Field of Search 526/173, 180, 526/335, 336; 502/131, 157, 167; 152/450; 528/229, 392; 525/280, 332.8, 332.9, 333.1, 333.2, 366

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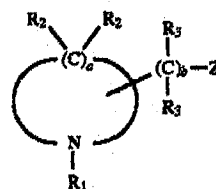
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Primary Examiner—P. Hampton-Hightower
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[57] ABSTRACT

A functionalized polymer comprising a polymeric segment, having at least one cyclic amine end group, defined according to formula (I)



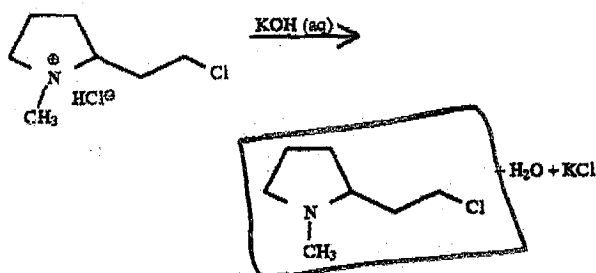
(I)

where Z is an anionically-polymerized polymer; R₁ is selected from the group consisting of organic groups containing from 1 to about 12 carbon atoms and a bridging bond; each R₂ is independently selected from the group consisting of hydrogen, organic groups containing from 1 to about 12 carbon atoms, and a bridging bond; each R₃ is independently selected from the group consisting of hydrogen and organic groups containing from 1 to about 12 carbon atoms; a is an integer from 4 to about 16; and b is an integer from 0 to about 12; and optionally including a bridge, formed by the selection of two of said bridging bonds, the bridge having 0 to about 6 carbon atoms between the bridging ring members; said polymer having been crosslinked. Also provided are vulcanizable compositions of matter, vulcanizates, and tires of the functionalized polymers.

25 Claims, No Drawings

pyrrolidine, which may be generated by at least two exemplary routes as is also discussed above: 1) by the reaction of a mixture of one equivalent of, for example, 2-(2-chloroethyl)-1-methyl pyrrolidine with about two atom equivalents of lithium metal; or 2) 2-(2-lithioethyl)-1-methyl pyrrolidine wherein 2-(2-chloroethyl)-1-methyl pyrrolidine is treated with two equivalents of t-butyllithium. The reactions are preferably performed in hexanes, cyclohexane, benzene, or mixtures thereof.

For greatest stability, the initiator precursors employed in the present invention are usually handled as their hydrohalide or hydro-hydrogen sulfate salts, which are treated with base just prior to their use in forming the initiators. In order to liberate the free halo organo amines, This can be explained according to the following exemplary reaction.



The amino alkyl lithium reagents of the invention may be formed in a solvent or solvent mixture, and then transferred to another solvent or solvent mixture for use in a polymerization reaction.

The initiators of this invention may optionally be treated with from about one to 500 equivalents of a monomer such as butadiene or isoprene, before the main (co) polymerization charge is made, although this is not required. Polymers according to the invention can be prepared with a relatively narrow molecular weight range distribution, with a substantial fraction of living C—Li chain ends adaptable to further functionalization or coupling, being obtained.

The initiator formation, polymerization, and coupling and/or termination may be performed in one reaction vessel, or second or third reactor vessels, or transfer lines from the original reactor can be used, by introducing the preformed initiator to the monomer mixture, or vice-versa. Polymerization and post-treatment conditions should be used that avoid the introduction of air and/or protic or other reactive contaminants, such as moisture, etc., and prolonged heating or storage at excessive temperatures should be avoided unless the live ends are stabilized. Moderate temperatures (from about 0° C. to about 100° C.) are preferred for the polymerizations and the terminations, although higher or lower temperatures may be used. Polymerization and post-treatment temperatures of from about 30° C. to 70° C. are especially preferred. The polymerization time may vary from a few minutes to days, depending on the temperature, solvent and presence of any donor solvent, the monomer structures, and the molecular weight desired.

Any suitable method for isolation of the terminated rubber or fluid may be used, for example: quenching with water, steam, an acid or an alcohol (these may be introduced during the desolventization step), and desolventization by drum drying, coagulation in alcohol, water or steam, extruder drying, vacuum drying, spray drying or any combination thereof. Desolventization by drum-drying, coagulation in alcohol, steam or hot water desolventization, extruder drying, vacuum drying, spray drying or combinations thereof are preferred. An antioxidant and/or antiozonant

compound is usually added to the polymer or polymer cement at or before this stage. In most of the experimental examples of this invention, alcohol coagulation followed by drum-drying or vacuum drying were used.

Upon drying, the elastomers are compounded in a carbon black-filled test stock (see Low-Oil Test Recipe, TABLE II), and the physical properties determined in comparison to those of related base polymers without the modifications. In practice, a wide variety of compounding recipes may be used to give favorable results with this invention, although hysteresis properties may vary from formulation to formulation, depending on the type and amount of carbon black and oil used, and so on. Certain other fillers, such as silica or hydrated silica may also be used. Furthermore, the polymers made with the initiators of this invention may be combined in proportions of 20 to 100 percent by weight with 80 to 0 percent by weight of other polymers to give elastomeric compositions with reduced hysteresis loss characteristics. The low molecular weight products made from the initiators of this invention may be used at low levels to influence the properties of mixtures with other fluids and/or particulates.

TABLE II

LOW-OIL TEST FORMULATION FOR EVALUATION OF HYSTERESIS

Ingredient	Mix Order	Parts per Hundred Parts of Rubber
Polymer	1	100
Naphthenic oil	2	10
Carbon black, N-351	3	55
ZnO	4	3
Antioxidant	5	1
Wax blend	6	2
Total Masterbatch:		171
Stearic acid		2
Sulfur		1.5
Accelerator		1
Total Final:		175.5
Masterbatch: 145°-155° C., 60 RPM		
(drop after 5 min, @ 155°-175° C.)		
Final: 77° to 95° C., 40 RPM		

EXAMPLE 1

A "one pot" preparation of 2-(2-lithioethyl)-1-methylpyrrolidine

2-(2-chloroethyl)-1-methylpyrrolidine was dissolved in cyclohexane and reacted with about two molar equivalents of t-butyllithium in pentane in an inert atmosphere including argon or nitrogen. The resulting mixture was agitated gently at room temperature for about an hour. The mixture was allowed to stand overnight and used to initiate the polymerization of butadiene and styrene as described in the following examples.

EXAMPLE 2

A "one pot" preparation of 3-lithiomethyl-1-methylpiperidine

Following the general procedure set forth in Example 1 hereinabove, 3-lithiomethyl-1-methylpiperidine was prepared from 3-chloromethyl-1-methylpiperidine.

EXAMPLE 3

Polymerization of styrene/butadiene mixtures using 2-(2-lithioethyl)-1-methylpyrrolidine

A polymerization was run using the initiator solution prepared according to Example 1 hereinabove, TABLE III.

