



No. 06-118158- -00004-0000

Fecha: 2008-06-14 11:34:28 - Del 2020 NULCRACION
PAIS: COLOMBIA - LUG: 378 - PAIS NACIONAL
CATEG: 06-118158- -00004-0000

**FORMULARIO UNICO DE OPOSICION
2000-12**

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OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

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**SOLICITUD
PUBLICADA**

Número del expediente: 06 118.158

Solicitante: SANOFI-AVENTIS

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo:

**PROCEDIMIENTO DE PREPARACIÓN DE DERIVADOS DE N-
PIPERIDIN-1,5-DIFENILPIRAZOL-3- CARBOXAMIDA.**

Gaceta: 583 de 18 de diciembre de 2007, N° de publicación 819.

3

OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: TECNOQUIMICAS S.A., Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: (1) 621.26.31 E-mail: info@reyes-abogados.com Fax: (1) 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial) 16 y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia). Artículo 30 (Reivindicaciones) y artículo 42 (oposiciones) de la Decisión 486 de la Comisión de la Comunidad Andina.

Justificación: Ver Anexo

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Comprobante de pago No

08-22736
08-22746

(Oposición) Fecha

Hoy 14 de 2008

(Prórroga) Fecha

Hoy 14 de 2008

6

Anexos:



Comprobante de pago de la tasa



Poderes, si fuere el caso



Pruebas de los fundamentos de la oposición



Documentos que acrediten el legítimo interés, si fuere el caso



Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas

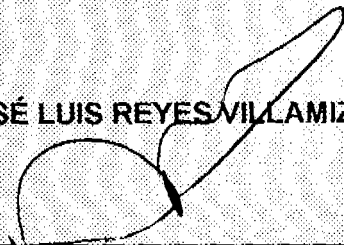


Copia de la oposición para el traslado al solicitante.

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA:



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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 06-118-158

TÍTULO SOLICITADO: "PROCEDIMIENTO DE PREPARACIÓN DE DERIVADOS DE N-PIPERIDIN-1,5-DIFENILPIRAZOL-3-CARBOXAMIDA".

PUBLICACIÓN: Gaceta 583 de 18 Diciembre 2007, N° de publicación 819.

PRIORIDAD: FR 0408111 de 22/07/2004

SOLICITANTE: SANOFI-AVENTIS.

APODERADO: EMILIO FERRERO

TRÁMITE: Presentación de Oposición

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente 06 090.489, por no cumplir con lo dispuesto por los artículos 14, 16 y 18 de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

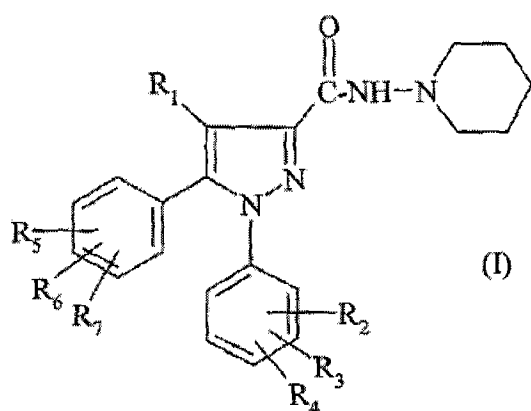
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II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTO DE LA OPOSICIÓN

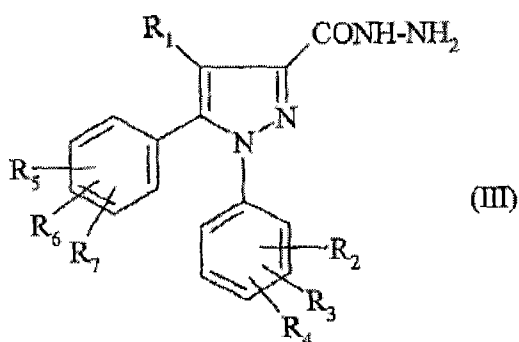
La solicitud en curso, que reivindica un procedimiento de preparación de compuestos de fórmula:



caracterizado porque se hace reaccionar un

derivado de pentano de fórmula: $X-(CH_2)_5-X'$ (II)

En la que X y X' representan cada uno independientemente un átomo de halógeno o un grupo YSo_2- en el que Y representa un grupo alquilo (C1-C4), perfluoroalquilo (C1-C4), fenilo no sustituido o sustituido con un grupo metilo, cloro o nitro, sobre un derivado de pirazol-3-carbohidrazida de fórmula:



carece por completo de los requisitos fundamentales para otorgársele el privilegio de patente de invención, tal y como lo demuestran los siguientes argumentos:

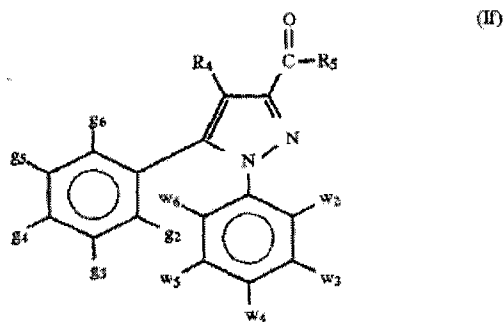
3.1 La solicitud Colombiana en trámite en su capítulo reivindicatorio, específicamente en sus reivindicaciones 1 y 11, expone la obtención de un compuesto que corresponde a rimonabant; dicho compuesto es un antagonista del receptor CB1 cannabinoide y es reconocida su utilidad como un agente anti-obesidad y anoréxico en el estado de la técnica, tal como lo pueden demostrar la publicación internacional WO 03/040105 publicada 15 de Mayo de 2003 y titulada "POLYMORPHOUS FORM OF RIMONABANT, PREPARATION METHOD AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME"; la publicación internacional WO 03/082256 publicada el 09 de octubre de 2003 y titulada "USE OF A CB1 CANNABINOID RECEPTOR ANTAGONIST FOR PRODUCING MEDICAMENTS WHICH ARE USEFUL FOR TREATING SEXUAL BEHAVIOUR PROBLEMS AND/OR FOR IMPROVING SEXUAL PERFORMANCES"; la publicación internacional WO 04/004665 publicada el 15 de enero de 2004 y titulada "SUBSTITUTED HETEROCYCLIC DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTI-OBESITY AGENTS AND METHOD"; la publicación internacional WO 04/009015 publicada el 29 de enero de 2004 y titulada "COMBINATION THERAPY FOR THE TREATMENT OF OBESITY"; la publicación científica publicada en 2002 y titulada "RIMONABANT: SR 141716, SR 141716¹."; y la publicación científica publicada en 2004 y titulada "RIMONABANT REDUCES RISK FACTORS FOR CARDIOVASCULAR DISEASE²"

¹ Rimonabant: SR 141716, SR 141716a. Drugs in R&D, 2002, Vol. 3 Issue 1, p65-66, 2p; (AN 6511695).

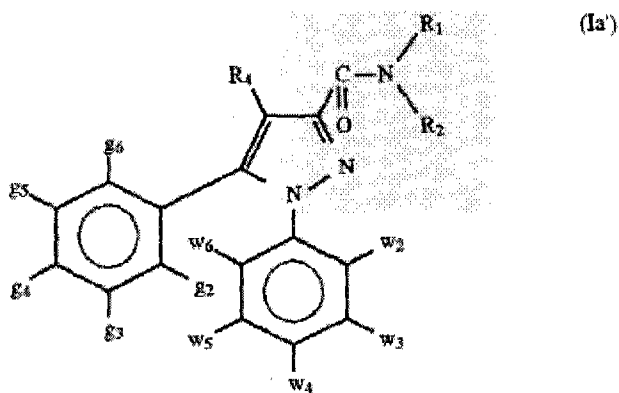
² Rimonabant reduces risk factors for cardiovascular disease. By: Poole, Raewyn. Inpharma Weekly, 3/20/2004 Issue 1429, p7-9, 3p, 2 charts; (AN 16066027).

3.2 La patente americana US 5,624,941 publicada el 29 de abril de 1997 y titulada "PYRAZOLE DERIVATIVES, METHOD OF PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT" revela:

the ketone derivatives of the formula

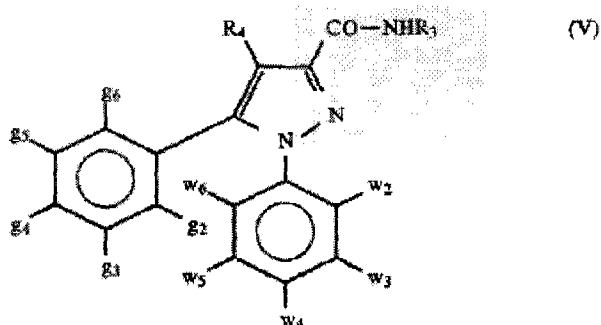


(...)



in which w_2, w_3, w_4, w_5 and w_6, g_2, g_3, g_4, g_5 and g_6 and R_4 are as defined above for (I). R_1 is hydrogen or a (C_1-C_6) -alkyl and R_2 is a non-aromatic C_3-C_{15} carbocyclic radical or a saturated 5- to 8-membered heterocyclic radical selected from 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl and 4-thiomorpholinyl, and their salts, are particularly advantageous.

(...)

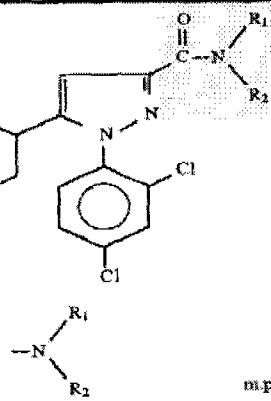
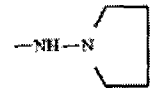
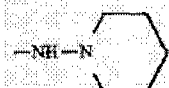
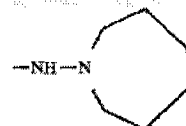


in which w_2, w_3, w_4, w_5 and w_6, g_2, g_3, g_4, g_5 and g_6 and R_4 and R_3 are as defined for (I), to give, by reduction with a metal hydride, the intermediate amines of the formula

(...)