(19) **United States**(12) **Patent Application Publication**
VOLKMANN et al.(10) Pub. No.: **US 2001/0007873 A1**(43) Pub. Date: **Jul. 12, 2001**(54) **2-AMINO-6-(2-SUBSTITUTED-4-PHENOXY)-
SUBSTITUTED-PYRIDINES**(76) Inventors: **ROBERT A. VOLKMANN, MYSTIC,
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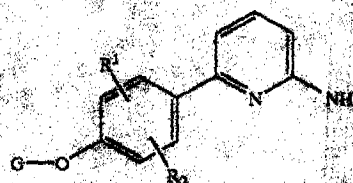
(*) Notice: This is a publication of a continued prosecution application (CPA) filed under 37 CFR 1.53(d).

(21) Appl. No.: **09/127,158**(22) Filed: **Jul. 31, 1998****Related U.S. Application Data**

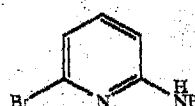
(63) Continuation-in-part of application No. PCT/IB98/00112, filed on Jan. 29, 1998. Non-provisional of provisional application No. 60/037,533, filed on Feb. 10, 1997.

Publication Classification(51) Int. Cl.⁷ **C07D 211/56; C07D 211/92;****C07D 211/84; A61K 31/44**(52) U.S. Cl. **514/329; 546/311; 546/223;****546/304; 514/352**(57) **ABSTRACT**

This present invention relates to compounds of the formula

wherein G, R¹ and R² are defined as in the specification; to pharmaceutical compositions containing them and to their use in the treatment and prevention of central nervous system and other disorders.

ture from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature, yields the corresponding compound of formula VIII. Alternatively, the reactant of formula VII can be replaced with another compound of the formula

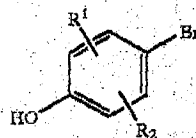


VIIA

[0044] wherein P is a nitrogen protecting group such as trityl, acetyl, benzyl, trimethylacetyl, t-butoxycarbonyl, benzyloxycarbonyl, trichloroethyloxycarbonyl or another appropriate nitrogen protecting group and wherein the hydrogen that is bonded to the protected nitrogen is absent when P is a protecting group that forms a ring with the protected nitrogen, as in the case of P=2,5-dimethylpyrrolyl. Such protecting groups are well known to those of skill in the art. The above compounds of the formula VIIA are either commercially available, known in the scientific literature or easily obtaining using well known methods and reagents.

[0045] The benzyl substituent can be removed from the compound of formula VIII by reacting such compound with ammonium formate in water or a lower alcohol solvent, or in a mixture of one or more of these solvents, at a temperature from about room temperature to about the reflux temperature of the reaction mixture. This reaction is preferably carried out at the reflux temperature in the presence of about 20% palladium hydroxide on carbon. The resulting compound of formula IX is then converted into the desired compound of formula IA by reacting it with hydroxylamine in a solvent selected from water, lower alcohols and mixtures of these solvents, at a temperature from about room temperature to about the reflux temperature of the solvent, preferably at about the reflux temperature.

[0046] The procedure of Scheme 1 can also be used to make compounds of the formula I wherein R¹ and R² are other than as specified above and depicted in the scheme. This can be accomplished by using a compound of the formula



IV'

[0047] as the starting material and then carrying out the series of reactions, as described above, that are represented in Scheme 1 as reactions IV→V→VI→VII→VIII IX→IA.

[0048] Scheme 2 illustrates a method for preparing compounds of the formula I wherein G is hydrogen into the corresponding compounds of formula I wherein G is other than hydrogen.

[0049] Referring to Scheme 2, a compound of the formula IA can be converted into the corresponding compound of formula IC by reacting it with the compound of the formula

GX, wherein X is iodo, chloro, or bromo, and G is CH₂CH₂NR³R⁴, and potassium carbonate in either dimethylformamide (DMF) or acetone at a temperature from about room temperature to about the reflux temperature of the mixture, preferably at about the reflux temperature. Compounds of the formulae IC can also be formed, as illustrated in Scheme 2, as by first preparing the corresponding compounds of formula IB and then converting them, if so desired, into the corresponding compounds of formula IC. Compounds of formula IB can be formed by reacting the corresponding compounds of formula IA with a compound of the formula GX, wherein X is defined as above and G is CH₂C(=O)NR³R⁴, and potassium carbonate, in either DMF or acetone, at a temperature from about room temperature to about the reflux temperature of the reaction mixture. This reaction also is preferably carried out at about the reflux temperature.

[0050] The resulting compounds of formula of IB can be converted into the corresponding compounds of formula IC by reacting them with lithium aluminum hydride and aluminum chloride in a THF solvent, or with borane in THF. Other aluminum hydride reducing agents can also be used, such as diisobutyl aluminum hydride. Diborane can also be used. This reaction is generally carried out at temperatures ranging from room temperature to about the reflux temperature of the reaction mixture, and is preferably carried out at the reflux temperature. Other appropriate solvents include other organic ethers such as ethyl ether, dioxane and glyme, THF is preferred solvent.

[0051] Scheme 3 illustrates how certain compounds of the formula I having different substituents R¹ and R² than are depicted in the processes of Scheme 1 can be prepared. Such compounds are prepared by a process similar to that depicted in Scheme 1, with the exception that the processes of Scheme 1 involved in the synthesis of compound VI are replaced with those depicted in Scheme 3. Specifically, when R² is hydrogen and R¹ is fluoro at the ortho position, the compound of formula X is converted to the corresponding phenylboronic acid in a manner analogous to the conversion of compounds of the formula V into those of the formula VI in Scheme 1. The resulting phenylboronic acid derivative is referred to in Scheme 3 as compound VIA. Similarly, as shown in Scheme 3, compounds of the formula I wherein R¹ and R² are both methyl and are both at an ortho position relative to the pyridine ring, may be prepared by converting the compound of formula XI, as shown in Scheme 3, into the corresponding phenylboronic acid derivative designated as compound VIB, in a manner analogous to the conversion of compounds of formula V into those of the formula VI in Scheme 1. The compounds of formulas VIA and VIB can then be transformed into the desired corresponding compounds of the formula I using procedures analogous to those shown in Scheme 1.

[0052] Scheme 4 exemplifies methods of preparing compounds of the formula I wherein G is NR³R⁴ and NR³R⁴ forms an N-methylpyrrolin-2-yl ring. Compounds of the formula I wherein G is NR³R⁴ and NR³R⁴ forms other nitrogen containing rings can be prepared in an analogous fashion. Referring to Scheme 4, the compound of formula ID is allowed to react with 3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester to form the compound of formula XII. Other nitrogen protecting groups such as -C(=O)OCH₂C₆H₅ and COOR (wherein R is benzyl, phenyl, t-butyl or a similar group) can be used to protect the pyrrolidine nitrogen. Also, the mesylate leaving group can be replaced with another appropriate leaving group. Prefer-

United States Patent [19]

Nakano et al.