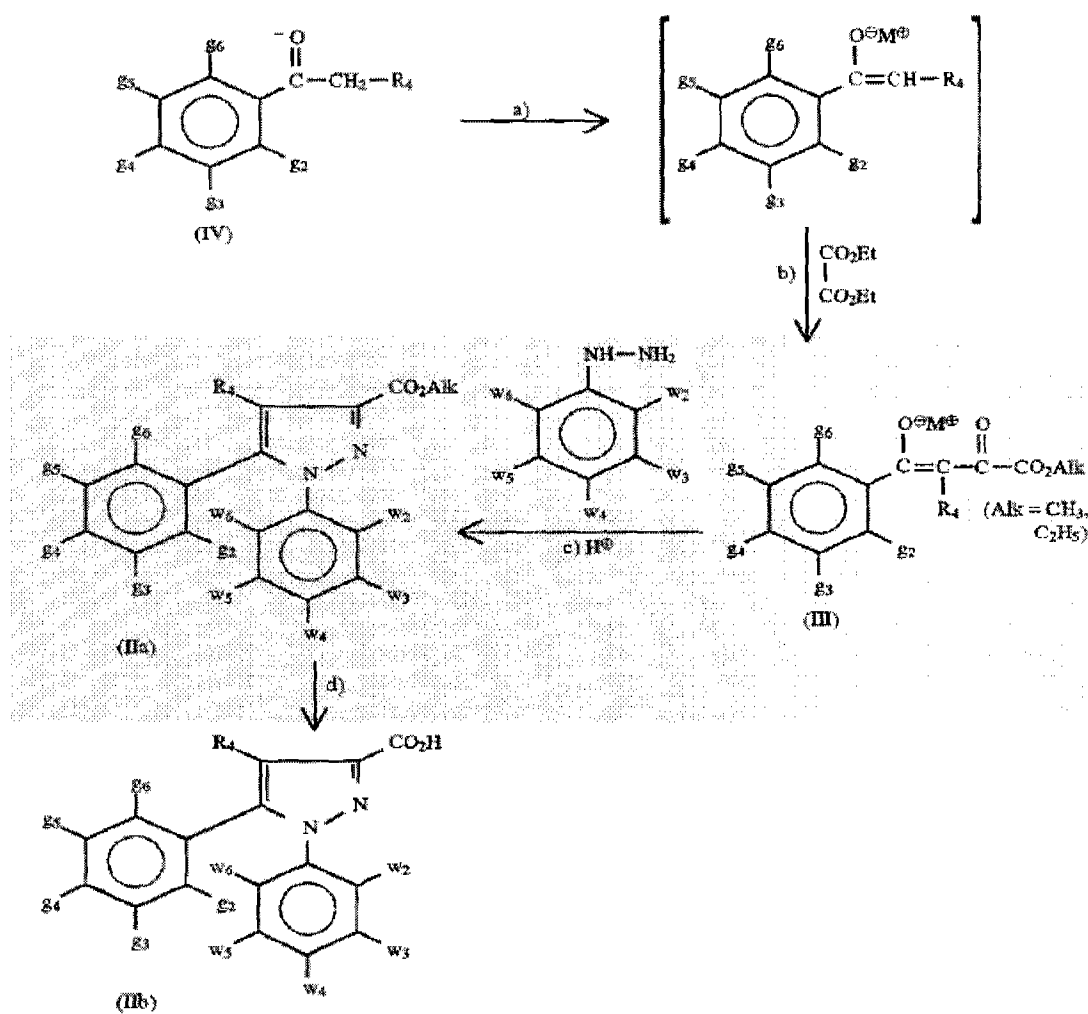
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TABLE I-continued

Example n°		m.p., °C. or [α] _D ²⁰ Salt
63		215 (dec) HCl
64		184
65		195 (dec) HCl

(Rimonabant)

SCHEME 1

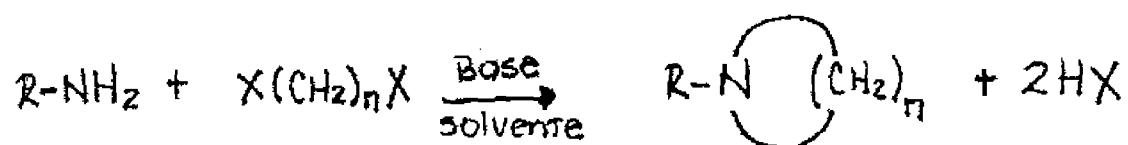


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En esta anterioridad se puede apreciar la obtención de compuestos del mismo tipo que los reivindicados por la solicitud colombiana en trámite, inclusive de la molécula de rimonabant (tabla 1), a través de un proceso que comprende la adición de fenilhidrazina al compuesto de fórmula III dando origen a la ciclación y obtención del anillo de pirazol sustituido en las posiciones 1, 3, 4 y 5.

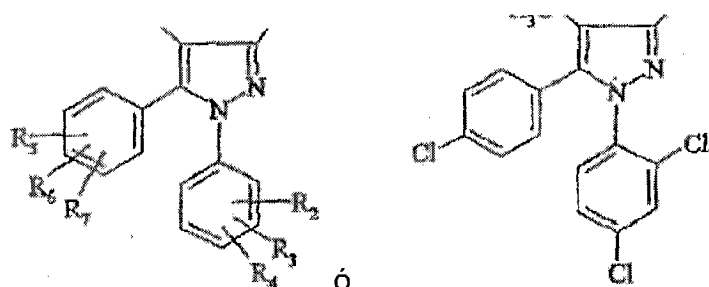
Si bien es cierto que los procesos presentan ciertos pasos diversos, no lo es menos que ambos permiten la obtención de los mismos compuestos derivados de pirazol, entre ellos la obtención de Rimonabant sin que el proceso reivindicado demuestra ventajas técnicas significativas frente al arte anterior, ni lleve a obtener un principio activo mejorado o distinto al conocido, circunstancia que compromete el nivel inventivo de la solicitud. *

3.3. Si bien es cierto no se encuentra en el estado del arte una revelación textual del proceso aquí descrito, no lo es menos que una persona medianamente versada en la materia y dedicada a la síntesis de compuestos, podría deducir con facilidad lo propuesto en la solicitud colombiana en trámite, y de esa manera desvirtuar al menos, el requisito de nivel inventivo de ésta, veamos:

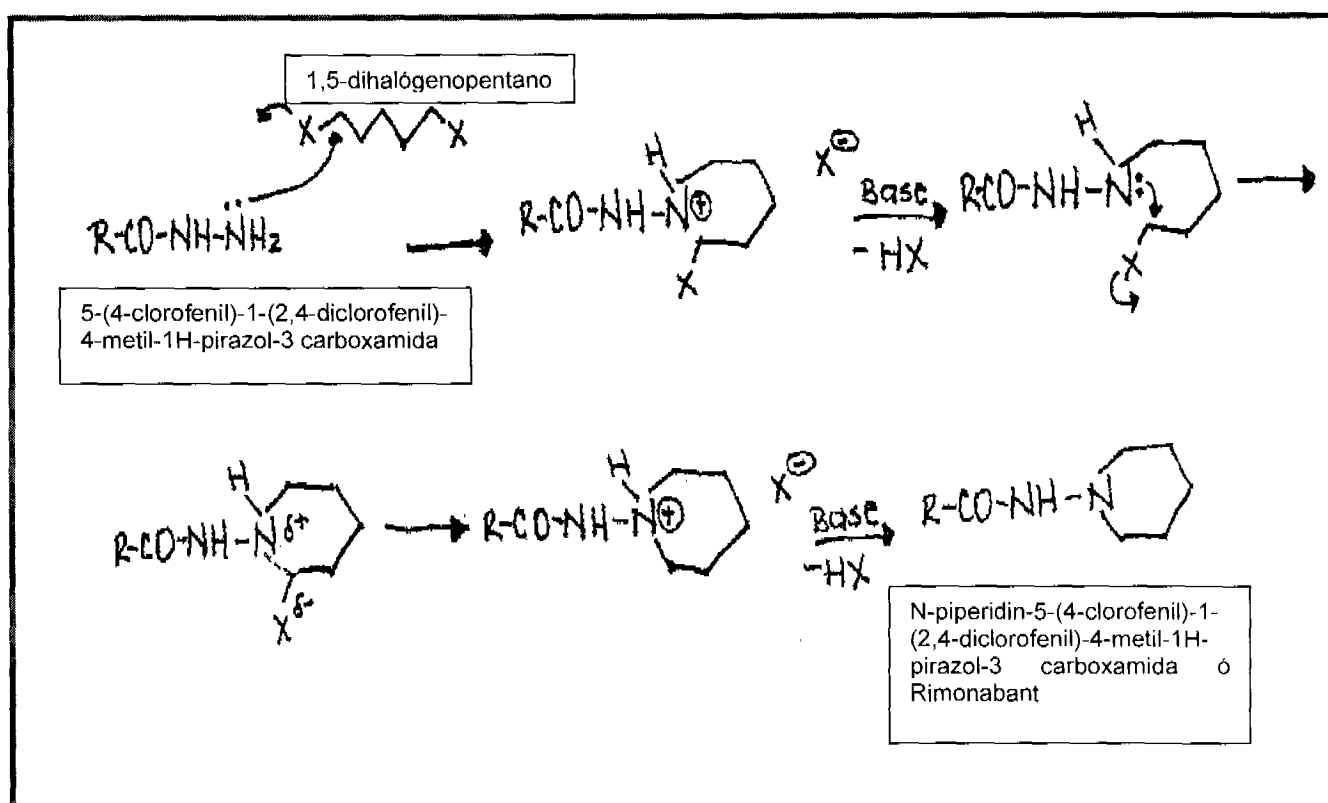


Si tenemos en cuenta lo planteado en el gráfico anterior, podríamos pensar que la reacción de heterociclización se da cuando las aminas primarias reaccionan con alquil-dihalogenuros (generando el enlace C-N) a través de reacciones de sustitución nucleofílica de tipo SN_2 por una doble N-alkilación de la amina de partida.

A continuación, se muestra de manera detallada lo que puede suceder en la reacción antes mencionada y que permitiría llegar a obtener el compuesto de fórmula (I) o Rimonabant, teniendo en cuenta que R=



, veamos:



Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

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V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La patente americana US 5,624,941 publicada el 29 de abril de 1997 y titulada "PYRAZOLE DERIVATIVES, METHOD OF PREPARING THEM ND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT" columnas 1 a 12 y 47.
- Portadas de: La publicación internacional WO 03/040105 publicada 15 de Mayo de 2003 y titulada "POLYMORPHOUS FORM OF RIMONABANT, PREPARATION METHOD AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME"; la publicación internacional WO 03/082256 publicada el 09 de octubre de 2003 y titulada "USE OF A CB1 CANNABINOID RECEPTOR ANTAGONIST FOR PRODUCING MEDICAMENTS WHICH ARE USEFUL FOR TREATING SEXUAL BEHAVIOUR PROBLEMS AND/OR FOR IMPROVING SEXUAL PERFORMANCES" y la publicación internacional WO 04/004665 publicada el 15 de enero de 2004 y titulada "SUBSTITUTED HETEROCYCLIC DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTI OBESITY AGENTS AND METHOD".
- Abstracts de: La publicación científica publicada en 2002 y titulada "RIMONABANT: SR 141716, SR 141716 ."; y la publicación científica publicada en 2004 y titulada "RIMONABANT REDUCES RISK FACTORS FOR CARDIOVASCULAR DISEASE "

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VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A., las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 23 # 7-39, de la ciudad de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.



US005624941A

113 +2
14**United States Patent** [19]

Barth et al.

[11] Patent Number: **5,624,941**[45] Date of Patent: **Apr. 29, 1997**

[54] **PYRAZOLE DERIVATIVES, METHOD OF PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT**

[75] Inventors: **Francis Barth**; **Pierre Casellas**, both of Montpellier; **Christian Congy**, Saint Gely du Fesc; **Serge Martinez**, Montpellier; **Murielle Rinaldi**, Saint Georges d'Orques; **Gilles Anne-Archard**, Toulouse, all of France

[73] Assignee: **Sanofi**, Paris, France

[21] Appl. No.: **348,881**

[22] Filed: **Nov. 29, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 168,237, Dec. 17, 1993, abandoned, which is a continuation-in-part of Ser. No. 79,870, Jun. 23, 1993, abandoned.

[30] **Foreign Application Priority Data**

Jun. 23, 1992	[FR]	France	92 07645
Dec. 2, 1993	[FR]	France	93 14444
Jul. 20, 1994	[FR]	France	94 08974

[51] **Int. Cl.⁶** **A61K 31/445**

[52] **U.S. Cl.** **514/326**; 514/212; 514/236.5; 514/341; 514/404; 514/406; 514/407; 544/127; 546/247; 546/211; 548/357.5; 548/364.1; 548/364.7; 548/371.7; 548/372.5; 548/374.1; 548/375.1

[58] **Field of Search** 546/211, 247; 548/374.1, 364.4, 357.5, 364.1, 364.7, 375.1, 371.7, 372.5; 544/127; 514/212, 236.5, 326, 341, 404, 406, 407

[56] **References Cited****U.S. PATENT DOCUMENTS**

3,449,350 6/1969 Walker 546/275.4

4,826,868	5/1989	Wachter et al.	514/407
5,013,837	5/1991	Ward et al.	544/143
5,051,518	9/1991	Murray et al.	548/375.1
5,134,142	7/1992	Matsuo et al.	514/255
5,164,381	11/1992	Wachter et al.	514/85

FOREIGN PATENT DOCUMENTS

0029363	5/1981	European Pat. Off.
0248594	12/1987	European Pat. Off.
0293220	11/1988	European Pat. Off.
0418845	3/1991	European Pat. Off.
0445781	9/1991	European Pat. Off.
0477049	3/1992	European Pat. Off.
0576357	12/1993	European Pat. Off.

OTHER PUBLICATIONS

Boyd et al., *Journal of the Chemical Society, Perkin Transactions 1*, vol. 21, 1973, pp. 2532-2535.

Fusco et al., *Tetrahedron Letters*, No. 46, 1967, pp. 4541-4544.

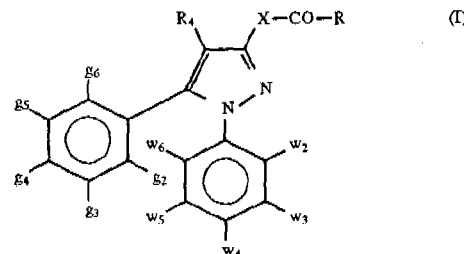
CA110:75489 (Feb. 1989).

Primary Examiner—Brian M. Burn

Attorney, Agent, or Firm—Bacon & Thomas

[57] **ABSTRACT**

The present invention relates to compounds of the formula:



These compounds are useful in pharmaceuticals in which cannabis is known to be involved.

30 Claims, No Drawings

**PYRAZOLE DERIVATIVES, METHOD OF
PREPARING THEM AND
PHARMACEUTICAL COMPOSITIONS IN
WHICH THEY ARE PRESENT**

The present application is a continuation-in-part application of U.S. Ser. No. 08/168,237, filed Dec. 17, 1993, now abandoned, which is a continuation-in-part application of U.S. Ser. No. 08/079,870, filed Jun. 23, 1993, now abandoned.

The present invention relates to novel pyrazole derivatives, to a method of preparing them and to the pharmaceutical compositions in which they are present.

Numerous pyrazole derivatives have been described in the literature; more particularly, EP-A-268554 and DE-A-3910248 claim pyrazoles possessing herbicidal properties. EP-A-430186 and JP-A-03031840 claim compounds useful for photography, and EP-A-418845 claims pyrazoles possessing antiinflammatory, analgesic and antithrombotic activity.

It has now been found that the pyrazoles forming the subject of the invention have a good affinity for the cannabinoid receptor and are therefore particularly valuable in the therapeutic areas in which cannabis is known to be involved.

Δ^9 -Tetrahydrocannabinol, or Δ^9 -THC, is the main active constituent extracted from *Cannabis sativa* (Tuner, 1985; In Marijuana 84, Ed. Harvey, D. Y., IRL Press, Oxford).

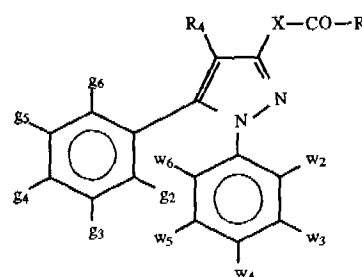
The effects of cannabinoids are due to an interaction with specific high-affinity receptors present in the central nervous system (Devane et al., Molecular Pharmacology, 1988, 34, 605-613) and peripheral nervous system (Nye et al., The Journal of Pharmacology and Experimental Therapeutics, 1985, 234, 784-791; Kaminski et al., 1992, Molecular Pharmacology, 42, 736-742; Munro et al., Nature, 1993, 365, 61-65).

Characterization of this receptor has been made possible by the development of specific synthetic ligands such as the agonists WIN 55212-2 (J. Pharmacol. Exp. Ther., 1993, 264, 1352-1363) or CP 55,940 (J. Pharmacol. Exp. Ther., 1988, 247, 1046-1051).

The therapeutic indications of cannabinoids pertain to a variety of areas such as the immune system, the central nervous system and the cardiovascular or endocrine system (Hollister, Pharmacological Reviews, 1986, 38, 1-20; Renv and Sinha, Progress in Drug Research, 1991, 36, 71-114, Cannabinoid receptor expression in human leucocytes, European Journal of Biochemistry, 1993, 214, 173-180).

More particularly, compounds possessing an affinity for the cannabinoid receptor are useful as immunomodulators and psychotropic agents, in thymic disorders, vomiting, myorelaxation, various types of neuropathy, memory disorders, dyskinesia, migraine, asthma, epilepsy and glaucoma or else in anticancer chemotherapy, in ischemia and angor, in orthostatic hypotension and in cardiac insufficiency.

Thus, according to one of its features, the present invention relates to the compounds of the formula



in which

g_2, g_3, g_4, g_5 and g_6 and w_2, w_3, w_4, w_5 and w_6 are identical or different and are independently hydrogen, a chlorine or bromine atom, a (C_1-C_3) -alkyl, a (C_1-C_3) alkoxy, a trifluoromethyl or a nitro group and g_4 is optionally a phenyl group;

R_4 is hydrogen or a (C_1-C_3) -alkyl;

X is either a direct bond or a group $-(CH_2)_xN(R_3)-$, in which R_3 is hydrogen or a (C_1-C_3) -alkyl and x is zero or one; and

R is

a group $-NR_1R_2$ in which R_1 and R_2 are independently a (C_1-C_6) -alkyl; an optionally-substituted non-aromatic (C_3-C_{15}) carbocyclic radical; an amino (C_1-C_4) alkyl group in which the amino is optionally disubstituted by a (C_1-C_3) -alkyl; a cycloalkyl- (C_1-C_3) alkyl in which the cycloalkyl is C_3-C_{12} ; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a (C_1-C_5) -alkyl or by a (C_1-C_5) -alkoxy; a phenyl (C_1-C_3) -alkyl; a diphenyl- (C_1-C_3) -alkyl; a naphthyl; an anthracenyl; a saturated 5- to 8-membered heterocyclic radical which is unsubstituted or substituted by a (C_1-C_3) -alkyl, by a hydroxyl or by a benzyl group; a 1-adamantylmethyl; an aromatic heterocycle unsubstituted or mono- or polysubstituted by a halogen, a (C_1-C_3) alkyl, a (C_1-C_5) -alkoxy; a (C_1-C_3) -alkyl substituted by an aromatic heterocycle unsubstituted or mono- or polysubstituted by a halogen, a (C_1-C_5) alkyl, a (C_1-C_5) -alkoxy, or else R_1 is hydrogen and R_2 is as defined above, or else R_1 and R_2 , together with the nitrogen atom to which they are bonded, form a saturated 5- to 8-membered heterocyclic radical, said heterocyclic radical being other than morpholine when w_2, w_3, w_4, w_5 and w_6 and g_2, g_3, g_4, g_5 and g_6 are all hydrogen;

a group R_2 as defined above when X is $-(CH_2)_xN(R_3)-$; or

a group R_5 when X is a direct bond, R_5 being a (C_1-C_3) -alkyl; a (C_3-C_{12}) -cycloalkyl which is unsubstituted or substituted by a (C_1-C_5) -alkyl; a phenyl- (C_1-C_3) -alkyl which is unsubstituted or substituted by a halogen or by a (C_1-C_5) -alkyl; a cycloalkyl- (C_1-C_3) -alkyl in which the cycloalkyl is C_3-C_{12} and is unsubstituted or substituted by a (C_1-C_5) -alkyl; or a 2-norbornylmethyl; or one of their salts, where appropriate.

The non-aromatic C_3-C_{15} carbocyclic radicals include saturated or unsaturated, fused or bridged monocyclic or polycyclic radicals, optionally terpene radicals. These radicals are optionally mono- or polysubstituted, said substituent(s) being different from a substituted carbonyl

group. Advantageously, the monocyclic radicals are substituted by at least one group selected among the (C₁-C₅) alkyl, (C₁-C₅)alkoxy, halogen or hydroxy groups, it being understood that in the case of terpenes or terpene radicals, for example bornyl, menthyl or menthenyl, the alkyl groups of the terpene are not considered as substituents.

The monocyclic radicals include cycloalkyls, for example cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclododecyl, which are unsubstituted or substituted by at least one (C₁-C₅)-alkyl, (C₁-C₅)-alkoxy, halogen or hydroxy groups.

The fused, bridged or spiranic bicyclic or tricyclic radicals include for example norbornyl, bornyl, isobornyl, noradamantyl, adamantyl and spiro[5.5]undecanyl, said radicals being unsubstituted or substituted by a (C₁-C₅)-alkyl.

Saturated 5- to 8-membered heterocyclic radical is understood as meaning a fused or bridged, non-aromatic monocyclic, bicyclic or tricyclic heterocyclic radical, the heteroatom being S, O or N, or a non-aromatic monocyclic heterocyclic radical containing a nitrogen atom and an oxygen or sulfur atom, said radicals being for example tetrahydrofuran-yl, tetrahydrothiofuran-yl, tropanyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl or quinuclidinyl, the 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl and 4-thiomorpholinyl radicals being advantageous.

The aromatic heterocycles can be monocyclic or bicyclic, for example pyrrolyl, pyridyl, indolyl, quinolinyl, thiazolyl or isoindazolyl, these aromatic heterocycles being unsubstituted or substituted for example by halogens, (C₁-C₅)-alkyl or (C₁-C₅)-alkoxy. The preferred aromatic heterocycles are pyridyl, pyrrolyl, indole groups, the radicals 2-indolyl or 3-indolyl are particularly preferred.

In formula (I) above, preferably at least one of the substituents w₁, w₃, w₄, w₅ and w₆ and g₂, g₃, g₄, g₅ and g₆ is other than hydrogen.

In formula (I) above, when R is a Group -NR₁R₂, preferably:

R₁ is hydrogen or a (C₁-C₆)-alkyl group and R₂ is as defined above for (I); or

R₁ and R₂ are each a (C₁-C₆)-alkyl group or a (C₃-C₆)-cycloalkyl group; or

R₁ is hydrogen or a (C₁-C₆)-alkyl group and R₂ is a cycloalkyl-(C₁-C₅)-alkyl group in which the cycloalkyl is C₃-C₁₂; a non-aromatic (C₃-C₁₅) carbocyclic radical which is unsubstituted or substituted as above mentioned; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a (C₁-C₅)-alkyl or by a (C₁-C₅)-alkoxy; a phenyl-(C₁-C₃)-alkyl or a (C₁-C₃)-alkyl substituted by a 2- or 3-indolyl.

Particularly preferably, when R in formula (I) is a group -NR₁R₂, R₁ is hydrogen or a (C₁-C₆)-alkyl and R₂ is a non-aromatic (C₃-C₁₅) carbocyclic radical, a cycloalkyl-(C₁-C₅)-alkyl in which the cycloalkyl is C₃-C₆, or a 2- or 3-indolyl-(C₁-C₅)-alkyl.