[11] Patent Number: 5,276,041

[45] Date of Patent: Jan. 4, 1994

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[21] Appl. No.: 972,306

[22] Filed: Nov. 5, 1992

[30] Foreign Application Priority Data

Nov. 8, 1991 [JP] Japan 3-321067

[51] Int. Cl.³ C07D 401/04; A61K 31/47

[52] U.S. Cl. 514/314; 546/156

[58] Field of Search 546/156; 514/314

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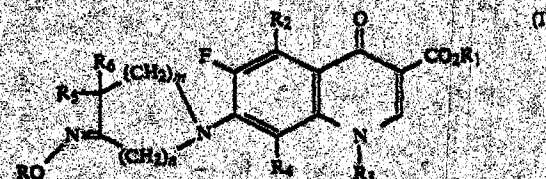
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isms".

Primary Examiner—David B. Springer
Attorney, Agent, or Firm—Oblon, Spivak, McClelland,
Maier & Neustadt

[57] ABSTRACT

An oxime derivative of the formula:



wherein R is a hydrogen atom or a C₁₋₅ alkyl group, R₁ is a hydrogen atom, a C₁₋₅ alkyl group or a carboxyl-protecting group, R₂ is a hydrogen atom, a halogen atom, a hydroxyl group or an amino group, R₃ is a C₃₋₇ cycloalkyl group, R₄ is a hydrogen atom, a halogen atom or a C₁₋₄ alkoxy group, each of R₅ and R₆ which may be the same or different, is a hydrogen atom or a C₁₋₅ alkyl group, or R₅ and R₆ together represent a C₂₋₄ alkylene group which forms together with the adjacent carbon atom a C₃₋₅ ring, provided that when R₂ is a hydrogen atom, R₄ is a C₁₋₄ alkoxy group, m is an integer of 0 or 1, and n is an integer of from 1 to 3; or its pharmaceutically acceptable salt.

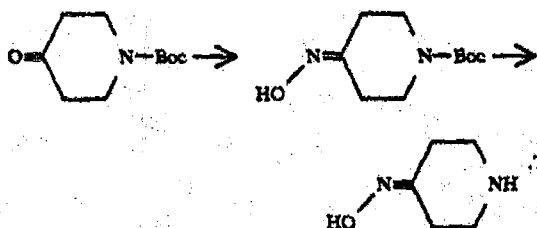
12 Claims, No Drawings

(DMSO- d_6) or deuterated chloroform ($CDCl_3$) solution, and the δ value was shown by ppm. The MS spectrum was measured by a spectrometer of QP1000EX Model (Shimadzu). The melting point was measured by a fine melting point measuring apparatus (manufactured by Yanagimoto) without correction.

REFERENCE EXAMPLE 1

4-hydroxyiminopiperidine trifluoroacetate

The above identified compound can be prepared in accordance with the following formulas.



15.5 g (77.6 mmol) of N-Boc-4-piperidone was refluxed for one hour in methanol in the presence of 7.0 g (100.8 mmol) of hydroxylamine hydrochloride and 14.1 ml (100.8 mmol) of triethylamine. Then, methanol was distilled off, and the residue was thoroughly washed with water in chloroform. The chloroform layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to give 10.6 g of N-Boc-4-hydroxyiminopiperidine as white powder.

Melting point: 92°-93° C.

MS(M/Z): 114(M⁺-Boc), 97(M⁺-OH), 85, 69, 56

¹H-NMR δ ($CDCl_3$): 1.48(9H,s), 2.32-2.37(2H,m), 2.60-2.64(2H,m), 3.50-3.57(4H,m).

Then, 10.6 g (49.5 mmol) of the above N-Boc-4-hydroxyiminopiperidine was gradually added into 80 ml of trifluoroacetic acid under cooling with ice, and the mixture was stirred at room temperature for 3 minutes. Trifluoroacetic acid was distilled off, and diethyl ether was added to the residue to give 11.0 g of the desired product as colorless powdery crystals.

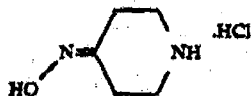
Melting point: 187°-190° C.

MS(M/Z): 114(M⁺-Boc), 97(M⁺-OH), 69.

¹H-NMR δ (DMSO- d_6): 2.44-2.48(2H,m), 2.67-2.71(2H,m), 3.12-3.23(4H,m), 9.20(2H,s), 10.81(1H,s).

REFERENCE EXAMPLE 2

4-hydroxyiminopiperidine hydrochloride



1.54 g (10.0 mmol) of 4-piperidone hydrochloride monohydrate was refluxed for one hour in 30 ml of methanol in the presence of 0.70 g (10.0 mmol) of hydroxylamine hydrochloride and 0.82 g (10.0 mmol) of sodium acetate. Then, methanol was distilled off, and the precipitate thereby formed was washed with isopropanol, and the mother liquor was distilled under reduced pressure. Diethyl ether was added to the residue thereby obtained for crystallization to give 0.45 g of the desired product as colorless powder.

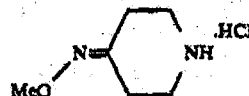
Melting point: 217°-220° C. (Decomposed).

MS(M/Z): 114(M⁺), 97(M⁺-OH), 85.

¹H-NMR δ (DMSO- d_6): 2.46-2.52(2H,m), 2.69-2.73(2H,m), 3.08-3.20(4H,m), 9.45(2H,s), 10.78(1H,s).

REFERENCE EXAMPLE 3

4-methoxyiminopiperidine hydrochloride



1.59 g of the desired product was obtained as colorless powder in the same manner as in Reference Example 2 except that 0.84 g (10.0 mmol) of O-methylhydroxylamine hydrochloride was used.

Melting point: 138°-140° C.

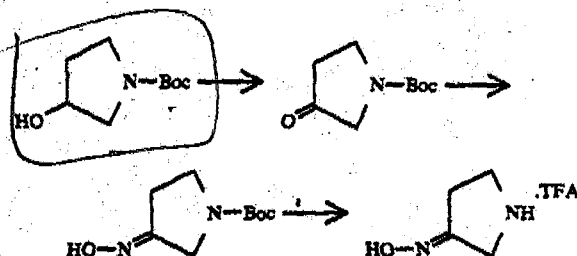
MS(M/Z): 128(M⁺), 97(M⁺-OMe), 82, 68, 56.

¹H-NMR δ ($CDCl_3$): 2.69-2.73(2H,m), 2.92-2.97(2H,m), 3.28-3.35(4H,m), 3.85(3H,s), 9.90(2H,s).

REFERENCE EXAMPLE 4

3-hydroxyiminopyrrolidine trifluoroacetate

The above-identified compound was prepared in accordance with the following formulas.



A solution of 5.76 ml of oxalyl chloride in 150 ml of methylene chloride was cooled to -70° C., and a solution of 9.37 ml of DMSO in 36 ml of methylene chloride and a solution of 11.23 g of N-Boc-3-pyrrolidinol in 84 ml of methylene chloride were sequentially added thereto. The mixture was stirred at -70° C. for 15 minutes, and 41.8 ml of triethylamine was added thereto. The mixture was gradually heated to room temperature, and then methylene chloride was distilled off. The obtained precipitate was washed with diethyl ether, and the mother liquor was subjected to silica gel column chromatography with a hexane-diethyl ether-type developer. The eluate was distilled under reduced pressure, and the residue was refluxed for one hour in methanol together with 4.82 g of hydroxylamine hydrochloride and 9.67 ml of triethylamine. Methanol was distilled off, and the precipitate was removed. The mother liquor was washed with water in chloroform. The chloroform layer was dried over anhydrous magnesium sulfate and then distilled under reduced pressure to give 9.23 g of N-Boc-3-hydroxyiminopyrrolidine.

Melting point: 116° C.

MS(M/Z): 200(M⁺), 145, 127, 111, 100, 83, 57.

¹H-NMR δ ($CDCl_3$): 1.48(9H,s), 2.67-2.72(2H,m), 3.60(2H), 4.14(2H,s), 8.68(1H,s)

Then, 4.6 g of the desired product was obtained as colorless powder in the same manner as in Reference



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409(19) **United States**(12) **Patent Application Publication** (10) Pub. No.: **US 2003/0139450 A1**

Yu et al.

(43) Pub. Date: **Jul. 24, 2003**(54) **SUBSTITUTED BENZIMIDAZOLE
ANTIVIRAL AGENTS****Related U.S. Application Data**(76) Inventors: **Kuo-Long Yu, Hamden, CT (US); Rita
Lee Civilello, Killingworth, CT (US);
Mark R. Krystal, Westport, CT (US);
Kathleen F. Kadow, Wallingford, CT
(US); Nicholas A. Meanwell, East
Hampton, CT (US)**(63) Continuation of application No. 09/354,958, filed on
Jul. 16, 1999, now abandoned.(60) Provisional application No. 60/093,387, filed on Jul.
20, 1998.**Publication Classification**

Correspondence Address:

STEPHEN B. DAVIS**BRISTOL-MYERS SQUIBB COMPANY****PATENT DEPARTMENT****P O BOX 4000****PRINCETON, NJ 08543-4000 (US)**(51) Int. Cl.⁷ **A61K 31/454; C07D 43/14;**
A61K 31/4192(52) U.S. Cl. **514/322; 514/394; 546/199;**
548/256(57) **ABSTRACT**(21) Appl. No.: **10/289,829**(22) Filed: **Nov. 7, 2002**

The present invention concerns antiviral compounds, their compositions, and use in the treatment of viral infections. More particularly, the invention provides benzimidazole derivatives for the treatment of respiratory syncytial virus infection.

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410

hydride in tetrahydrofuran to give the title compound in 38% yield:

[0158] IR(KBr, cm^{-1}): 3412, 2929, 2465, 1800, 1615, 1520, 1457.

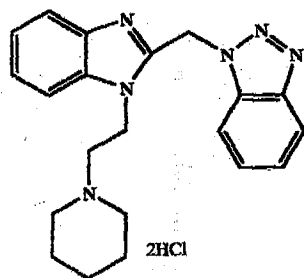
[0159] ^1H NMR (CD_3OD) δ 2.13-2.26 (m, 4H), 3.64-3.85 (m, 6H), 5.05-5.11 (m, 2H), 6.59 (s, 2H), 7.49-7.76 (m, 5H), 7.89 (d, $J=7.9$ Hz, 1H), 8.02 (d, $J=8.4$ Hz, 1H), 8.09 (d, $J=8.7$ Hz, 1H).

[0160] MS m/e 347 (MH^+).

EXAMPLE 15

1-(2-Piperidin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl-1H-benzotriazole Dihydrochloride

[0161]



[0162] The general coupling procedure was applied using 1-(2-chloroethyl)-piperidine hydrochloride and sodium hydride in tetrahydrofuran to give the title compound in 10% yield:

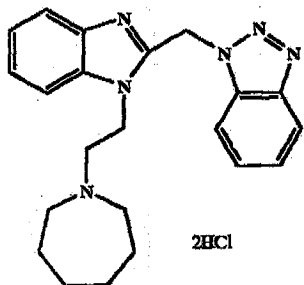
[0163] ^1H NMR (CD_3OD) δ 1.95-2.15 (m, 6H), 3.10-3.20 (m, 2H), 3.50-3.80 (m, 4H), 5.10-5.20 (m, 2H), 6.62 (bs, 2H), 7.50-7.76 (m, 5H), 7.93 (d, $J=8.0$ Hz, 1H), 8.02 (d, $J=8.4$ Hz, 1H), 8.10 (d, $J=8.4$ Hz, 1H).

[0164] MS m/e 361 (MH^+).

EXAMPLE 16

1-(2-Azepin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl-1H-benzotriazole Dihydrochloride

[0165]



[0166] The general coupling procedure was applied using 2-(hexamethyleneimino)ethyl chloride hydrochloride and

sodium hydride in tetrahydrofuran to give the title compound in 27% yield:

[0167] IR(KBr, cm^{-1}): 3430, 2928, 2472, 1727, 1455, 1362.

[0168] ^1H NMR (CD_3OD) δ 1.82 (bs, 4H), 2.04 (bs, 4H), 3.42-3.44 (m, 2H), 3.56-3.74 (m, 4H), 5.18-5.23 (m, 2H), 6.67 (s, 2H), 7.52-7.77 (m, 5H), 8.00 (d, $J=8.4$ Hz, 1H), 8.04 (d, $J=8.4$ Hz, 1H), 8.11 (d, $J=8.4$ Hz, 1H).

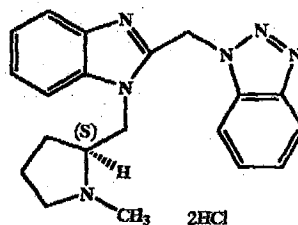
[0169] MS m/e 375 (MH^+).

[0170] Anal. Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_6 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$: C, 56.16; H, 7.23; N, 13.10 Found: C, 56.28; H, 6.86; N, 13.27.