The preferred alkyl groups are methyl, ethyl, propyl and isopropyl.

In formula (I) above, R is advantageously a group -NR₁R₂ preferably selected from the radicals (I) to (74) below.

When R₁ and R₂, with the nitrogen atom to which they are bonded, are a heterocyclic radical, this is preferably a 5-, 6- or 7-membered saturated heterocycle and can contain another heteroatom, especially oxygen or sulfur, for example a pyrrolidine, a piperidine, a hexahydroazepine, a morpholine or a thiomorpholine, with the limitation specified above.

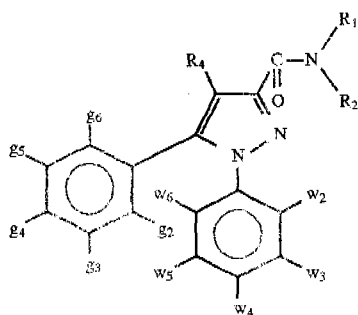
The radicals represented by R as defined for (I) are preferably radicals selected from:

- (1) propylamino
- (2) butylamino
- (3) isopropylamino
- (4) dipentylamino
- (5) 2-(N,N-diethylamino)ethylamino
- (6) benzylamino
- (7) 2-phenylethylamino
- (8) 3-phenylpropylamino
- (9) 3,3-diphenylpropylamino
- (10) phenylamino
- (11) 3-chlorophenylamino
- (12) 4-methylphenylamino
- (13) cyclopropylamino
- (14) cyclopentylamino
- (15) cyclohexylamino
- (16) cycloheptylamino
- (17) cyclooctylamino
- (18) cyclododecylamino
- (19) 2-methylcyclohexylamino
- (20) 3-methylcyclohexylamino
- (21) cis-4-methylcyclohexylamino
- (22) trans-4-methylcyclohexylamino
- (23) cis-4-tert-butylcyclohexylamino
- (24) trans-4-tert-butylcyclohexylamino
- (25) 4-hydroxycyclohexylamino
- (26) 2-methoxycyclohexylamino
- (27) 4-ethylcyclohexylamino
- (28) 2,6-dimethylcyclohexylamino
- (29) N-methylcyclohexylamino
- (30) N,N-dicyclohexylamino
- (31) endo-2-norbornylamino (or endo-bicyclo[2.2.1]heptan-2-amino)
- (32) exo-2-norbornylamino (or exo-bicyclo[2.2.1]heptan-2-amino)
- (33) 1-adamantylamino
- (34) 2-adamantylamino
- (35) 1-noradamantylamino
- (36) (1R)-bornylamino
- (37) (1R)-isobornylamino
- (38) spiro[5.5]undecanylamino
- (39) cyclohexylmethylamino
- (40) 1-adamantylmethylamino
- (41) (2-tetrahydrofuran-yl)methylamino
- (42) 2-(N-methyl-2-pyrrolyl)ethylamino
- (43) 2-(2-pyridinyl)ethylamino
- (44) (2-indolyl)methylamino
- (45) N-methyl(2-indolyl)methylamino
- (46) 2-(3-indolyl)ethylamino
- (47) N-methyl-2-(3-indolyl)ethylamino
- (48) 4-(N-benzylpiperidinyl)amino
- (49) 3-quinuclidylamino
- (50) exo-bicyclo[3.2.1]octan-2-amino
- (51) bicyclo[2.2.2]octan-2-amino
- (52) 3-chlorobicyclo[3.2.1]oct-3-en-2-amino
- (53) bicyclo[2.2.2]oct-2-en-5-amino
- (54) exo-bicyclo[3.2.1]octan-3-amino
- (55) endo-bicyclo[3.2.1]octan-3-amino
- (56) endo-7-oxabicyclo[2.2.1]heptan-2-amino
- (57) exo-7-oxabicyclo[2.2.1]heptan-2-amino
- (58) endo-tricyclo[5.2.1.0^{2,6}]decan-8-amino
- (59) N-ethyl-1-adamantylamino
- (60) tricyclo[2.2.1.0^{2,6}]heptan-3-amino
- (61) bicyclo[3.3.1]nonan-9-amino
- (62) endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amino (or fenchylamino)

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- (63) (1R, 2S-endo)-(+)-bicyclo[2.2.1]heptan-2-amino
 (64) (1R,2R-exo)-(-)-bicyclo[2.2.1]heptan-2-amino
 (65) (1S,2R-endo)-(-)-bicyclo[2.2.1]heptan-2-amino
 (66) (1S,2S-exo)-(+)-bicyclo[2.2.1]heptan-2-amino
 (67) 1-piperidinylamino
 (68) 1-pyrrolidinylamino
 (69) 1-hexahydroazepinylamino
 (70) 4-morpholinylamino
 (71) 4-thiomorpholinylamino
 (72) N-methyl-exo-bicyclo[2.2.1]heptan-2-amino
 (73) N-ethyl-exo-bicyclo[2.2.1]heptan-2-amino
 (74) N-propyl-exo-bicyclo[2.2.1]heptan-2-amino

Of the products of formula (I) above, those of formula (Ia) below are advantageous; in particular, the compounds of formula (Ia'):



in which w₂, w₃, w₄, w₅ and w₆, g₂, g₃, g₄, g₅ and g₆ and R₄ are as defined above for (I), R₁ is hydrogen or a (C₁-C₆)-alkyl and R₂ is a non-aromatic C₃-C₁₅ carbocyclic radical or a saturated 5- to 8-membered heterocyclic radical selected from 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl and 4-thiomorpholinyl, and their salts, are particularly advantageous.

Of the products of formula (I), those of formulae (Ia), (Ib), (Ic), (Id), (Ie) and (If) below, in which at least one of the substituents w₂, w₃, w₄, w₅ and w₆ and g₂, g₃, g₄, g₅ and g₆ is other than hydrogen, R₁ is hydrogen or a (C₁-C₆)-alkyl, R₂ is as defined above, R₃ is hydrogen or a (C₁-C₃)-alkyl group, R₄ is hydrogen or methyl and R₅ is a cycloalkyl (C₁-C₃)-alkyl, the cycloalkyl being C₃-C₆, or a phenyl (C₁-C₃)-alkyl which is unsubstituted or substituted on the aromatic ring by a methyl group or a fluorine or chlorine atom, and their salts, where appropriate, are particularly advantageous.

In these latter particularly advantageous products,

when R₁ is a (C₁-C₆)-alkyl, the methyl, ethyl, propyl and isopropyl groups are preferred;

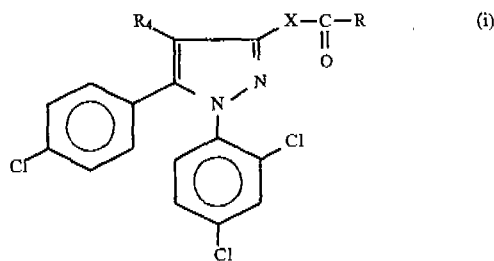
when R₃ is a (C₁-C₃)-alkyl, the methyl group is preferred;

the preferred groups R₂ are non-aromatic C₃-C₁₅ carbocyclic radicals which are unsubstituted or substituted by a (C₁-C₄)-alkyl, especially methyl, ethyl, propyl, isopropyl or t-butyl, or by two or three methyl groups, for example a methyl-, ethyl- or t-butyl-cyclohexyl radical or a dimethyl- or trimethylcyclohexyl radical, cycloalkyl-(C₁-C₃)-alkyl radicals in which the cycloalkyl is C₃-C₆; (C₁-C₃)-alkyl radicals substituted by a 2- or 3-indolyl group; 2- and 3-indolyl radicals; and 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl and 4-thiomorpholinyl radicals; and

the preferred groups R₅ are cyclohexylmethyl, cyclohexylethyl, benzyl, 4-methylbenzyl and phenethyl radicals.

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Of the products of formula (I) above, those of formula (i):



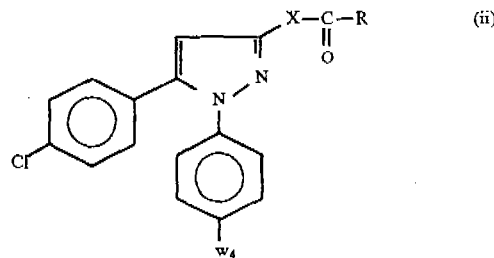
in which R₄, X and R are as defined-above for (I), and their salts, are very advantageous, especially when R₄ is hydrogen or a methyl group or when R₄ is hydrogen or methyl and X is a direct bond.

The compounds of formula (i) in which R₄ is hydrogen or methyl, X is a direct bond and R is a group —NR₁R₂ in which R₁ is hydrogen or a methyl group and R₂ is a non-aromatic C₃-C₁₅ carbocyclic radical or a saturated 5- to 8-membered heterocyclic radical selected from 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl and 4-thiomorpholinyl, and their salts, are particularly preferred.

Especially preferred is the compound of formula (i) in which R₄ is methyl, X is a direct bond and R is a group —NR₁R₂ in which R₁ is hydrogen and R₂ is 1-piperidinyl, as well as its pharmaceutically acceptable salts and their solvates.

Other particularly preferred compounds of formula (i) are those in which R₄ is hydrogen or methyl, X is —(CH₂)_xN(R₃)— and R is —NR₁R₂, x being zero or one, R₁ being hydrogen, R₃ being hydrogen or a methyl group and R₂ being a phenyl which is unsubstituted or substituted by one or two halogen atoms, a (C₁-C₃)-alkyl group or a (C₁-C₃)-alkoxy group, or a non-aromatic C₃-C₁₅ carbocyclic radical, and their salts.

Of the compounds of formula (I), those of formula (ii):



in which X and R are as defined above for (I) and w₄ is a methyl or methoxy group, especially those of formula (ii) in which w₄ is a methyl or methoxy group, X is a direct bond and R is a group —NR₁R₂ in which R₁ is hydrogen or a methyl group and R₂ is a non-aromatic C₃-C₁₅ carbocyclic radical, and their salts, are also advantageous.

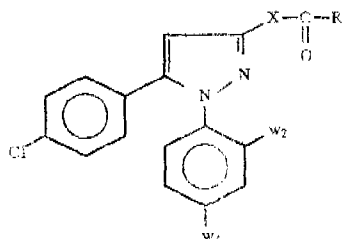
An advantageous subclass comprises the compounds of formula (ii) in which w₄ is a methyl or methoxy group, X is a group —(CH₂)_xN(R₃)— in which x is zero or one and R₃ is hydrogen or a methyl group, and R is a group —NR₁R₂ in which R₁ is hydrogen and R₂ is a phenyl which is unsubstituted or substituted by one or two halogen atoms, a (C₁-C₃)-alkyl group or a (C₁-C₃)-alkoxy group, or a non-aromatic C₃-C₁₅ carbocyclic radical, or their salts.

Other valuable compounds according to the present invention are those of formula (I) in which w₂, w₃, w₄, w₅ and w₆, g₂, g₃, g₄, g₅ and g₆ and R₄ and X are as defined above for (I) and R is a group —NR₁R₂ in which R₁ is

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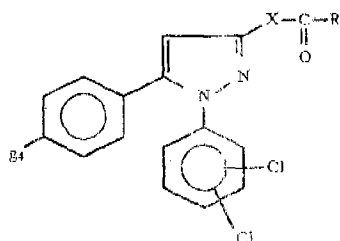
hydrogen or a (C₁-C₆) alkyl group and R₂ is a 2- or 3-indolyl-(C₁-C₃)-alkyl group or a 2- or 3-indolyl group, and their salts.