EXAMPLE 17

(S)-1-[1-Methyl-2-pyrrolidin-2-yl-methyl]-1H-benzimidazol-2-ylmethyl-1H-benzotriazole Dihydrochloride

[0171]



[0172] The required (S)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride was prepared according to the procedure reported by S. D. Kimball et al, *J. Med. Chem.* 1992, 35, 780-793. The general coupling procedure was applied using sodium hydride as a base in *N,N*-dimethylformamide to give the title compound as a dihydrochloride salt (17% yield):

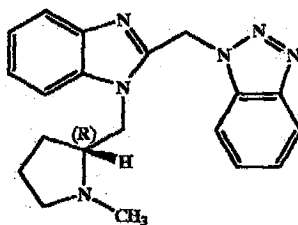
[0173] ^1H NMR (CD_3OD) δ 2.00-2.30 (m, 4H), 3.29 (s, 3H), 3.56-3.90 (m, 2H), 4.20-4.30 (m, 1H), 5.10 (dd, $J=9.3$, 15.1 Hz, 1H), 5.30 (dd, $J=5.7$, 15.1 Hz, 1H), 6.76 (bs, 2H), 7.52-7.77 (m, 6H), 8.01-8.13 (m, 2H).

[0174] MS m/e 347 (MH^+).

EXAMPLE 18

(R)-1-[1-Methyl-2-pyrrolidin-2-yl-methyl]-1H-benzimidazol-2-ylmethyl-1H-benzotriazole

[0175]



[0176] The required starting material (R)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride was prepared

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(51) International Patent Classification⁷: A61K 31/404,
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(21) International Application Number: PCT/US03/02692

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
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(84) Designated States (*regional*): ARIPO patent (GH, GM,
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03/068221 A1

(54) Title: INDOLE, AZAINDOLE AND RELATED HETEROCYCLIC PYRROLIDINE DERIVATIVES

(57) Abstract: This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the invention is concerned with amido niverazine derivatives. These compounds possess unique antiviral

Solvent B: 10% H₂O / 90% MeOH / 0.1% Trifluoroacetic Acid

Compounds purified by preparative HPLC were diluted in MeOH (1.2 mL) and purified using the following methods on a Shimadzu LC-10A automated preparative HPLC system or on a Shimadzu LC-8A automated preparative HPLC system with detector (SPD-10AV UV-VIS) wavelength and solvent systems (A and B) the same as above.

Preparative HPLC Method (i.e., compound purification)

Purification Method: Initial gradient (40% B, 60% A) ramp to final gradient (100% B, 0% A) over 20 minutes, hold for 3 minutes (100% B, 0% A)

Solvent A: 10% MeOH / 90% H₂O / 0.1% Trifluoroacetic Acid

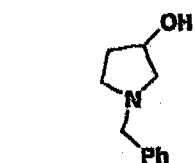
Solvent B: 10% H₂O / 90% MeOH / 0.1% Trifluoroacetic Acid

Column: YMC C18 S5 20x100 mm column

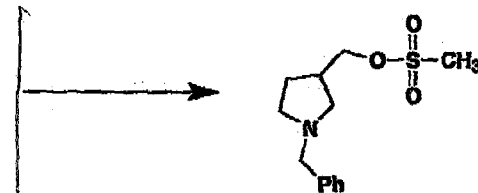
Detector Wavelength: 220 nm

Intermediate 1

Methanesulfonic acid 1-benzyl-pyrrolidin-3-ylmethyl ester



1-Benzyl-pyrrolidin-3-ol



Methanesulfonic acid 1-benzyl-pyrrolidin-3-ylmethyl ester



US006214832B1

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

(10) Patent No.: **US 6,214,832 B1**
(45) Date of Patent: **Apr. 10, 2001**

(54) **BIS-PIPERIDINYL-PYRIMIDIN-2-ONES AS
ALPHA 1A ADRENERGIC RECEPTOR
ANTAGONISTS**

(75) Inventors: **Michael A. Patane, Harleysville; Mark
G. Bock, Hatfield, both of PA (US)**

(73) Assignee: **Merck & Co., Inc., Rahway, NJ (US)**

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

(21) Appl. No.: **09/099,660**

(22) Filed: **Jun. 17, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/050,126, filed on Jun. 18,
1997.

(51) Int. Cl.⁷ **C01D 461/14; C07D 413/14;
A61K 31/513; A61K 31/519; A61P 31/08**

(52) U.S. Cl. **514/258; 514/259; 514/274;
544/278; 544/280; 544/284; 544/316**

(58) Field of Search **544/278, 280,
544/284, 316; 514/274, 258, 259**

(56) **References Cited**

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(List continued on next page.)

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(List continued on next page.)

Primary Examiner—Mukund J. Shah

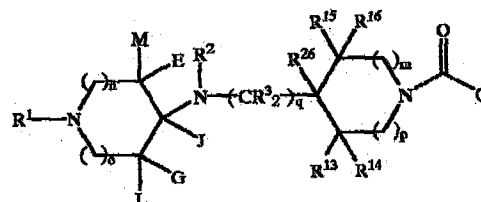
Assistant Examiner—Thomas McKenzie

(74) Attorney, Agent, or Firm—Catherine D. Fitch;
Kenneth R. Walton; Melvin Winokur

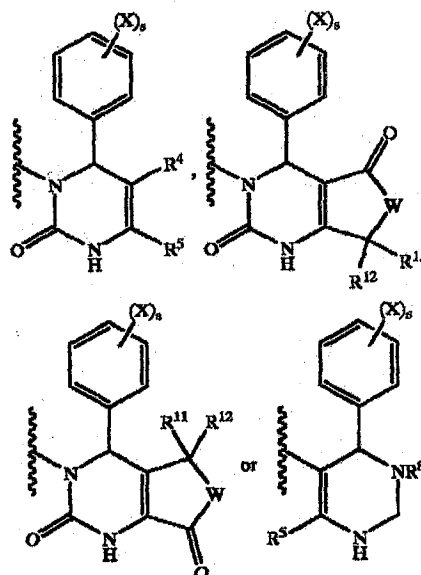
(57) **ABSTRACT**

Pyrimidinone, oxazolidinone, and (alkyl)aryl derivatives, their synthesis, and their use as alpha 1a adrenergic receptor antagonists are disclosed. One application of these compounds is in the treatment of benign prostatic hyperplasia. These compounds are selective in their ability to relax smooth muscle tissue enriched in the alpha 1a receptor subtypes without at the same time inducing hypertension. One