Of the latter, the products of formula (iii):



in which X is as defined above for (I), R is a group —NR₁R₂ in which R₁ is hydrogen or a (C₁-C₆)-alkyl and R₂ is a 2- or 3-indolyl-(C₁-C₃)-alkyl group or a 2- or 3-indolyl group, and either w₂ is hydrogen and w₄ is a methyl or methoxy group or w₂ and w₄ are a chlorine atom, and their salts, are particularly valuable.

Of the products included in formula (I) above, those of formula (iv):



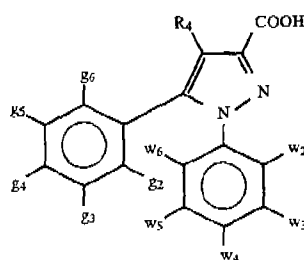
in which X and R are as defined above for (I) and g₄ is a bromine atom or a methyl or trifluoromethyl, and their salts, are also valuable.

In preferred products of formula (iv), the two chlorine atoms are in the 2,3-, 2,4-, 2,5- or 3,4-positions, and in these preferred products of formula (iv), those in which X is a direct bond and R is a group —NR₁R₂ in which R₁ is hydrogen or a (C₁-C₆)-alkyl and R₂ is a non-aromatic carbocyclic radical containing from 3 to 15 carbon atoms are particularly preferred.

The salts, where appropriate, of the compounds according to the present invention, especially of those of formulae (I), (Ia'), (i), (ii) and (iii) above and (Ia), (Ib), (Ic), (Id), (Ie) and (If) below, include both those with mineral or organic acids which permit a suitable separation or crystallization of the products, such as picric acid or oxalic acid, and those with acids which form pharmaceutically acceptable salts such as the hydrochloride, hydrobromide, sulfate, hydrogensulfate, dihydrogenphosphate, methanesulfonate, methylsulfate, oxalate, maleate, fumarate, naphthalene-2-sulfonate, glyconate, gluconate, citrate, isethionate and paratoluene-sulfonate.

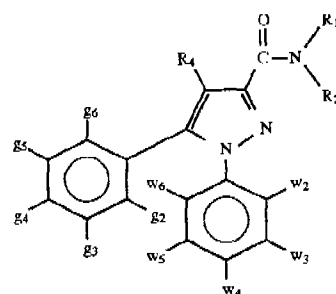
According to another of its features, the present invention relates to a method of preparing the compounds (I), which comprises treating a pyrazole-3-carboxylic acid derivative of the formula

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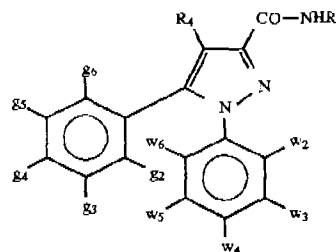
(IIa)

in which w₂, w₃, w₄, w₅ and w₆, g₂, g₃, g₄, g₅ and g₆ and R₄ are as defined for (I), or one of its activated forms, namely one of its esters or acid chlorides, * either with an amine of the formula HNR₁R₂, in which R₁ and R₂ are as defined for (I), to give the amides of the formula



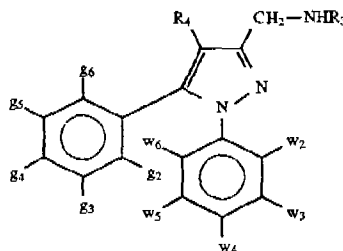
(Ia)

in which w₂, w₃, w₄, w₅ and w₆, g₂, g₃, g₄, g₅ and g₆ and R₄, R₁ and R₂ are as defined for (I), * or optionally with a primary amine R₃NH₂, in which R₃ is as defined for (I), to give the intermediate amides (V) of the formula



(V)

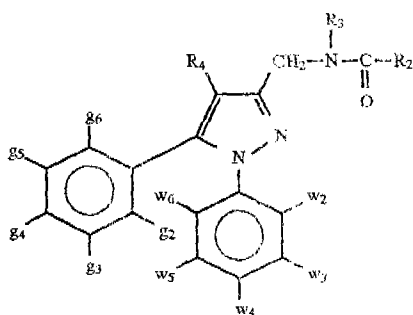
in which w₂, w₃, w₄, w₅ and w₆, g₂, g₃, g₄, g₅ and g₆ and R₄ and R₃ are as defined for (I), to give, by reduction with a metal hydride, the intermediate amines of the formula



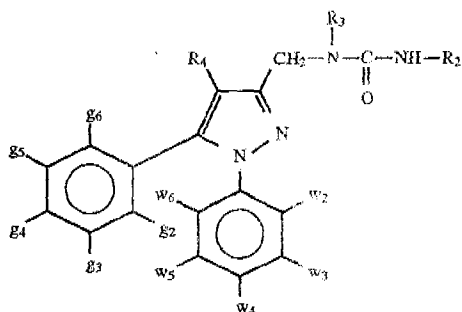
(VI)

in which w₂, w₃, w₄, w₅ and w₆, g₂, g₃, g₄, g₅ and g₆ and R₄ and R₃ are as defined for (I), which are converted to the amide or urea of the formula

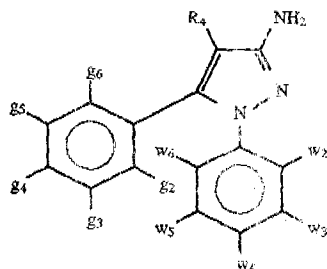
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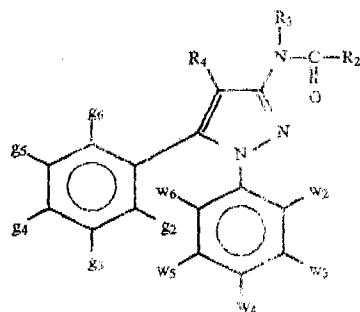
or



in which w_2, w_3, w_4, w_5 and w_6, g_2, g_3, g_4, g_5 and g_6 and R_2, R_3 and R_4 are as defined for (I), by reaction with an acid chloride of the formula $R_2\text{COCl}$ or, respectively, an isocyanate of the formula $R_2\text{—N=C=O}$, in which R_2 is as defined for (I), or with a diphenylphosphoryl azide derivative in a basic medium, followed by an acid treatment, to give the intermediate amine of the formula



in which w_2, w_3, w_4, w_5 and w_6, g_2, g_3, g_4, g_5 and g_6 and R_4 are as defined for (I), which is reacted with an acid chloride $R_2\text{COCl}$ or an isocyanate $R_2\text{—N=C=O}$ to give respectively the amides and ureas of the formulae



and

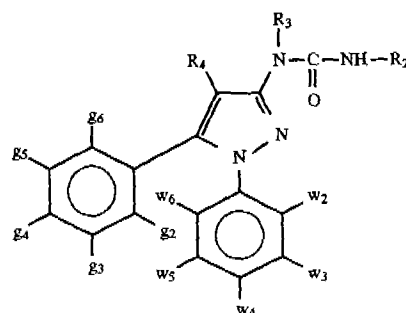
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-continued

(Ib)

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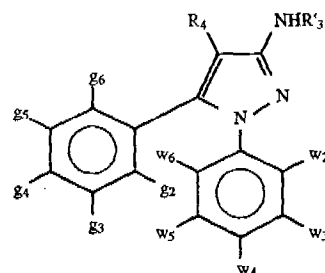


(Ie)

15 in which w_2, w_3, w_4, w_5 and w_6, g_2, g_3, g_4, g_5 and g_6 and R_4 are as defined for (I) and R_3 is hydrogen, the same compounds in which R_3 is other than hydrogen being prepared from the above primary amine (VII) converted to a secondary amine of the formula

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(VIIb)

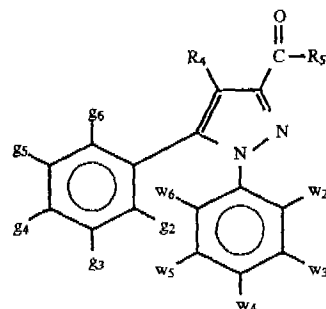
in which w_2, w_3, w_4, w_5 and w_6, g_2, g_3, g_4, g_5 and g_6 and R_4 are as defined for (I) and R'_3 is (C_1-C_2) -alkyl, which are then reacted with an acid chloride $R_2\text{COCl}$ or an isocyanate $R_2\text{—N=C=O}$ to give the amides and ureas of formulae (Id) and (Ie) as defined above in which R_3 is other than hydrogen, * or with an organomanganese reagent $R_5\text{MnX}_1$, in which R_5 is as defined for (I) and X_1 is a halogen, to give the ketone derivatives of the formula

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(Id)



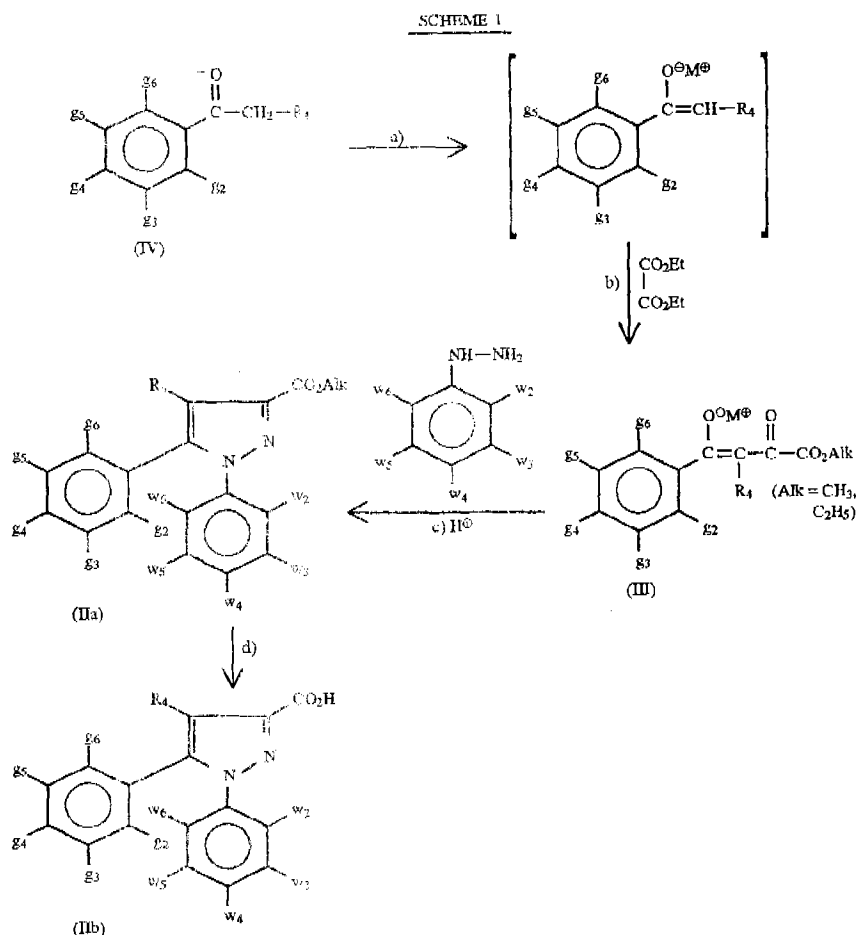
(If)

the resulting compounds then being converted to one of their salts, where appropriate.