Therefore, one utility of the instant compounds is to provide acute relief to males suffering from benign prostatic hyperplasia, by permitting less hindered urine flow. Another utility of the instant compounds is provided by combination with a human 5-alpha reductase inhibitory compound, such that both acute and chronic relief from the effects of benign prostatic hyperplasia are achieved. Among the disclosed derivatives are piperidinyl aminoalkylpiperidinyl pyrimidinones, including those of formula:



wherein Q is



R¹ is selected from unsubstituted, mono- or poly-substituted phenyl wherein the substituents on the phenyl are independently selected from halogen, CF₃, cyano, nitro, N(R⁷)₂, NR⁷COR¹⁹, NR⁷CON(R¹⁹)₂, NR⁷SO₂R¹⁹, NR⁷SO₂N(R¹⁹)₂, OR⁶, (CH₂)₀₋₄CO₂R⁷, (CH₂)₀₋₄CON(R⁷)₂, or C₁₋₄ alkyl; or unsubstituted, mono- or poly-substituted pyridyl, pyrazinyl, thienyl, thiazolyl, furanyl, quinazolinyl or naphthyl wherein the substituents on the pyridyl, pyrazinyl, thienyl, thiazolyl, furanyl, quinazolinyl or naphthyl are independently selected from CF₃, cyano, nitro, amino, (CH₂)₀₋₄CO₂R⁷, (CH₂)₀₋₄CON(R⁷)₂, (CH₂)₀₋₄SO₂N(R⁷)₂, (CH₂)₀₋₄SO₂R⁶, phenyl, OR⁶, halogen, C₁₋₄ alkyl or C₃₋₈ cycloalkyl;

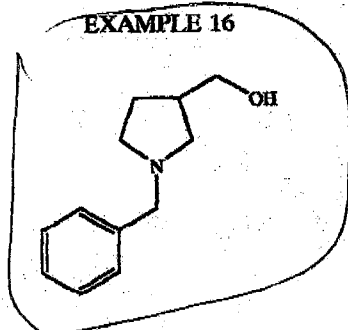
m and p are each integers from zero to two, wherein the sum m+p=2; n and o are each integers from zero to two, wherein the sum n+o=2; q is an integer of from zero to three, provided that when q is zero, R²⁶ is hydrogen; s is an integer of from zero to four; and

E, G, J, L, M, W, X, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁹ and R²⁶ are defined herein.

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Anal. Calcd for $C_{20}H_{24}N_2O_2$. 0.05 $CHCl_3$ +0.60 H_2O :
C=74.01, H=7.54, N=11.89. Found: C=74.06, H=7.51,
N=11.57. MS (FAB) 455 (M+1)

EXAMPLE 16

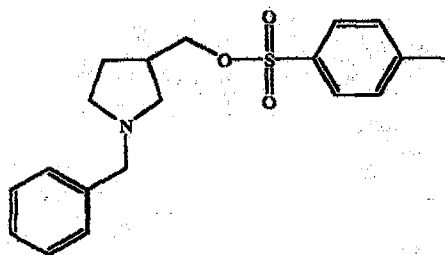


N-1-Benzyl-3-hydroxymethyl pyrrolidine (25)

A solution of Methyl 1-benzyl-5-oxo-3-pyrrolidinecarboxylate (24) (10.0 g, 42.8 mmol) in 175 ml of dichloromethane was added dropwise to a cooled solution of 1.5 M DIBAL-H (143 mL, 214 mmol) at $-78^\circ C$. After stirring at room temperature for 48 hours the solution was cooled to $0^\circ C$ and added 25 mL methanol dropwise. The solution was added 250 mL saturated aqueous Rochelle salts and extracted with chloroform. The combined organics were dried over $MgSO_4$, filtered and the solvents removed in vacuo to give the crude alcohol. The crude product was purified by chromatography on silica gel (7% MeOH/ $CHCl_3$) to afford the title compound.

^1H NMR ($CDCl_3$, 400 MHz) 7.33–7.24 (m, 5H), 3.70–3.66 (m, 1H), 3.59–3.48 (m, 4H), 2.86–2.80 (m, 1H), 2.66–2.63 (d, 1H), 2.51–2.47 (t, 1H), 2.34–2.28 (m, 2H), 2.05–1.96 (m, 1H), 1.75–1.67 (m, 1H).

EXAMPLE 17



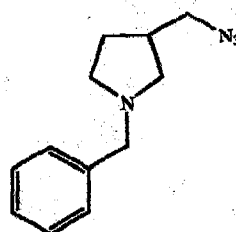
Toluene-4-sulfonic acid 1-benzyl-pyrrolidin-3-methyl ester (26)

To a cooled ($0^\circ C$) solution of 25 (1.0 g, 5.2 mmol) in 100 ml of chloroform was added para-toluenesulfonic anhydride (2.5 g, 7.8 mmol), and triethylamine (2.1 ml, 15 mmol). The resulting solution was stirred at room temperature for 24 hours. The solution was subsequently washed with water, dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude material was purified by chromatography on silica gel to afford the desired product.

^1H NMR ($CDCl_3$, 400 MHz) 7.78–7.76 (d, 2H), 7.33–7.23 (m, 7H), 3.94–3.92 (m, 2H), 3.53 (s, 2H), 2.58–2.43 (m, 6H), 2.27–2.24 (m, 1H), 1.97–1.88 (m, 1H),

38

EXAMPLE 18

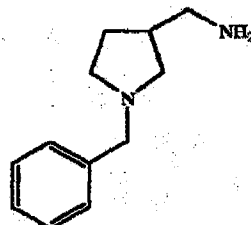


N-1-Benzyl-3-azidomethyl pyrrolidine (27)

A solution of 26 (1.26 g, 3.64 mmol) and sodium azide (0.474 g, 7.29 mmol) in 100 ml of DMF was heated to $70^\circ C$ for 24 hours. After cooling to room temperature the solvent was removed in vacuo and the residue partitioned between chloroform and water. The organics were dried over $MgSO_4$, filtered and the solvent removed in vacuo to afford the azide.

^1H NMR ($CDCl_3$, 400 MHz) 7.34–7.22 (m, 5H), 3.60–3.59 (d, 2H), 3.28–3.26 (m, 2H), 2.70–2.66 (m, 1H), 2.57–2.54 (t, 1H), 2.44–2.38 (m, 2H), 2.31–2.27 (m, 1H), 2.04–1.98 (m, 1H), 1.51–1.45 (m, 1H).

EXAMPLE 19

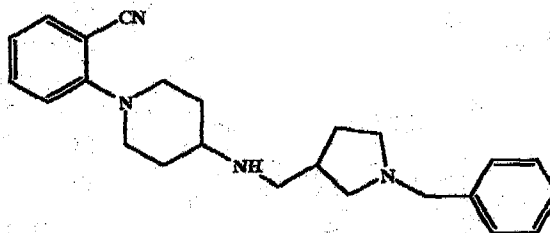


N-1-Benzyl-3-aminomethyl pyrrolidine (28)

A solution of 27 (0.71 g, 3.2 mmol), triphenylphosphine (1.7 g, 6.5 mmol), THF (50 mL), and water (5 mL) was heated to reflux for 24 hours. After cooling to room temperature the solvent was removed in vacuo and the residue purified by chromatography on silica gel (90:9:1 $CHCl_3$:MeOH: NH_4OH) to afford the amine.

^1H NMR ($CDCl_3$, 400 MHz) 7.33–7.22 (m, 5H), 3.60–3.58 (d, 2H), 2.76–2.72 (m, 1H), 2.60–2.58 (m, 3H), 2.52–2.47 (m, 1H), 2.24–2.17 (m, 2H), 2.00–1.95 (m, 1H), 1.48–1.42 (m, 1H), 1.12 (br s, 2H).

EXAMPLE 20



Compound (29)

The title compound was prepared from 28 and 3 using the procedure described for the preparation of 4.

^1H NMR ($CDCl_3$, 400 MHz) 7.54–7.52 (d, 1H),

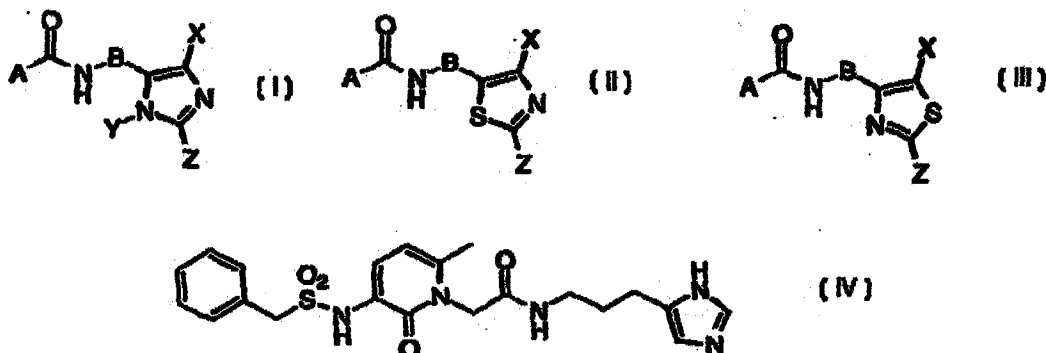
914
220

D10
421
415

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(54) Title: THROMBIN INHIBITORS



(57) Abstract

A compound which inhibits human thrombin and has structure (I) or (II) or (III) and pharmaceutically acceptable salts thereof, wherein compounds such as (IV) are useful for inhibiting formation of blood platelet aggregates in blood in a mammal.

DII
422
416**Step A: 3-Hydroxy-N-t-butoxycarbonylpiperidine**

Di-t-butylidicarbonate (21 g, 96 mmol) was added to a mixture of 3-hydroxypiperidine hydrochloride (12 g, 87 mmol) and triethylamine (24.5 ml, 176 mmol) in methylene chloride (500 ml) at 0°C.

- 5 After stirring for 2 h, the reaction mixture was washed well with water and dried (MgSO₄). Concentration gave the title compound. ¹H NMR (CDCl₃) δ 1.46 (s, 9 H), 1.60-1.89 (m, 4 H), 3.04-3.16 (m, 2 H), 3.52 (br s, 1 H), 3.73 (m, 2 H).

10 Step B: 3-Methanesulfonyloxy-N-t-butoxycarbonylpiperidine

Methanesulfonic anhydride (996 mg, 5.72 mmol) was added to a mixture of 3-hydroxy-N-t-butoxycarbonylpiperidine (959 mg, 4.76 mmol) and triethylamine (0.86 ml, 6.19 mmol) in methylene chloride (30 ml) at 0°C. After stirring for 1 h, the reaction mixture was washed with saturated NaHCO₃ and dried (Na₂SO₄). Concentration gave the title compound. ¹H NMR (CDCl₃) δ 1.46 (s, 9 H), 1.77-2.17 (m, 4 H), 3.05 (s, 3 H), 3.14-3.49 (m, 2 H), 3.62 (m, 2 H), 4.72 (br s, 1 H).

Step C: 3-Azido-N-t-butoxycarbonylpiperidine

- 20 Lithium azide (1.35 g, 27.6 mmol) was added to a solution of 3-methanesulfonyloxy-N-t-butoxycarbonylpiperidine (1.54 g, 5.51 mmol) in DMF (20 ml) and the resulting mixture heated at 60°C for 48 h. Removal of the solvent *in vacuo* and chromatographic purification (3:1 hexane / ethyl acetate) of the residue afforded the title compound. ¹H
- 25 NMR (CDCl₃) δ 1.46 (s, 9 H), 1.75 (m, 2 H), 1.96 (m, 2 H), 3.13 (br s, 1 H), 3.46 (m, 2 H), 3.57 (m, 2 H).

Step D: 3-Amino-N-t-butoxycarbonylpiperidine

- 30 A solution of 3-azido-N-t-butoxycarbonylpiperidine (850 mg) in ethyl acetate (50 ml) was hydrogenated in the presence of 10% Pd/C (550 mg) at atmospheric pressure for 2.5 h. The reaction mixture was then filtered through Celite and the filtrate concentrated *in vacuo* to give the title compound. ¹H NMR (CDCl₃) δ 1.46 (s, 9 H), 1.66-2.05 (m, 4 H), 2.57 (br s, 1 H), 2.78 (m, 4 H), 3.80 (br d, 2 H).
- 35



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United States Patent [19]
D'Ambra et al.[11] **Patent Number:** **5,817,651**
[45] **Date of Patent:** **Oct. 6, 1998**D11
423
417[54] **3-ARYLCARBONYL-1-(C-ATTACHED-N-HETERYL)-1H-INDOLES**[75] **Inventors:** Thomas Edward D'Ambra, North Greenbush; Edward Richard Bacon; Malcolm Rice Bell, both of East Greenbush; Philip Michael Carabateas, Schodack; Michael Allen Elissenstat, West Sand Lake; Virendra Kumar, Colonie; John Peter Mallamo, Kinderhook; Susan Jean Ward, East Greenbush, all of N.Y.[73] **Assignee:** Sanofi, Paris, France[21] **Appl. No.:** 783,161[22] **Filed:** Jan. 14, 1997**Related U.S. Application Data**

[62] Division of Ser. No. 213,777, Mar. 16, 1994, Pat. No. 5,607,933, which is a division of Ser. No. 807,032, Sep. 26, 1991, Pat. No. 5,234,737, which is a division of Ser. No. 484,759, Feb. 26, 1990, Pat. No. 5,068,234.