In a preferential procedure, the pyrazoles of formula (I) can be synthesized from the corresponding esters by conversion of the ester group to an amide, urea or ketone via the acid and the acid chloride.

Said esters are synthesized by applying the method described in Berichte, 1887, 20, 2185.

The reaction scheme for the preparation of the compounds (I) via their methyl or ethyl esters ($\text{Alk}=\text{CH}_3$ or C_2H_5) is represented by SCHEME 1 below:



The first step a) consists in preparing an alkali metal salt of an acetophenone derivative of formula (IV), in which R_4 and g_2, g_3, g_4, g_5 and g_6 are as defined above for (I), to which an equimolar amount of diethyl oxalate is then added (step b) to give the ketoester of formula (III).

In the case where $R_4=H$, the alkali metal will preferably be sodium and the salt of the ketoester (III) ($Alk=CH_3$) will be obtained according to Bull. Soc. Chim. Fr., 1947, 14, 1098, using sodium methylate in methanol to perform step a).

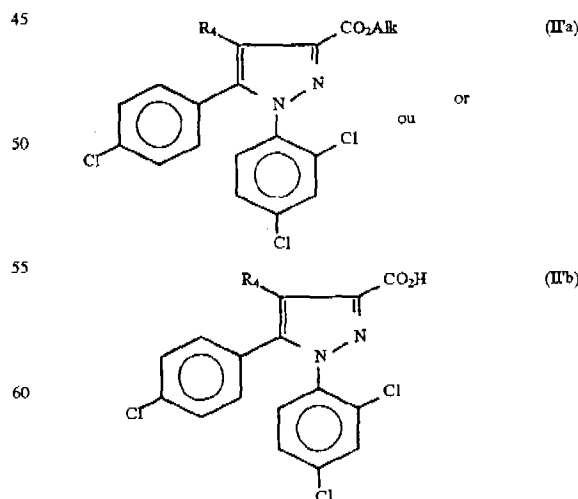
In the case where $R_4=CH_3$, the alkali metal will preferably be lithium and the salt of the ketoester (III) ($Alk=C_2H_5$) will be obtained according to J. Heterocyclic Chem. 1989, 26, 1389, using the lithium salt of hexamethyldisilazane in ethyl ether to perform step a).

The alkali metal salts (III) prepared in this way are then refluxed in acetic acid with an excess of a hydrazine derivative (step c). Precipitation in ice water gives the 3-pyrazole esters (IIa).

These esters (IIa) are then converted to their acids (IIb) by reaction with an alkaline agent, for example potassium hydroxide, followed by acidification (step d).

In SCHEME 1 above, the esters of formula (IIa) in which w_2 and w_4 are a chlorine atom, w_3, w_5 and w_6 are hydrogen, g_4 is a chlorine atom, g_2, g_3, g_5 and g_6 are hydrogen and Alk is a (C_1-C_5) -alkyl, and the corresponding acids (IIb), are novel key intermediates for the preparation of the particu-

larly advantageous compounds (i) and therefore represent a further feature of the invention; these compounds have formula (II'a) or (II'b):



When X is a direct bond, the amides according to the invention of formula (Ia):

TABLE I-continued

Example n°		mp °C. or $[\alpha]_D^{20}$ Salt
59		96
60		95
61		179
62		172
63		215 (dec) HCl
64		184
65		195 (dec) HCl
66		158
67		147

120
121

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION
EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété
Intellectuelle
Bureau international



(43) Date de la publication internationale
15 mai 2003 (15.05.2003)

PCT

(10) Numéro de publication internationale

WO 03/040105 A1

(51) Classification internationale des brevets⁷ :

C07D 231/14, A61P 35/00, A61K 31/455

(74) Mandataire : THOURET-LEMAITRE, Elisabeth
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(21) Numéro de la demande internationale :

PCT/FR02/03765

(81) États désignés (national) : AE, AG, AI., AM, AT, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, 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, SD, SE, SG, SI,
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
VN, YU, ZA, ZM, ZW.

(22) Date de dépôt international :

4 novembre 2002 (04.11.2002)

(25) Langue de dépôt :

français

(26) Langue de publication :

français

(30) Données relatives à la priorité :

01/14579 8 novembre 2001 (08.11.2001) FR

(84) États désignés (régional) : brevet ARIPO (GH, GM, KE,
LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), brevet
eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet
européen (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), brevet
OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG).

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Publiée :

avec rapport de recherche internationale

En ce qui concerne les codes à deux lettres et autres abrégia-
tions, se référer aux "Notes explicatives relatives aux codes et
abréviations" figurant au début de chaque numéro ordinaire de
la Gazette du PCT.

WO 03/040105 A1

(54) Title: POLYMORPHOUS FORM OF RIMONABANT, PREPARATION METHOD AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

(54) Titre : FORME POLYMORPHIQUE DE RIMONABANT, SON PROCÉDE DE PRÉPARATION ET LES COMPOSITIONS PHARMACEUTIQUES EN CONTENANT

(57) Abstract: The invention concerns a novel crystalline polymorph of rimonabant, its preparation method and pharmaceutical compositions containing said novel polymorph

(57) Abrégé : La présente invention concerne un nouveau polymorphe cristallin du rimonabant, son mode de préparation et les compositions pharmaceutiques contenant ce nouveau polymorphe.

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION
EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété
Intellectuelle
Bureau international



(43) Date de la publication internationale
9 octobre 2003 (09.10.2003)

PCT

(10) Numéro de publication internationale
WO 03/082256 A2

(51) Classification internationale des brevets :
A61K 31/00, 31/454, A61P 15/00

(21) Numéro de la demande internationale :
PCT/FR03/00964

(22) Date de dépôt international : 27 mars 2003 (27.03.2003)

(25) Langue de dépôt : français

(26) Langue de publication : français

(30) Données relatives à la priorité :
02/03961 28 mars 2002 (28.03.2002) FR

(71) Déposant (pour tous les États désignés sauf US) :
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(81) États désignés (national) : AE, AG, AI, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, 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, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SI, TJ, TM, TN, TR, TT, TZ, UA, UG, US, CZ,
VC, VN, YU, ZA, ZM, ZW.

(84) États désignés (régional) : brevet ARIPO (GH, GM, KE,
LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), brevet
eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet
européen (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SI, SK,
TR), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Publiée :

sans rapport de recherche internationale, sera republiée
dès réception de ce rapport

En ce qui concerne les codes à deux lettres et autres abrévia-
tions, se référer aux "Notes explicatives relatives aux codes et
abréviations" figurant au début de chaque numéro ordinaire de
la Gazette du PCT

(54) Title: USE OF A CB1 CANNABINOID RECEPTOR ANTAGONIST FOR PRODUCING MEDICAMENTS WHICH ARE
USEFUL FOR TREATING SEXUAL BEHAVIOUR PROBLEMS AND/OR FOR IMPROVING SEXUAL PERFORMANCES

(54) Titre : UTILISATION D'UN ANTAGONISTE DES RECEPTEURS AUX CANNABINOÏDES CB1 POUR LA PREPARA-
TION DE MÉDICAMENTS UTILES POUR TRAITER LES DYSFONCTIONNEMENTS DES COMPORTEMENTS SEXUELS
ET/OU AMÉLIORER LES PERFORMANCES SEXUELLES

(57) Abstract: The invention relates to the use of a CB1 cannabinoid receptor antagonist, especially rimonabant and
N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide and the pharmaceutically acceptable salts
and solvates thereof, for producing medicaments which are useful for treating sexual behaviour problems and/or for improving
sexual performances.

(57) Abrégé : Utilisation d'un antagoniste des récepteurs aux cannabinoïdes CB1 en particulier le rimonabant et le N pipéri-
dino-5-(4-bromophényl)-1-(2,4-dichlorophényl)-4éthylpyrazole-3-carboxamide ainsi que leurs sels et leurs solvats pharmaceutique-
ment acceptables pour la préparation de médicaments utiles pour traiter les dysfonctionnements des comportements sexuels et/ou
améliorer les performances sexuelles.

WO 03/082256 A2

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/004665 A2

(51) International Patent Classification⁷: **A61K**
(21) International Application Number:
PCT/US2003/022149

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(22) International Filing Date: 2 July 2003 (02.07.2003)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/394,508 9 July 2002 (09.07.2002) US

(81) Designated States (*national*): AF, AG, AI, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GI, GR, GU,
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, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SI, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

(72) Inventors; and

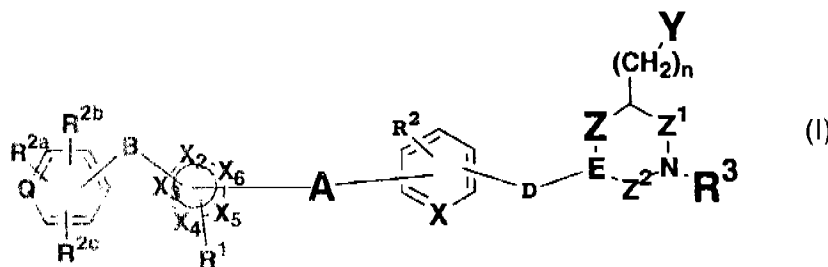
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Published:

*without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: SUBSTITUTED HETEROCYCLIC DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTI-OBESITY AGENTS AND METHOD



(57) Abstract: Formula, where: (i) Z' is $(CH_2)_n$ or C=O; Z'' is $(CH_2)_p$ or C=O; D is -CH= or C=O or $(CH_2)_m$ where m is 0, 1, 2 or 3; n = 0, 1 or 2; p = 1 or 2; q = 0, 1 or 2; Q is C or N; A is $(CH_2)_x$ where x is 1 to 5, or A is $(CH_2)_x^1$ where x^1 is 1 to 5 with an alkenyl bond or an alkynyl bond embedded anywhere in the chain, or A is $(CH_2)_x^2-O-(CH_2)_x^3$ where x^2 is 0 to 5 and x^3 is 0 to 5, provided that at least one of x^2 and x^3 is other than 0; B is a bond or is $(CH_2)_x^4$ where x^4 is 1 to 5; X is CH or N; X_2 is C, N, O or S; X_3 is C, N, O or S; X_4 is C, N, O or S; X_5 is C, N, O or S; X_6 is C, N, O or S; provided that at least one of X_2 , X_3 , X_4 , X_5 and X_6 is N; and at least one of X_2 , X_3 , X_4 , X_5 and X_6 is C; R' is H or alkyl; R² is H, alkyl, alkoxy, halogen, amino, substituted amino or cyano; R^{2a}, R^{2b} and R^{2c} may be the same or different and are selected from H, alkyl, alkoxy, halogen, amino, substituted amino or cyano; and R³, E, Z and Y are as defined herein.

124 23
123

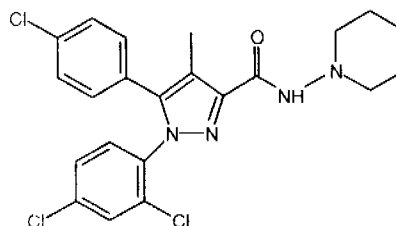
ADIS R&D PROFILE

Drugs R&D 2002; 3 (1): 65-66
1174 5886/02/0001-0065/\$22.00/0

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Rimonabant

SR 141716, SR 141716a



Adis Comments

Rimonabant [SR 141716, SR 141716A] is a neurokinin 3 antagonist and selective cannabinoid CB1 receptor antagonist developed by Sanofi. In mid-1999, Sanofi merged with Synthelabo to form Sanofi-Synthelabo. In a rodent model, rimonabant has demonstrated memory-enhancing properties in preclinical trials, but commercial development in this indication does not appear to be actively ongoing.