[51] **Int. Cl.⁶** A01N 43/00; C07D 267/02; C07D 413/00; C07D 401/00[52] **U.S. Cl.** 514/210; 540/544; 544/143; 546/201; 548/491[58] **Field of Search** 514/414, 210, 514/211, 212, 323, 253, 235.2; 540/544, 602; 544/143, 405; 546/201, 277.4; 548/491[56] **References Cited****U.S. PATENT DOCUMENTS**

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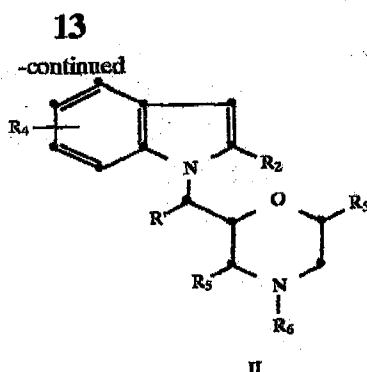
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[57]

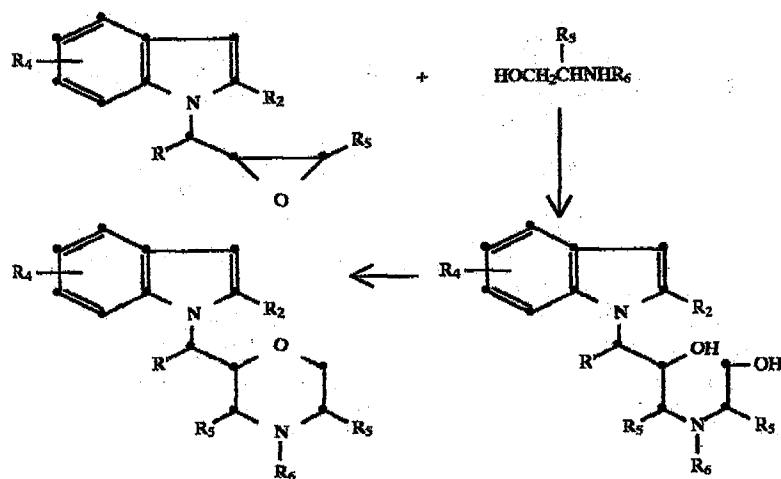
ABSTRACT2-R₂—R₄-substituted-3-R₃—CO-1-[(C-attached-N-heteryl)-(Alk)_n]-1H-indoles useful as analgesic, anti-rheumatic, anti-inflammatory or anti-glaucoma agents.**11 Claims, No Drawings**



where R_2 and R_4 have the meanings given above and R' , R_5 and R_6 are each hydrogen or lower-alkyl.

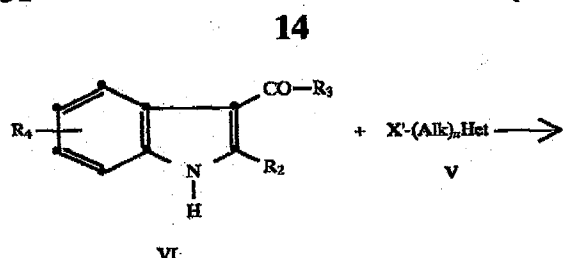
As indicated by the reaction sequence, this method affords a means of preparing compounds of Formula II where Het is 2-morpholinyl with a lower-alkyl group in either or both of the 3- and 6-positions.

A method for the preparation of compounds of Formula II where Het is 2-morpholinyl with a lower-alkyl group in either or both of the 3- and 5-positions involves reaction of a 2- R_2 - R_4 -1-(3- R_5 -2,3-epoxy-1-propyl)-1H-indole prepared as described above with a 2-(N- R_6)-2- R_5 -ethanolamine and reaction of the resulting 2- R_2 - R_4 -substituted-1-[2-hydroxy-3-[N-(2-hydroxy-1- R_5 -ethylamino)-3- R_5 -3-N- R_6]propyl]-1H-indole with a di-lower-alkyl azodicarboxylate in the presence of triphenylphosphine or a tri-lower-alkylphosphine to produce the desired product of Formula II. The cyclization reaction is carried out in an organic solvent inert under the conditions of the reaction, for example MDC, EDC or THF, and is usually exothermic and requires cooling with an external ice bath. The method is illustrated by the reaction sequence:



where R' , R_2 , R_4 , R_5 and R_6 have the meanings given above.

Another approach to the preparation of the final products of Formula I comprises reaction of a 2- R_2 - R_4 -substituted-3-arylcarbonylindole of Formula VI with an appropriate C-attached-[X'-(Alk) $_n$]-N-heterocycle of Formula V using the same conditions described above for the first described method for preparation of the compounds of Formula II. The



where R_2 , R_3 , R_4 , Alk, Het and n have the meanings given above for Formula I, and X' is halogen or toluenesulfonyloxy (tosyloxy).

Under the conditions of the above-described reaction, the halo or tosyloxy (Alk) $_n$ -N-heterocycle sometimes undergoes rearrangement resulting in either ring expansion or ring contraction of the heterocyclic ring. In such cases, the product isolated may consist entirely of the rearranged product or a mixture of the latter and the expected unrearranged product thus necessitating separation of the products by conventional purification procedures such as fractional crystallization or chromatography. For example, we have found that use of 1-methyl-2-chloromethylpiperidine as the alkylating agent results in the formation of compounds where the piperidinylmethyl group undergoes ring expansion to the 1-methyl-3-azepinyl group. On the other hand, in our experience, use of either 1-methyl-3-tosyloxypiperidine or 1-ethyl-3-chloropiperidine as the alkylating agents produces, as the principal products, the compounds where the piperidine ring has undergone ring contraction to the 1-methyl-2-pyrrolidinylmethyl and the 1-ethyl-2-pyrrolidinylmethyl groups, respectively.

Another method for preparing the final products of Formula I comprises reacting a 2- R_2 - R_4 -substituted-3- R_3 -arylcarbonyl-1-lower-alkylsulfonyl- or 1-arylsulfonyl-1H-indole of Formula VII with a hydroxy-(Alk) $_n$ -N-heterocycle

of Formula VIII in the presence of a strong base, for example sodium or potassium hydride or potassium or cesium carbonate in an anhydrous, organic solvent inert under the conditions of the reaction, for example toluene, dioxane, acetonitrile, THF, DMF or DMSO, at temperatures from ambient up to the boiling point of the solvent, in accordance



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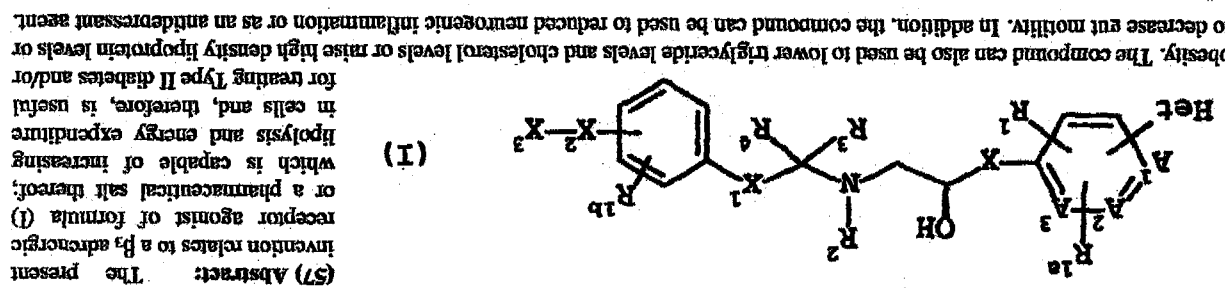
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(54) Title: β_3 ADRENERGIC AGONISTS

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