Rimonabant has entered phase III clinical studies for the treatment of obesity. In phase IIb clinical studies, patients with obesity receiving rimonabant achieved significant weight loss, and showed an excellent safety profile.

Rimonabant reportedly at phase IIa for schizophrenia.

Table I. Features and properties

Chemical Name	N-Piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide
Molecular Formula	C ₂₂ H ₂₁ Cl ₃ N ₄ O
CAS Number	168273-06-1
WHO ATC code	A05A (Anticobesity Preparations, Excl. Diet Products); N05A-X (Other antipsychotics); N07X (Other Nervous System Drugs)
EphMRA ATC code	A6A (Anticobesity Preparations, Excluding Dietetics); N5A (Antipsychotics); N7 (Other CNS Drugs including Antismoking Products)
Originator	Sanofi-Synthelabo, France
Highest Development Phase	II
Properties	
Mechanism of action	Cannabinoid CB1 receptor antagonists; Neurokinin 3 antagonists
Pharmacodynamics	Potential memory-enhancing and antipsychotic activity

Profile

Adverse Events

In a double-blind, placebo-controlled study in 167 patients with obesity, rimonabant (20 mg/daily) showed no effect on tolerability during the 4-month duration of the study.^[1]

Pharmacodynamics

Alzheimer's Disease and Memory Enhancement

Rimonabant (0.3 mg/kg, i.p.) demonstrated a memory-enhancing effect on a spatial working social short-term memory paradigm, the ability to recognition of a previously explored site. The effect of the drug was partly reversed by scopolamine. Rimonabant also reduced memory function in aged rats and mice.^[2]

Rimonabant (0.3–1 mg/kg, i.p.) had no significant effect on learning/memory performance in mice with fimbria-fornix lesion or scopolamine-induced behavioural deficits.^[3]

Therapeutic Trials

Obesity

In a double-blind, placebo-controlled study in 167 patients with obesity, rimonabant (5, 10 or 20 mg/daily) for 16 weeks significantly reduced weight compared with placebo. The decrease in weight continued during the 4-month duration of the study.^[1]

In 20 patients with body mass index of ≥ 30 ,

Table B. Drug development history

Oct 2001	Phase-II for Obesity in France (Unknown route)
May 2001	Rimonabant is the p11N for SR 141716
Aug 2000	Phase-II for Schizophrenia in Unknown (Unknown route)
Aug 2000	Phase-II for Obesity in France (Unknown route)
Aug 1999	Sanofi has merged with Synthelabo to form Sanofi-Synthelabo
Jan 1997	Phase-II for Cognition disorders in France (Unknown route)
Dec 1995	Preclinical for Cognition disorders in France (Unknown route)

rimonabant 20 mg, od for 7 days reduced hunger, caloric intake and bodyweight compared with placebo.^[1]

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2. Terranova J-P, Storme J-J, Lafen N, et al., Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR 141716. *Psychopharmacology*, 126: 165-172, Jul 1995, France. [English]
3. Châtel V, Castel JC, Kelche C. Effects of the selective CB1 cannabinoid receptor antagonist, SR 141716A, on cognitive performance in intact, brain-damaged and scopolamine-treated rats. *Behavioural Pharmacology* 9 (Suppl 1): 25, Aug 1998, France. [English]
4. Heshmati H, Châtel V, Boffice E, et al., SR141716, a selective cannabinoid (CB1) receptor antagonist, reduces hunger, caloric intake and body weight in overweight or obese men. *Obesity Research*, 9 (Suppl 3): 70, Sep 2001, USA. [English]

Rimonabant reduces risk factors for cardiovascular disease

- Raewyn Poole -

Treatment with rimonabant (Acomplia), a selective CB₁ receptor blocker, is effective in reducing bodyweight in overweight/obese patients with untreated dyslipidaemia, and also results in prolonged cessation of smoking without significant weight gain, according to two phase III studies presented at the 53rd Annual Scientific Session of the American College of Cardiology [New Orleans, US; March 2004].¹ In the first study, prolonged abstinence from smoking was achieved in significantly more rimonabant 20mg, compared with placebo, recipients; no significant increase in bodyweight was observed among these patients. The second study showed that rimonabant was effective in reducing bodyweight and waist circumference, and improving serum lipid profiles, in overweight or obese patients with dyslipidaemia. Furthermore, a significant reduction from baseline in the number of patients with metabolic syndrome was observed with rimonabant 20mg. These studies suggest that, subject to approval, rimonabant will be the first drug to target multiple risk factors for cardiovascular disease.

Rimonabant is the first in a new class of drugs that act on the endocannabinoid system, which is believed to be involved in the regulation of food uptake and energy expenditure and in tobacco dependence. Overeating, excessive fat accumulation and chronic tobacco use lead to overactivation of the endocannabinoid system. By blocking the CB₁ receptor, rimonabant helps to normalise the endocannabinoid system; this can result in weight loss and improved metabolism of lipids and glucose in overweight or obese patients, or enable the cessation of smoking without significant increases in bodyweight.

Rimonabant improves quit rate

The effects of rimonabant in smoking cessation were evaluated in STRATUS-US,* a randomised, double-blind, parallel-group study that enrolled 787 smokers at 11 centres in the US. At baseline, patients smoked an average of 23 cigarettes per day and had previously attempted to stop smoking an average of four times.

Patients received rimonabant 5mg (n = 262), rimonabant 20mg (261), or placebo (261), once daily for 10 weeks, and were monitored for a further 42 weeks after completing treatment. Patients were motivated to quit and received weekly counseling; although they were allowed to smoke during the first two weeks of treatment, the target for smoking cessation was day 15. No diet or exercise recommendations were made.

The primary efficacy measure was the proportion of patients who reported abstaining from smoking for the final 4 weeks of the treatment period. Abstinence was verified by measuring carbon monoxide levels in expired air (≤ 10 ppm) and plasma concentrations of cotinine, the principle metabolite of nicotine (≤ 8 µg/L).

Prolonged abstinence achieved...

A significantly higher proportion of patients treated with rimonabant 20mg, compared with placebo recipients, achieved prolonged abstinence from smoking [see table 1]. The odds of quitting were doubled among rimonabant 20mg, compared with placebo, recipients; odds ratios for abstinence among the intention to treat population and among patients who completed the full 10-week treatment course were 2.0 and 3.2, respectively. There was no significant difference between the rimonabant 5mg and placebo group

... without weight gain

No significant change from baseline in weight gain was observed among rimonabant 20mg recipients [see table 1]. When grouped according to their bodyweight classification at baseline, rimonabant recipients from all classes had significantly reduced weight gain, compared with placebo-treated patients. Furthermore, reductions in

bodyweight (mean of 0.1–0.4kg) were observed among overweight and obese patients who were treated with rimonabant 20mg; in contrast, there was a mean increase of 1.7–2.1kg among overweight or obese placebo recipients.

Dual effect likely to appeal to smokers

"Smoking is one of the leading modifiable risk factors for heart disease and we have very few medications available to help people stop smoking," said Dr Robert Anthenelli from the University of Cincinnati College of Medicine, US. "STRATUS-US suggests that rimonabant may have a distinctive dual effect that could prove to be critical in helping patients to quit smoking while reducing the likelihood of weight gain". The prospect of weight gain after cessation of smoking can be a deterrent for smokers, particularly women. Thus, a treatment that would enable them to quit smoking without gaining weight is likely to hold considerable appeal.

Table 1: Effects of rimonabant on smoking cessation and bodyweight

	Placebo	Rimonabant	
		5mg	20mg
Prolonged abstinence from smoking (% of patients):			
Intent-to-treat population	16.1	15.6	27.6*
Patients completing 10 weeks' treatment	20.6	20.2	36.2*
Mean change from baseline in bodyweight, adjusted for quit status and grouped according to baseline weight* (kg):			
Normal weight	+1.7	+1.3	+0.5**
Overweight	+1.7	+1.1	-0.1†
Grade I obesity	+1.7	+1.4	-0.1*
Grade II or III obesity	+2.1	+1/4	-0.4‡
* p < 0.005 vs placebo			
** p ≤ 0.01 vs placebo			
† p < 0.0001 vs placebo			
‡ p < 0.001 vs placebo			
* WHO weight classification by body mass index (BMI): Normal range = 18.5–24.9 kg/m ² ; overweight = 25–29.9 kg/m ² ; grade I obesity = 30–34.9 kg/m ² , grade II obesity = 35–39.9 kg/m ² and grade III obesity ≥ 40 kg/m ² .			

Benefits beyond weight loss

A second study presented at the meeting assessed the efficacy of rimonabant in reducing bodyweight in overweight or obese patients with untreated dyslipidaemia. RIO-Lipids,** a randomised, double-blind, parallel-group study enrolled 1036 patients with a BMI of 27–40 kg/m² and elevated triglyceride levels or a high total-cholesterol:HDL-cholesterol ratio.

Following a single-blind 4-week period in which all

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Rimonabant reduces risk factors – continued

patients received placebo, they were assigned to treatment with rimonabant 5mg (n = 345), rimonabant 20mg (346), or placebo (342), once daily for 1 year. Although no specific dietary modifications were prescribed, patients were required to reduce their food intake by 600 Calories per day and were given nutritional guidance.

Weight and abdominal fat reduced

Rimonabant produced significant, dose-dependent reductions in bodyweight, compared with placebo. After 1 year of treatment, the majority of rimonabant 20mg recipients had achieved reductions in bodyweight of $\geq 5\%$ and $\geq 10\%$, relative to baseline [see table 2]. Patients who received rimonabant 20mg had lost an average of 8.6kg, compared with a reduction in bodyweight from baseline of only 2.3kg in the placebo group ($p < 0.001$). Patients treated with rimonabant 5mg also lost significantly more weight than those in the placebo group, although the difference was not as marked as with the 20mg dose.

Importantly, the weight loss observed among patients completing 1 year of treatment with rimonabant 20mg was accompanied by a significant 9.1cm reduction from baseline in waist circumference ($p < 0.001$ versus placebo). Patients treated with rimonabant 5mg also had a significant reduction in waist circumference, compared with placebo recipients, although this was less than in the rimonabant 20mg group. This reduction in waist circumference indicates that rimonabant provides benefits in addition to those of generalised weight loss, as abdominal obesity itself is a risk factor for cardiovascular disease.

Table 2. Effects of rimonabant on bodyweight and metabolic syndrome at 1 year

	Placebo	Rimonabant 5mg	Rimonabant 20mg
Patients with reductions of $\geq 5\%$ in bodyweight from baseline (%)			
Intention-to-treat population	19.5	33*	58.4*
Patients completing 1 year of treatment	27.6	44.8*	72.9*
Patients with reductions of $\geq 5\%$ in bodyweight from baseline (%)			
Patients completing 1 year of treatment	10.3	16.3	44.3*
Patients with metabolic syndrome (%)			
Baseline	51.9	50.8	52.9
1 year	4*	40	25.8*
* $p \leq 0.001$ vs placebo			
** $p < 0.005$ vs placebo			

Improved lipid profile

Significant improvements in serum lipid profiles were observed in patients treated with rimonabant 20mg for 1 year. Relative to baseline, HDL-cholesterol levels increased by an average of 23% and triglyceride levels decreased by an average of 15% among patients receiving rimonabant 20mg (both $p < 0.001$ versus placebo). Although a significant increase in HDL-cholesterol levels was observed in rimonabant 5mg compared with placebo, recipients at 1 year, there was no difference between the two groups with respect to triglycerides.

A shift in LDL-cholesterol particle size was observed at 1 year, with rimonabant 20mg recipients having a 4.7% reduction in the proportion of small particles and an increase of 6.3% in the proportion of large LDL-

cholesterol particles, compared with placebo recipients ($p = 0.002$ and $p < 0.001$ versus placebo, respectively). Small, dense LDL-cholesterol particles are more atherogenic and associated with a greater cardiovascular risk than larger LDL-cholesterol particles.

Among a subgroup of patients in whom these parameters were measured, an increase in adiponectin levels and a reduction in leptin levels were observed after 1 year of treatment with rimonabant 20mg, compared with placebo (both $p \leq 0.001$ versus placebo).

Furthermore, levels of C-reactive protein (CRP), an inflammatory marker associated with cardiovascular risk, were reduced from baseline by 27% in the rimonabant 20mg group, compared with a reduction of only 11% among placebo recipients ($p < 0.01$).

Positive effect on metabolic syndrome

At the 20mg dose level, rimonabant was also shown to improve insulin sensitivity; furthermore, the proportion of patients with metabolic syndrome was reduced, relative to baseline, in this group at 1 year.[†] A 2-hour Oral Glucose Tolerance Test showed that rimonabant 20mg recipients metabolised glucose more efficiently than placebo-treated patients, and had a reduction from baseline in blood glucose levels of 9%, compared with 4% in the placebo group ($p < 0.001$). This improved glycaemic control was achieved with a 22% reduction from baseline in insulin levels in the rimonabant 20mg group, compared with a 2% increase among placebo-treated patients ($p < 0.001$). Treatment with the lower rimonabant dose did not significantly reduce the proportion of patients with metabolic syndrome, compared with placebo.

"Remarkable" effects

"In this study, rimonabant was effective in reducing abdominal obesity, which is now known to be a major independent risk factor for cardiovascular disease," said Dr Jean-Pierre Despres from Laval University and Laval Hospital Center in Quebec City, Canada. "While the weight loss seen was clinically relevant, what is truly remarkable in this study was the significant effect that rimonabant had on improving associated cardiovascular risk factors such as waist circumference, and glucose and lipid profiles".

Favourable tolerability profiles

Rimonabant was generally well tolerated in both studies, with most adverse events being mild and transient. Adverse events among rimonabant recipients included nausea, upper respiratory tract infections and dizziness. The discontinuation rates, including discontinuation due to adverse events, were similar for rimonabant 5mg and 20mg and placebo in both studies. There were no concerns over cardiovascular safety, or over depression and anxiety (assessed using the Hospital Anxiety and Depression scale).

* STRATUS = Studies with Rimonabant And Tobacco Use

** RIO = Rimonabant In Obesity

[†] "Metabolic syndrome" is a combination of health risks and conditions that increase the likelihood of developing diabetes or cardiovascular disease. Patients with metabolic syndrome have ≥ 3 of the following: abdominal obesity (waist circumference of > 102 cm for men or > 88 cm for women), BP $\geq 130/85$ mmHg, triglyceride levels of ≥ 150 mg/dL, HDL-cholesterol levels of < 40 mg/dL for men or < 50 mg/dL for women, and abnormal

Rimonabant reduces risk factors – continued

fasting glucose levels (≥ 110 mg/dL).

1. Dale L, et al. Effects of rimonabant in the reduction of major cardiovascular risk factors: results from the STRATUS-US trial (smoking cessation in smokers motivated to quit) and the RIO-LIPIDS trial (weight reducing and metabolic effects in overweight/obese patients with dyslipidaemia. 53rd Annual Scientific Session of the American College of Cardiology: Late Breaker Abstracts: (1 page), abstr. 409-1 (plus oral presentation), 9 Mar 2004. 80049955

► **Editorial comment:** Rimonabant (Sanofi-Synthelabo) is in phase III of clinical development for the treatment of obesity and smoking withdrawal in the US and Europe.

CCI 779 active in refractory metastatic renal cancer

CCI 779*, an ester analogue of cisplatin, shows activity and has manageable toxicity in patients with refractory metastatic renal cancer, say US-based researchers.

This study involved 111 such patients who were randomised to receive weekly IV infusions of CCI 779 at a dose of 25mg (n = 36), 75mg (38), or 250mg.** Treatment continued until evidence of disease progression or unacceptable toxicity.

The objective response rate for the entire population was 7%, with complete, partial and minor responses obtained in 0.9%, 6.3% and 26.1% of patients, respectively, and disease stabilisation for ≥ 24 weeks in an additional 17.1%. The median time to progression was 5.8 months. Similar efficacy was obtained with weekly doses of 25-, 75- or 250mg.

CCI 779 was associated with maculopapular rash in 76% of patients, mucositis in 70% of patients and asthenia in 50% of patients. Grade 3-4 events included hyperglycaemia (17%), hypophosphataemia (13%), anaemia (9%), and hypertriglyceridaemia (6%).

"Additional study of this agent, either alone or in combination, in appropriately selected patients is warranted", conclude the researchers.

* Wyeth; phase III for renal cancer and phase II for breast cancer, cancer, multiple sclerosis, and prostate cancer.

** The study was supported by Wyeth Research, US.

Atkins MB, Hidaigo M, Stadler WH, Logan TJ, Dattaraj S, et al. Randomized phase II study of multiple dose levels of CCI-779, novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *Journal of Clinical Oncology*, 22: 906-913, Mar 5, 1 Mar 2004. 80098751

News in brief...

■ The small molecule nitric oxide neutraliser, NOX 100*, appears to be beneficial in septic shock, according to phase IIIa clinical trial data presented at the Sixth World Congress on Trauma, Inflammation, Shock and Sepsis in Munich, Germany, on 3 March 2004. This multicentre study involved 56 patients with severe septic shock according to SIRS** criteria, who were randomised to receive IV infusions of NOX 100 at a dosage of 1 mg/kg/hour, 3 mg/kg/hour, 6 mg/kg/hour, 12 mg/kg/hour, or saline placebo, and all other standard supportive therapies considered appropriate by the clinical investigators. After 48 hours haemodynamic response rates were 29, 79, 70 and 63% in the NOX 100 1mg, 3mg, 6mg and 12mg dosage groups, respectively, and

50% in the placebo group. Corresponding 30-day survival rates were 71, 57, 50, 63 and 43%, respectively. NOX 100 was not associated with any adverse events.

Seven phase III studies involving a total of > 13 000 patients are being conducted; four of these studies will evaluate rimonabant in obesity (RIO-North America, RIO-Europe, RIO-Lipids and RIO-Diabetes) and the other three will assess its effects in smoking cessation (STRATUS-US, STRATUS-Europe and STRATUS-Worldwide). This phase III trial programme is expected to be completed by the end of 2004.

* Medinix; phase II for septic shock in the US

** systemic inflammatory response syndrome

Medinix. Medinix Announces the Presentation of NOX-100 Septic Shock Clinical Results at The Sixth World Congress on Trauma, Inflammation, Shock and Sepsis in Munich, Germany on March 3, 2004. Media Release: 8 Mar 2004. Available from: URL: <http://www.medinix.com> 809017095

■ The humanised anti-CD25 monoclonal antibody daclizumab* has improved pulmonary function in a double-blind phase II asthma trial. Patients with chronic, persistent asthma whose disease was not well controlled with high doses of inhaled corticosteroids (n = 114) were randomised in a 3:1 ratio to receive ten doses of daclizumab or placebo at 2-weekly intervals in addition to inhaled corticosteroids. Daclizumab was administered as an initial IV dose of 2 mg/kg followed by subsequent IV doses of 1 mg/kg. At 12 weeks, patients receiving daclizumab experienced a mean increase in FEV₁ of 4.4% of baseline, compared to placebo patients who experienced a mean decrease of 1.5% (p = 0.05). Secondary clinical endpoints supported these findings.

* Protein Design Labs; phase II in the US for asthma. Daclizumab has been launched for renal transplant rejection.

Protein Design Labs Inc. Protein Design Labs Reports Positive Results in Phase II Clinical Trial Of Daclizumab in Asthma. Media Release: 15 Mar 2004. Available from: URL: <http://www.pdl.com> 809032341

■ The immunomodulating agent abetimus* can successfully reduce proteinuria in patients with systemic lupus erythematosus (SLE), according to additional data from a phase III and a phase II/III trial. Among patients with high-affinity antibodies to abetimus [Riquent], those receiving the drug were significantly more likely than those receiving placebo to achieve a $\geq 50\%$ reduction from baseline in the amount of protein in their urine at week 52; these results were observed from measures of 24-hour protein in the phase III trial (41% of abetimus recipients versus 28% of placebo recipients) and in the phase II/III trial (44% versus 18%).

* La Jolla Pharmaceuticals; preregistration in the US for lupus nephritis

La Jolla Pharmaceutical Company. La Jolla Pharmaceutical to Present Additional Riquent(R) Results At SG Cowen Healthcare Conference. Media Release: 11 Mar 2004. Available from: URL: <http://www.ljpc.com> 809032281

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AA 328677
NOTARIA TERCERA
ENCUENTRO 30

ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No.4.539) -----

En la ciudad de Cali, Capital del Depar-
tamento del Valle del Cauca, República de
Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: -----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
por escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----

SEGUNDO: Que en tal carácter, por este público instrumento /concede Poder Especial
pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de
Bogotá, identificado con C.C. # 79.152.473 de Isaquén, abogado en ejercicio, portador
de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo
concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y
oposición a patentes de invención, modelos y dibujos industriales y el registro de
licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad,
medidas cautelares, concesión de licencias y en general los procesos civiles, penales,
administrativos o contencioso-administrativos relacionados con estos derechos u otros de
diferente naturaleza; acciones y procesos que promovamos o se nos promuevan; y c) para

Como Notario Veintitres de este Círculo
hago constar que esta fotocopia coincide
con su fotocopia autentica que he tenido
a la vista.
13 AGO 2007
WILLY VALENZUELA
NOTARIO VEINTITRES
Bogotá D.C. - Colombia

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00523

LUZ MERY CORREA
ELABORACION DE ESCRITURAS
Notaría 3 de Cali

que en todos los asuntos arriba determinados, , tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.

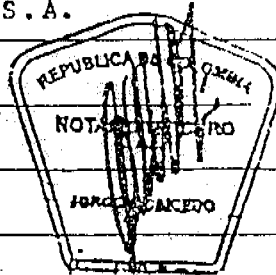
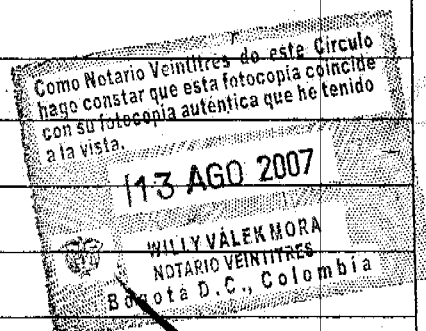
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No. 5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Juan m Barberi

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO