

TRIANA, URIBE & MICHELSEN

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03112574 00000005

Folios: 3

Fecha (AMD): 2005-10-10 12:46:52

Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

MINISTERIO DE COMERCIO INDUSTRIA Y TURISMO
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E.

S.

D.

REFERENCIA : SOLICITUD DE PATENTE DE INVENCION NUEVOS
COMPUESTOS INHIBIDORES DE
FOSFODIESTERASA PARA EL TRATAMIENTO DE
LA IMPOTENCIA EXPEDIENTE No. 03112574

CODIGO : 01 - 01 - 09

Yo, **LAURA MICHELSEN NIÑO**, mayor y vecina de esta ciudad, identificada como aparece al pie de mi firma, obrando en mi calidad de apoderada de **LIU BAOSHUN**, domiciliado en la ciudad de Beijing, China, por medio de la presente me permito solicitar que se efectúe el examen de patentabilidad de la invención de la referencia, teniendo en cuenta lo siguiente:

1. Que el artículo 44 de la Decisión 486 de la Comunidad Andina establece que dentro del plazo de seis (6) meses contados desde la publicación de la solicitud el solicitante debe pedir que se examine si la invención es patentable.
2. Que la patente de la referencia fue publicada en la Gaceta de Propiedad Industrial No. 554 del veintinueve (29) de julio de 2005, y como tal se está dentro del término indicado para solicitar el mencionado examen.
3. Adjunto a la presente anexo el recibo de pago No. 05 – correspondiente a los derechos oficiales por el presente trámite.

De la Señora Jefe,

LAURA MICHELSEN NIÑO

C.C. No. 39.783.287 de Usaquén

T.P.A. No. 45.265 del C.S de la J.

BAOSHUN12/HIPR
COLO 1574 0301 16313

81
35

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINDUSTRIA Y COMERCIO
Radicación : 03112574 00000000 Folios: 3
Fecha (ARD): 2005-10-10 15:46:52
Trámite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 78,051
FECHA : OCTUBRE 7 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
TRIANA URIBE & MICHELSEN CONSIGNACION		BANCO POPULAR	050-00110-6	42209482	07/10/2005	1,241,340.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	86 EXAMEN DE PATENTABILIDAD DE MODEL	248,000.00
		TOTAL :	\$ 248,000.00

CON: DOSCIENTOS CUARENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2020
Bogotá D C

Doctor(a)
LAURA MICHELSEN NIÑO.
Apoderado(a)

REFERENCIA:

Radicación N°	03-112574
Solicitud internacional	PCT/CN02/00433
Fecha límite fase nacional	29/01/2004
Trámite	011
Evento	379
Actuación	416
Oficio N°	258
Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase

Dado en Bogotá D C,

23 MAR 2004



DORIS ELENA POLO CORDOBA
Jefe División de Nuevas Creaciones (E).

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-112574

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **554** DE

FECHA **29 DE JULIO DE 2005** EL TERMINO HABIL EÑALADO POR LA LEY

EXPIRA EL **25 DE OCTUBRE DEL 2005**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO__ _X__ _

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



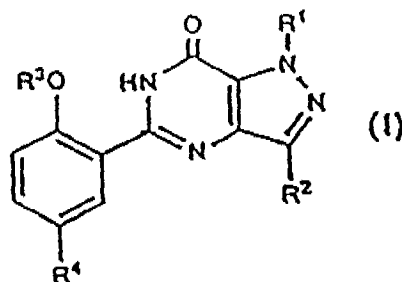
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/505	A1	(11) International Publication Number: WO 94/28902 (43) International Publication Date: 22 December 1994 (22.12.94)
(21) International Application Number: PCT/EP94/01580 (22) International Filing Date: 13 May 1994 (13.05.94) (30) Priority Data: 9311920.4 9 June 1993 (09.06.93) GB (71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (71) Applicant (for all designated States except GB US): PFIZER RESEARCH AND DEVELOPMENT COMPANY, N.V./S.A. [IE/IE]; Alexandra House, Earlsfort Centre, Earlsfort Terrace, Dublin (IE). (71) Applicant (for JP only): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ELLIS, Peter [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). TERRETT, Nicholas, Kenneth [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).	(74) Agents: MOORE, James, William et al.; Pfizer Limited, European Patent Dept., Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (81) Designated States: AU, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.	

(54) Title: PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE

(57) Abstract

The use of a compound of formula (I) wherein R¹ is H; C₁-C₃ alkyl; C₁-C₃ perfluoroalkyl; or C₃-C₅ cycloalkyl; R² is H; optionally substituted C₁-C₆ alkyl; C₁-C₃ perfluoroalkyl; or C₃-C₆ cycloalkyl; R³ is optionally substituted C₁-C₆ alkyl; C₁-C₆ perfluoroalkyl; C₃-C₅ cycloalkyl; C₃-C₆ alkenyl; or C₃-C₆ alkynyl; R⁴ is optionally substituted C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkanoyl, (hydroxy)C₂-C₄ alkyl or (C₂-C₃ alkoxy)C₁-C₂ alkyl; CONR⁵R⁶; CO₂R⁷; halo; NR⁵R⁶; NHSO₂NR⁵R⁶; NHSO₂R⁸; SO₂NR⁹R¹⁰; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl; R⁵ and R⁶ are each independently H or C₁-C₄ alkyl, or together with the



nitrogen atom to which they are attached form an optionally substituted pyrrolidinyl, piperidino, morpholino, 4-N(R¹¹)-piperazinyl or imidazolyl group; R⁷ is H or C₁-C₄ alkyl; R⁸ is optionally substituted C₁-C₃ alkyl; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form an optionally substituted pyrrolidinyl, piperidino, morpholino or 4-N(R¹²)-piperazinyl group; R¹¹ is H; optionally substituted C₁-C₃ alkyl; (hydroxy)C₂-C₃ alkyl; or C₁-C₄ alkanoyl; R¹² is H; optionally substituted C₁-C₆ alkyl; CONR¹³R¹⁴; CSNR¹³R¹⁴; or C(NH)NR¹³R¹⁴; and R¹³ and R¹⁴ are each independently H; C₁-C₄ alkyl; or substituted C₂-C₄ alkyl; or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man; a pharmaceutical composition for said treatment; and a method of said treatment of said male animal with said pharmaceutical composition or with said either entity.

88
88PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE

This invention relates to the use of a series of pyrazolo[4,3-d]pyrimidin-7-ones for the treatment of impotence.

Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c. injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E₁, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been

86
27

2

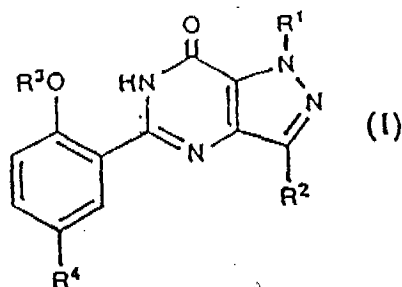
shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004, namely in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Unexpectedly, it has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of a compound of formula (I):

84
9/0



wherein R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;
 R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;
 R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
 R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7 ; C_2-C_4 alkanoyl optionally substituted with NR^5R^6 ; (hydroxy) C_2-C_4 alkyl optionally substituted with NR^5R^6 ; (C_2-C_3 alkoxy) C_1-C_2 alkyl optionally substituted with OH or NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halo; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;
 R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4- $N(R^{11})$ -piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

88
dl

4

R^7 is H or C_1-C_4 alkyl;

R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6 ;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidiny, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy) C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy) C_2-C_6 alkyl; (hydroxy) C_2-C_6 alkyl; ($R^{13}R^{14}N$) C_2-C_6 alkyl; ($R^{13}R^{14}NOC$) C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$;

and R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy) C_2-C_4 alkyl; or (hydroxy) C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms, alkenyl and alkynyl groups having four or more carbon atoms, alkoxy groups having three carbon atoms and alkanoyl groups having four carbon atoms may be straight chain or branched chain. Halo means fluoro, chloro, bromo or iodo.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. Furthermore, certain compounds of formula (I) which contain alkenyl groups

89
92

may exist as cis-isomers or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. Compounds of formula (I) can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl or allyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; acetyl optionally substituted with NR^5R^6 ; hydroxyethyl optionally substituted with NR^5R^6 ; ethoxymethyl optionally substituted with OH or NR^5R^6 ; $CH=CHCN$; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H ; Br; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with $NR^{13}R^{14}$ or $CONR^{13}R^{14}$; R^{11} is H, methyl, benzyl, 2-

90
93

6

hydroxyethyl or acetyl; R^{12} is H, C_1 - C_3 alkyl, (hydroxy) C_2 - C_3 alkyl, $CSNR^{13}R^{14}$ or $C(NH)NR^{13}R^{14}$; and R^{13} and R^{14} are each independently H or methyl.

A more preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is C_1 - C_3 alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $CH_2NR^5R^6$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $CH_2OCH_2CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, $CONR^5R^6$, CO_2H , Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, $SO_2NR^9R^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4- $N(R^{11})$ -piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4- $N(R^{12})$ -piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, C_1 - C_3 alkyl, 2-hydroxyethyl or $CSNH_2$.

A particularly preferred group of compounds of formula (I) is that wherein R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $COCH_2NR^5R^6$, $CONR^5R^6$, $SO_2NR^9R^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4- $N(R^{11})$ -piperazinyl group; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- $N(R^{12})$ -piperazinyl group; R^{11} is methyl or acetyl; and R^{12} is H, methyl, 2-propyl or 2-hydroxyethyl.

Especially preferred individual compounds of the invention include:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

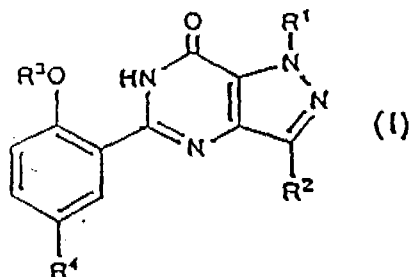
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

21
74

13

CLAIMS

1. The use of a compound of formula (I):



wherein R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl; or C_3-C_5 cycloalkyl;
 R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;
 R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
 R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7 ; C_2-C_4 alkanoyl optionally substituted with NR^5R^6 ; (hydroxy) C_2-C_4 alkyl optionally substituted with NR^5R^6 ; (C_2-C_3 alkoxy) C_1-C_2 alkyl optionally substituted with OH or NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halo; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;
 R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4- $N(R^{11})$ -piperazinyl

92
95

14

or imidazolyl group wherein said group is optionally substituted with methyl or OH;
 R^7 is H or C_1-C_4 alkyl;
 R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6 ;

R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-

piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy) C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy) C_2-C_6 alkyl; (hydroxy) C_2-C_6 alkyl; ($R^{13}R^{14}N$) C_2-C_6 alkyl; ($R^{13}R^{14}NOC$) C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$;

and R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy) C_2-C_4 alkyl; or (hydroxy) C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

2. The use according to claim 1 wherein in the compound of formula (I) R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl or allyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; acetyl optionally substituted with NR^5R^6 ; hydroxyethyl optionally substituted with NR^5R^6 ; ethoxymethyl optionally substituted with OH or NR^5R^6 ; $CH=CHCN$; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; $CONR^5R^6$; CO_2H ; Br; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or pyridyl or

93
96

15

imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH; R^7 is H or t-butyl; R^8 is methyl or $\text{CH}_2\text{CH}_2\text{CH}_2\text{NR}^5\text{R}^6$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a piperidino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with $\text{NR}^{13}\text{R}^{14}$ or $\text{CONR}^{13}\text{R}^{14}$; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; R^{12} is H, $\text{C}_1\text{-C}_3$ alkyl, (hydroxy) $\text{C}_2\text{-C}_3$ alkyl, $\text{CSNR}^{13}\text{R}^{14}$ or $\text{C}(\text{NH})\text{NR}^{13}\text{R}^{14}$; and R^{13} and R^{14} are each independently H or methyl.

3. The use according to claim 2 wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is $\text{C}_1\text{-C}_3$ alkyl; R^3 is ethyl, n-propyl or allyl; R^4 is $\text{CH}_2\text{NR}^5\text{R}^6$, $\text{COCH}_2\text{NR}^5\text{R}^6$, $\text{CH}(\text{OH})\text{CH}_2\text{NR}^5\text{R}^6$, $\text{CH}_2\text{OCH}_2\text{CH}_3$, $\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{OCH}_2\text{CH}_2\text{NR}^5\text{R}^6$, $\text{CH}=\text{CHCON}(\text{CH}_3)_2$, $\text{CH}=\text{CHCO}_2\text{R}^7$, CONR^5R^6 , CO_2H , Br, $\text{NHSO}_2\text{NR}^5\text{R}^6$, $\text{NHSO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NR}^5\text{R}^6$, $\text{SO}_2\text{NR}^9\text{R}^{10}$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-N(R^{11})-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-carbamoylpiperidino or 4-N(R^{12})-piperazinyl group; R^{11} is H, methyl, benzyl, 2-hydroxyethyl or acetyl; and R^{12} is H, $\text{C}_1\text{-C}_3$ alkyl, 2-hydroxyethyl or CSNH_2 .

4. The use according to claim 3 wherein in the compound of formula (I) R^1 is methyl or ethyl; R^2 is n-propyl; R^3 is ethyl, n-propyl or allyl; R^4 is $\text{COCH}_2\text{NR}^5\text{R}^6$, CONR^5R^6 , $\text{SO}_2\text{NR}^9\text{R}^{10}$ or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholino or 4-N(R^{11})-piperazinyl

94
17

16

group; R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a 4-N(R¹²)-piperazinyl group; R¹¹ is methyl or acetyl; and R¹² is H, methyl, 2-propyl or 2-hydroxyethyl.

5. The use according to claim 4 wherein the compound of formula (I) is selected from:

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

6. A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, together



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 463 756 A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: **91305137.1**

(51) Int. Cl.⁵: **C07D 487/04, A61K 31/505,
A61K 31/635**

(22) Date of filing: **07.06.91**

(30) Priority: **20.06.90 GB 9013750**

(43) Date of publication of application:
02.01.92 Bulletin 92/01

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: **Pfizer Limited**
Ramsgate Road
Sandwich Kent CT13 9NJ(GB)

(84) **GB**

Applicant: **PFIZER INC.**
235 East 42nd Street
New York, N.Y. 10017(US)

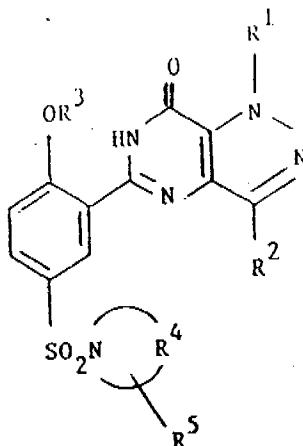
(84) **BE CH DE DK ES FR GR IT LI LU NL SE AT**

(72) Inventor: **Bell, Andrew Simon**
Pfizer Central Research
Sandwich, Kent CT13 9NJ(GB)
Inventor: **Brown, David, Dr.**
Pfizer Central Research
Sandwich, Kent CT13 9NJ(GB)
Inventor: **Terrett, Nicholas Kenneth, Dr.**
Pfizer Central Research
Sandwich, Kent CT13 9NJ(GB)

(74) Representative: **Moore, James William, Dr.**
Pfizer Limited Ramsgate Road
Sandwich Kent CT13 9NJ(GB)

(54) **Pyrazolopyrimidinone antianginal agents.**

(57) Compounds of the formula:



(I)

wherein R¹ is H, C₁-C₃ alkyl, C₃-C₅ cycloalkyl or C₁-C₃ perfluoroalkyl; R² is H, C₁-C₆ alkyl optionally substituted by OH, C₁-C₃ alkoxy or C₃-C₆ cycloalkyl, or C₁-C₃ perfluoroalkyl; R³ is C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₇ cycloalkyl, C₁-C₆ perfluoroalkyl or (C₃-C₆ cycloalkyl)C₁-C₆ alkyl; R⁴ taken together with the nitrogen atom to which it is attached completes a pyrrolidinyl, piperidino, morpholino, or 4-N-(R⁵)-piperazinyl group; R⁵ is H, C₁-C₄ alkyl, C₁-C₃ alkoxy, NR⁷R⁸, or CONR⁷R⁸; R⁶ is H, C₁-C₆ alkyl, (C₁-C₃ alkoxy) C₂-C₆ alkyl, hydroxy C₂-C₆ alkyl, (R⁷R⁸N)C₂-C₆ alkyl, (R⁷R⁸NCO)C₁-C₆ alkyl, CONR⁷R⁸, CSNR⁷R⁸ or C(NH)NR⁷R⁸; R⁷ and R⁸ are each independently H, C₁-C₄ alkyl, (C₁-C₃ alkoxy)C₂-C₄ alkyl or hydroxy C₂-C₄ alkyl; and

EP 0 463 756 A1

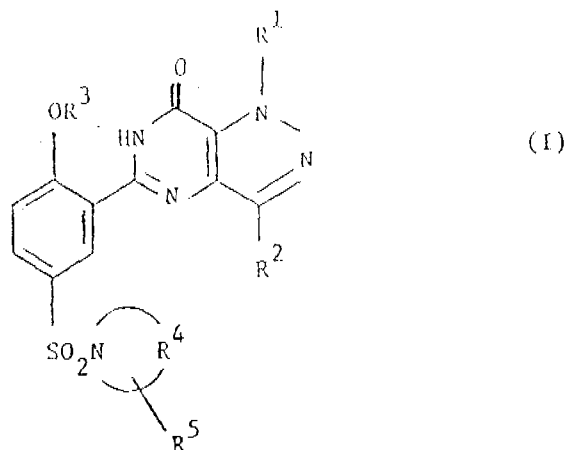
97
100

This invention relates to a series of pyrazolo[4,3-d]pyrimidin-7-ones, which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE), having utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial platelet anti-aggregatory, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

European patent application EP-A-0201188 discloses certain pyrazolo[4,3-d]pyrimidin-7-ones as adenosine receptor antagonists and PDE inhibitors, useful in the treatment of cardiovascular disorders such as heart failure or cardiac insufficiency. However these compounds are neither particularly potent PDE inhibitors, nor are they claimed to be selective inhibitors of cGMP PDE.

The compounds of the present invention are of the formula (I):



wherein

R¹ is H, C₁-C₃ alkyl, C₃-C₅ cycloalkyl or C₁-C₃ perfluoroalkyl;

R² is H, C₁-C₆ alkyl optionally substituted by OH, C₁-C₃ alkoxy or C₃-C₆ cycloalkyl, or C₁-C₃ perfluoroalkyl;
R³ is C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₇ cycloalkyl, C₁-C₆ perfluoroalkyl or (C₃-C₆ cycloalkyl)-C₁-C₆ alkyl;

R⁴ taken together with the nitrogen atom to which it is attached completes a pyrrolidinyl, piperidino, morpholino, or 4-N-(R⁶)-piperazinyl group;

R⁵ is H, C₁-C₄ alkyl, C₁-C₃ alkoxy, NR⁷R⁸, or CONR⁷R⁸;

R⁶ is H, C₁-C₆ alkyl, (C₁-C₃ alkoxy) C₂-C₆ alkyl, hydroxy C₂-C₆ alkyl, (R⁷R⁸N)C₂-C₆ alkyl, (R⁷R⁸NCO)C₁-C₆ alkyl, CONR⁷R⁸, CSNR⁷R⁸ or C(NH)NR⁷R⁸;

R⁷ and R⁸ are each independently H, C₁-C₄ alkyl, (C₁-C₃ alkoxy)C₂-C₄ alkyl or hydroxy C₂-C₄ alkyl; and pharmaceutically acceptable salts thereof.

In the above definition, unless otherwise indicated, alkyl or perfluoroalkyl groups having three or more carbon atoms may be straight or branched chain. In addition alkenyl or alkynyl groups having four or more carbon atoms, or alkoxy groups having three carbon atoms, may be straight or branched chain.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers or diastereoisomers. The invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate and tartrate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of the formula (I) is that wherein R¹ is H, methyl or ethyl; R² is C₁-C₃ alkyl optionally substituted by OH or methoxy; R³ is C₂-C₃ alkyl or allyl; R⁴ taken together with the nitrogen atom to which it is attached completes a piperidino or 4-N-(R⁶) piperazinyl group; R⁵ is H, NR⁷R⁸ or CONR⁷R⁸; R⁶ is H, C₁-C₃ alkyl, hydroxy C₂-C₃ alkyl, CONR⁷R⁸, CSNR⁷R⁸ or C(NH)NR⁷R⁸; and R⁷ and R⁸ are each independently H or methyl.

A particularly preferred group of compounds of the formula (I) is that wherein R¹ is methyl; R² is n-propyl; R³ is ethyl, n-propyl or allyl; R⁴ taken together with the nitrogen atom to which it is attached completes a 4-N-(R⁶) piperazinyl group; R⁵ is H; and R⁶ is H, C₁-C₃ alkyl or 2-hydroxyethyl.

Especially preferred individual compounds of the invention include:

5-[2-allyloxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

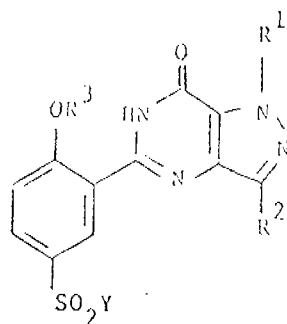
5-{2-ethoxy-5-[4-(2-propyl)piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)piperazinylsulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-methyl-5-[5-piperazinylsulphonyl]-2-n-propoxyphenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

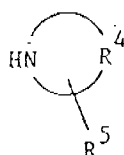
and 5-{5-[4-(2-hydroxyethyl)piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The compounds of the general formula (I) may be prepared by the reaction of a compound of the general formula (II):



(II)

(wherein R¹, R² and R³ are as previously defined, and Y represents a halogen atom, preferably a chlorine atom) with a compound of the general formula (III):



(III)

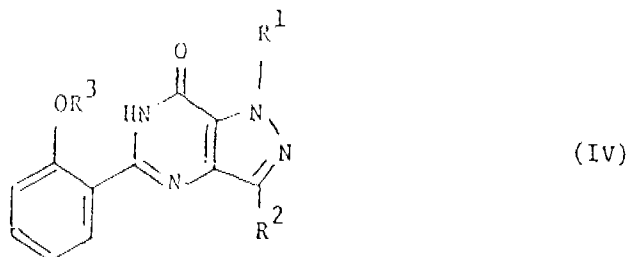
wherein R⁴ and R⁵ are as previously defined.

The reaction is generally carried out at room temperature, preferably in the presence of a solvent, for example an alkanol containing one to three carbon atoms, using an excess of (III) to scavenge the acid by-

98
102

product (HY).

Compounds of the general formula (II) may be prepared from compounds of the general formula (IV):

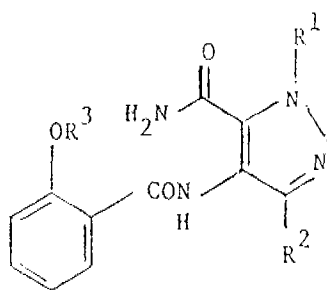


15 (wherein R¹, R² and R³ are as previously defined) by the application of known methods for the introduction of a SO₂Y group (wherein Y is as previously defined) into an aromatic ring, for example, when Y represents a chlorine atom, by the action of chlorosulphonic acid at or near 0°C.

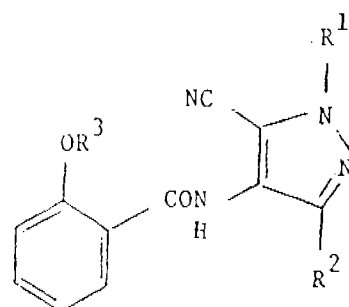
When R³ is a group susceptible to removal under the chlorosulphonylation conditions, e.g. allyl, said group can be introduced in the final stage of the synthesis. Thus the phenol of the general formula (IV), wherein R³ is H, and R¹ and R² are as previously defined, which is obtainable by Pd⁺-mediated deprotection of the O-allyl analogue as illustrated by Example 25, is chlorosulphonylated to provide a compound of the general formula (II), wherein Y is Cl, R³ is H, and R¹ and R² are as previously defined. The latter is then reacted with the appropriate amine (III) to afford a compound of the general formula (I), wherein R³ is H, and R¹, R², R⁴ and R⁵ are as previously defined, which is finally O-alkylated to furnish a compound of the general formula (I), wherein R¹, R², R³, R⁴ and R⁵ are as defined for formula (I). The alkylation may be effected under standard conditions using the appropriate alkyl halide, e.g. allyl bromide, in the presence of a base such as potassium carbonate, in a suitable solvent, e.g. 2-butanone, at the reflux temperature of the reaction mixture. Alternatively, the alkylation may be achieved under conventional Mitsunobu reaction conditions.

30 In the case of other compounds of formula (IV) which may be incompatible with the chlorosulphonylation reaction conditions, e.g. those wherein R² is hydroxy C₁-C₆ alkyl, the hydroxy group can be protected with an acyl group such as acetyl or benzoyl. Said protecting group is subsequently removed at the final stage of the synthesis, under standard base hydrolysis conditions, to give compounds of the general formula (I) wherein R² is hydroxy C₁-C₆ alkyl, and R¹, R³, R⁴ and R⁵ are as defined for formula (I).
35 These latter compounds may also be obtained incidentally, as by-products, by chlorosulphonylation of the corresponding alkoxy analogues, i.e. compounds of the general formula (IV) wherein R² is (C₁-C₃ alkoxy)C₁-C₆ alkyl, followed by reaction of the crude product with the required amine (III), as illustrated by Example 48.

Compounds of the general formula (IV) may be prepared from compounds of the general formula (V):



(V)



(VI)

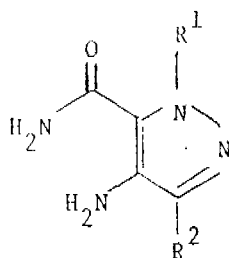
55 (wherein R¹, R² and R³ are as previously defined) by the application of known cyclisation methods for pyrimidinone ring formation. Thus, for example, the cyclisation may be effected by the treatment of (V) with a base such as sodium hydroxide or potassium carbonate, optionally in the presence of hydrogen peroxide,

100
103

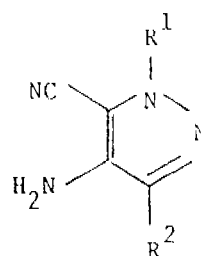
in an ethanol-water medium at reflux temperature for 2-40 hours. Under these conditions the related nitrile of general formula (VI), wherein R^1 , R^2 and R^3 are as previously defined, may also be employed as the precursor to (IV).

In an alternative cyclisation procedure, compounds of the general formula (IV) may be obtained by treatment of (V) with polyphosphoric acid at or near 140°C for 6-18 hours.

Compounds of the general formulae (V) and (VI) may be prepared from compounds of the general formulae (VII) and (VIII) respectively:

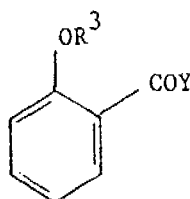


(VII)



(VIII)

(wherein R^1 and R^2 are as previously defined) by reaction with a compounds of general formula (IX):



(IX)

(wherein R^3 and Y are as previously defined).

The reaction is generally carried out using an excess of (IX) in the presence of an excess of an aliphatic tertiary amine such as triethylamine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylamino-pyridine, in an inert solvent such as dichloromethane at 0°C to 25°C for 2-6 hours.

The amines of formula (III), the aminopyrazoles of formulae (VII) and (VIII), and the acyl halides of formula (IX), when not commercially available, can be obtained by conventional synthetic procedures, in accordance with literature precedent, from readily accessible starting materials using standard reagents and reaction conditions.

Certain of the compounds of the general formula (I), wherein R^4 taken together with the nitrogen atom to which it is attached completes a 4-N-(R^6)-piperazinyl group and R^6 is as previously defined but not hydrogen, may be prepared directly from the corresponding 4-N-unsubstituted piperazine analogue, that is a compound of the general formula (I) wherein R^6 is hydrogen, using appropriate standard synthetic procedures.

All of the above reactions are entirely conventional and appropriate reagents and conditions for their performance can readily be established by reference to standard text books and to the examples provided hereafter. Alternatives and variations will also be evident to the person skilled in the art to enable all the compounds defined by formula (I) to be prepared.

The biological activities of the compounds of the present invention were determined by the following test methods.

Phosphodiesterase activity

Compound affinities for cGMP and cAMP PDEs are assessed by determination of their IC_{50} values (the

101
104

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., Enero 25 de 2008

Abogado
LAURA MICHELSEN NIÑO

ASUNTO	Radicación	03 - 112574
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	2366
	Folios	27

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒
No. Sol. Internacional	PCT/CN02/00433		
Fecha de Presentación Internal.	Junio 21 de 2002		

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:

1. Documentos estudiados

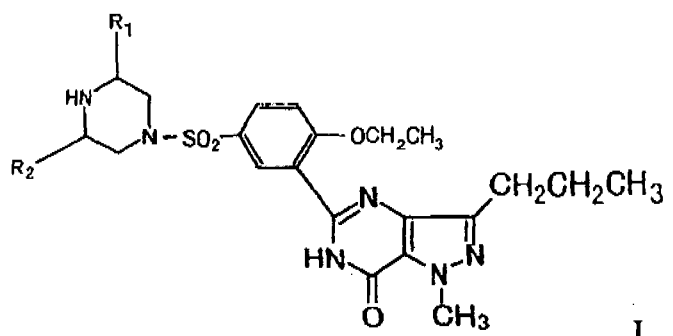
- 1.1. Descripción: Folios: 4 a 19 (como se radicó inicialmente)
- 1.2. Reivindicaciones: Folios: 20 a 26 (como se radicó inicialmente)
- 1.3. Prioridad: CN 01129691.7 del 29 de Junio de 2001

2. Objeto de la invención

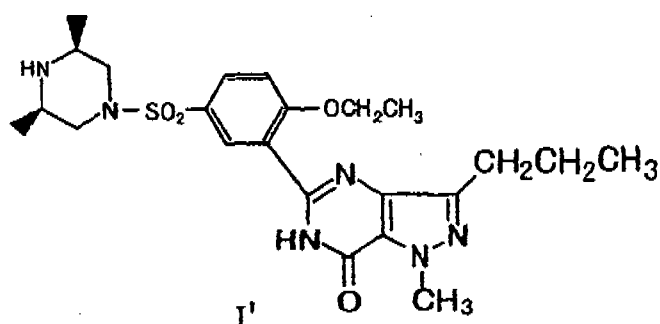
- Título: "NUEVOS COMPUESTOS INHIBIDORES DE FOSFODIESTERASA PARA EL TRATAMIENTO DE LA IMPOTENCIA" Modificado en Folio 66.

El objeto de la presente solicitud de patente de invención consiste en:

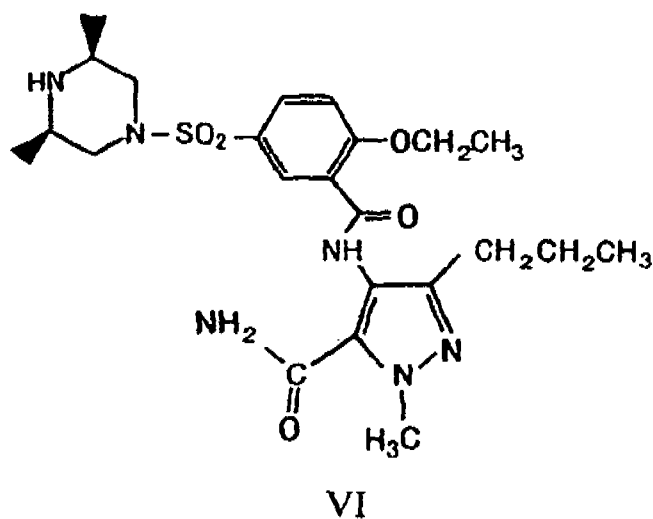
- Reivindicaciones de la 1 a la 2: Un Compuesto de fórmula (I):



- **Reivindicación 3:** Método para preparar el Compuesto de Fórmula (I')



- **Reivindicación 4:** Un Compuesto de fórmula (VI):



- **Reivindicaciones de la 5 a la 6:** Una composición farmacéutica, de un compuesto de fórmula (I)
- **Reivindicaciones de la 7 a la 8:** Usos

El **problema planteado en la presente solicitud** es suministrar compuestos que sean inhibidores selectivos de la fosfodiesterasa; y los cuales son útiles en el tratamiento de enfermedades de la impotencia tal como la disfunción eréctil masculina.

Para **resolver este problema técnico**, la **solicitud en estudio proporciona** un compuesto de fórmula (I) y una composición farmacéutica del mismo.

El objeto de la invención definido anteriormente se clasifico de acuerdo con la IPC: **A61K 31/505**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

- En la **Reivindicación 3**: en el ítem (d), se solicita aclarar en el texto la correspondencia de compuesto obtenido (IV); ya que el mismo no corresponde al obtenido en la reacción (VI).
- En la **Reivindicación 5**: Cuando se este definiendo los componentes de una composición farmacéutica, la misma en su definición no debe incluir usos. Se solicita se aclara la misma.
- En las **Reivindicaciones 1**: las palabras y/o expresiones: "iguales o diferentes"; no es concisa, y es muy amplia; por tanto no permite delimitar allí la materia a proteger.

Por lo anteriormente expuesto, es preciso requerir al interesado para que señale el verdadero alcance de su invención.

4. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486)

Las **reivindicaciones** de la **7** a la **8** reclaman USO, y de acuerdo con la legislación Colombiana, el uso reclamado NO se considera para protección por patente.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: **Junio 29 de 2001**

Teniendo en cuenta la fecha indicada 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; **aclarando, que esta búsqueda se realizó únicamente para aquellas partes que parecen ser claras y/o concisas:**

Nº	Documento	Título	Fecha de publicación
D1	WO 94/28902	PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF IMPOTENCE	Diciembre 22 de 1994
D2	EP 0463756	PYRAZOLOPYRIMIDINONE ANTIANGINAL AGENTS	Junio 07 de 1991

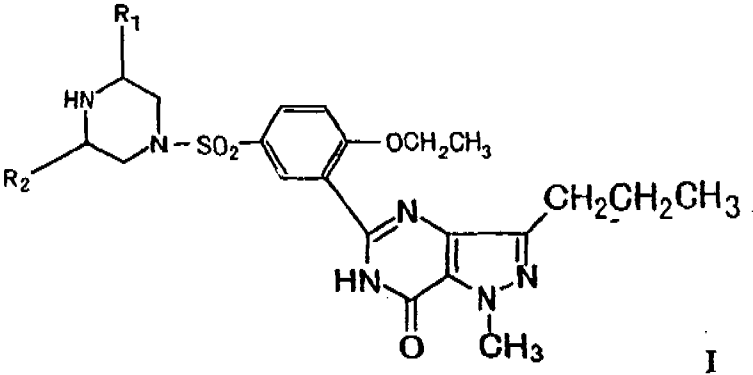
6. Análisis de patentabilidad (artículo 14 D486)

104
107

6.1 Novedad (artículo 16 D486)

La Novedad se evaluó por comparación entre lo solicitado y lo encontrado en el estado de la técnica.

- **Reivindicaciones** de la 1 a la 2: Un Compuesto de fórmula (I):



- **Reivindicaciones** de la 5 a la 6: Una composición farmacéutica, de un compuesto de fórmula (I)

La solicitud del Compuesto de fórmula (I) se encuentra ampliamente divulgada en la publicación **WO 94/28902**, como a continuación se evidencia:

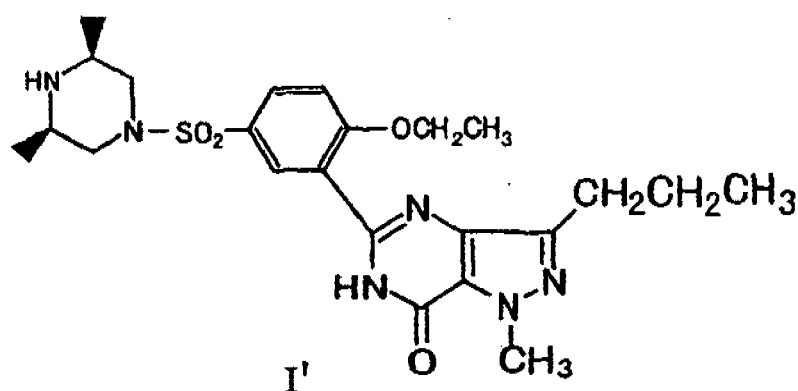
CARACTERISTICAS ESENCIALES DE LA SOLICITUD COLOMBIANA No. 03-112574	D1 = WO 94/28902
Un compuesto de fórmula (I): I R1= Alquilo C1-6 R2= Alquilo C1-6	Un compuesto de fórmula (I): (I) R1= H, Alquilo C1-3 R2= H, Alquilo C1-6 R3= Alquilo C1-6 R4= SO2NR9R10 R9 y R10= unidos al átomo de N, para formar Piperazinilo, opcionalmente sustituido con Alquilo de C1-4 Págs. 13 y 14 Reivindicaciones del documento

Teniendo en cuenta el objeto de la invención y la materia descrita en la anterioridad **D1**, esta dependencia se permite señalar que existe afectación al requisito de Novedad, ya que resulta idéntico al publicado en el estado de la técnica. Es decir que el Compuesto de fórmula (I) como tal, no es nuevo; como tampoco es nueva la composición farmacéutica del mismo.

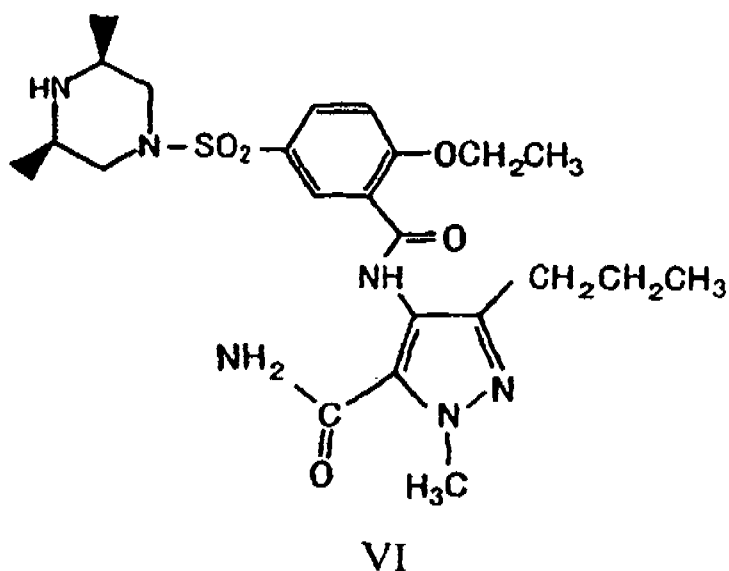
6.2 Nivel inventivo (artículo 18 D486)

El Nivel Inventivo se evaluó por comparación entre lo solicitado y lo encontrado en el estado de la técnica.

- **Reivindicación 3:** Método para preparar el Compuesto de Fórmula (I')

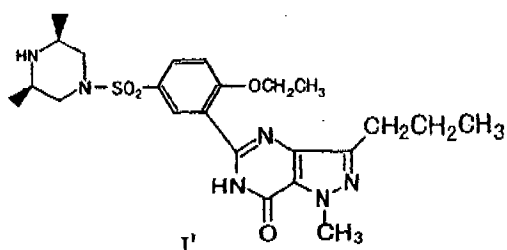


- **Reivindicación 4:** Un Compuesto de fórmula (VI):

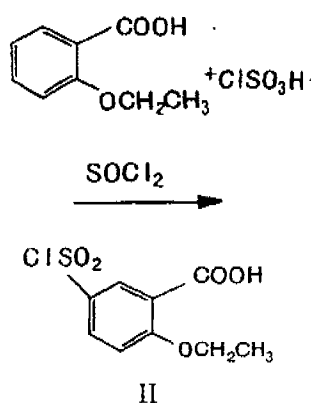


**CARACTERÍSTICAS ESENCIALES DE LA
SOLICITUD COLOMBIANA No. 03-112574**

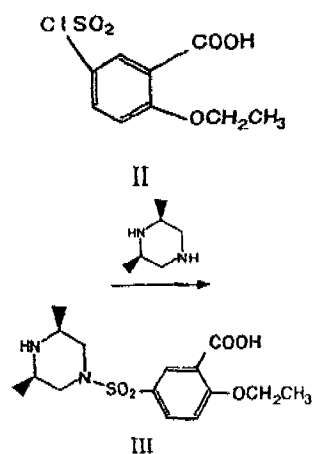
1. Un método para la preparación de un compuesto de fórmula (I'):



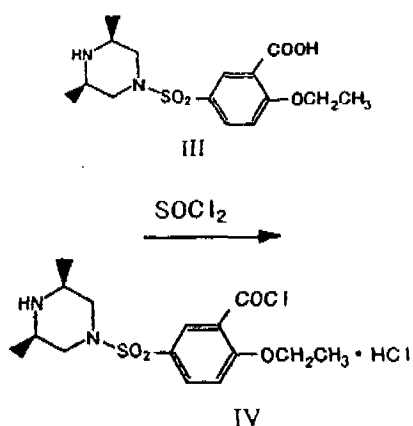
(a) Reacción:



(b) Reacción:



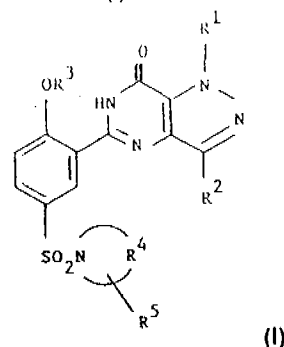
(c) Acilar:



(d) Reacción, en presencia de 4-dimetilaminopiridina y trietilamina:

D2 = EP 0463756

1. Un procedimiento para la preparación de un compuesto de fórmula (I):



R1= Alquilo C1-3

R2= Alquilo C1-6

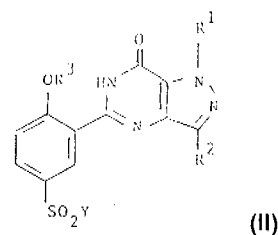
R3= Alquilo C1-6

R4= Tomado conjuntamente con el átomo de Nitrógeno al que esta unido completamente a un grupo 4-N-(R6)-Piperazinilo

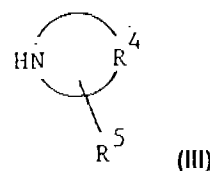
R5= Alquilo C1-4

R6= Alquilo C1-6

Los Compuestos de fórmula general (I) pueden prepararse por reacción de un compuesto de fórmula general (II):

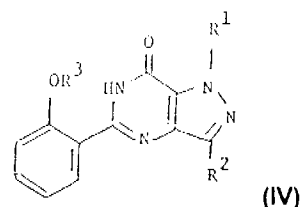


+



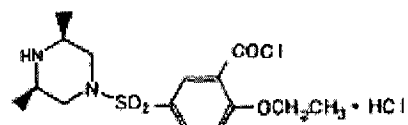
Reacción a temperatura ambiente en presencia de un disolvente

Los Compuestos de fórmula general (II) pueden prepararse a partir de compuestos de fórmula general (IV):

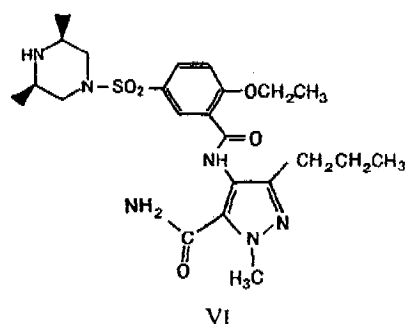
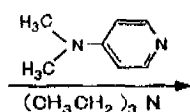
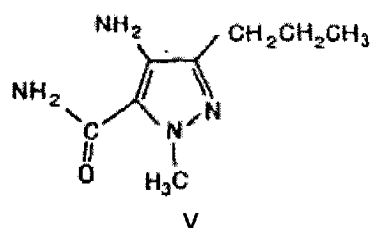


Nota:

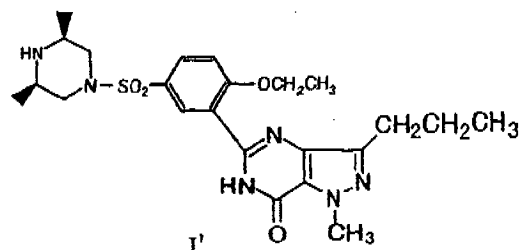
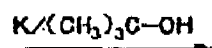
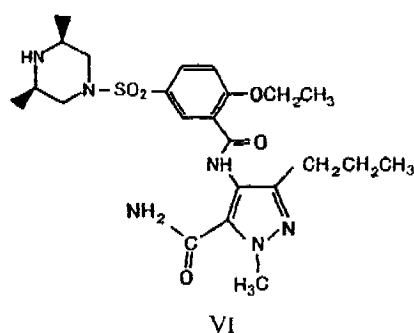
- Por procedimientos conocidos en el arte, se realiza la introducción de un grupo SO₂Y en un anillo aromático. Por ejemplo cuando Y representa un átomo de Cl por acción del ácido clorosulfónico a o



+



(e) Ciclizar:

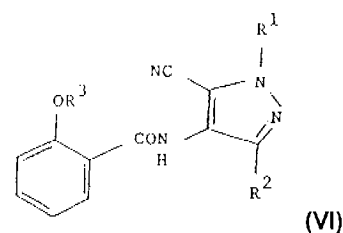
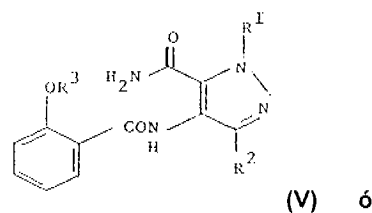


cerca de los 0°C.

- Cuando R3 es un grupo susceptible de ser eliminado en las condiciones del clorosulfonación; dicho grupo puede introducirse en la etapa final de síntesis.



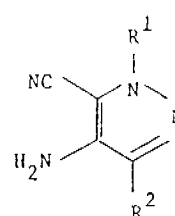
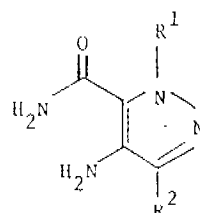
Los Compuestos de fórmula general (IV) pueden prepararse a partir de compuestos de fórmula general (V) ó (VI):



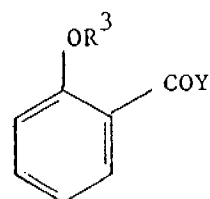
Por aplicación de procedimientos de ciclación ya conocidos en el estado del arte, para la formación del anillo de pirimidona.



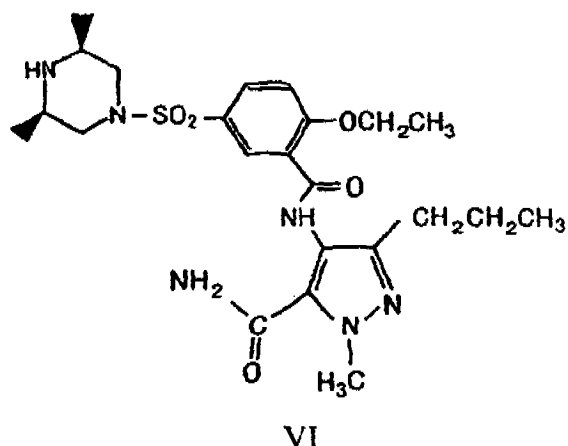
Los Compuestos de fórmula general (V) y (VI) pueden prepararse a partir de compuestos de fórmulas generales (VII) y (VIII):



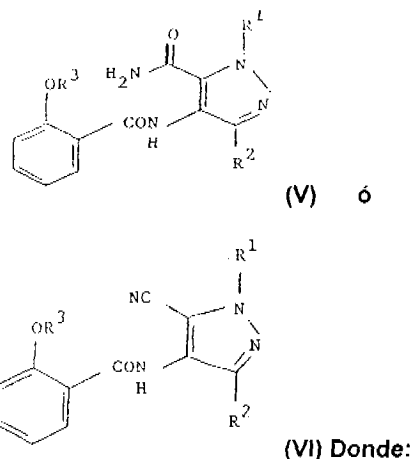
Esta reacción en presencia de una amina terciaria alifática (triethylamina) que actúa como fijador del subproducto ácido opcional en presencia de un catalizador tal como lo es la 4-dimetilaminopiridina.



2. Un compuesto de fórmula (VI):



2. Un compuesto de fórmula (V) o (VI):



R1= Alquilo C1-3
R2= Alquilo C1-6
R3= Alquilo C1-6

Nota:

- Por procedimientos conocidos en el arte, se realiza la introducción de un grupo SO₂Y en un anillo aromático. Por ejemplo cuando Y representa un átomo de Cl por acción del ácido clorosulfónico a o cerca de los 0°C.

Páginas 1 a 6 del documento.

Método de preparación de compuestos de fórmula (I'):

Comparando las características esenciales de la solicitud, las cuales corresponden a un método para la preparación de un compuesto de fórmula (I'); el **documento del estado de la técnica más cercano es D2**, que divulga un Procedimiento para la preparación de un compuesto de fórmula (I), divulgando reacciones convencionales como por ejemplo: introducción de grupos SO₂ en un anillo aromático, preparaciones de las aminas de fórmula (III), los aminopirazoles de fórmulas (VII) y (VIII) y los haluros de acilo de fórmula (IX) a partir de procesos ya conocidos en el estado de la técnica.

La **única diferencia con D2 de la presente solicitud** es que en ésta el método de preparación se utiliza una Piperazina 4-N-disustituida. Pero esto **NO parece conceder un efecto técnico inesperado** ya que para el experto en la materia basándose en este documento y en su conocimiento básico hubiese llegado a definir un método similar, de manera que **un experto en la materia lo lograría fácil y obviamente** sin necesidad de emplear **Habilidad Inventiva** para dicho método de preparación de los compuestos de fórmula (I').

Ya que **no hay un efecto técnico apreciable** ni datos en la memoria descriptiva que así lo confirmen; el **Problema Técnico Objetivo** fundamental de la Invención Reivindicada **no puede definirse**, en suministrar compuestos que sean inhibidores selectivos de la fosfodiesterasa; y los cuales sean útiles en el tratamiento de enfermedades de la impotencia tal como la disfunción eréctil masculina.

Así que, el problema planteado en la solicitud, **sería solucionado fácilmente por el experto en la materia** ya que hubiese sido obvio plantear un método similar teniendo en cuenta **D2**.

Compuesto de fórmula (VI):

Comparando las características esenciales de la solicitud, las cuales corresponden a un compuesto de fórmula (VI); el **documento del estado de la técnica más cercano es D2**, ya que divulga un compuesto de fórmula (V) y otro de fórmula (VI), acotando en ellos que se pueden aplicar procedimientos conocidos de ciclación para la formación del anillo de pirimidona. Por ejemplo la ciclación del compuesto (V) puede realizarse por tratamiento con una base, opcionalmente en presencia de peróxido de hidrógeno, en un medio de metanol-agua a temperatura de reflujo durante 2 a 40 horas. De igual manera sugieren que por procedimientos ya conocidos en el estado de la técnica éstos compuestos pueden introducir un grupo SO₂ en un anillo aromático.

La **única diferencia con D2 de la presente solicitud** es que en ésta el método de preparación se utiliza con una Piperazina 4-N-disustituida. Pero esto **NO parece conceder un efecto técnico inesperado** ya que para el experto en la materia basándose en este documento y en su conocimiento básico hubiese llegado a definir un método similar, de manera que **un experto en la materia lo lograría fácil y obviamente** sin necesidad de emplear **Habilidad Inventiva** para obtener dicho compuesto de formula (VI).

Ya que **no hay un efecto técnico apreciable** ni datos en la memoria descriptiva que así lo confirmen; el **Problema Técnico Objetivo** fundamental de la Invención Reivindicada **no puede definirse**, en suministrar compuestos que sean inhibidores selectivos de la fosfodiesterasa; y los cuales sean útiles en el tratamiento de enfermedades de la impotencia tal como la disfunción eréctil masculina.

Así que, el problema planteado en la solicitud, **sería solucionado fácilmente por el experto en la materia** ya que hubiese sido obvio obtener un compuesto igual teniendo en cuenta **D2**.

Como resultado de lo anterior se considera que:

- **EL Método para la preparación de un compuesto de fórmula (I')**
- **Y el Compuesto de fórmula VI**

Carecen de Nivel Inventivo; ya que la **Método para la preparación de un compuesto de fórmula (I')** es **alternativo** a los previamente conocidos en el estado de la técnica y el **Compuesto de fórmula VI** se obtiene a través del mismo método de preparación.

7. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO 94/28902	1 a 2 y 5 a 6	Novedad
D2	EP 0463756	3 y 4	Nivel Inventivo

113

110

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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
15 FEB 2008

CONCEPTO TÉCNICO No. 53	EXAMINADOR TÉCNICO Código No. 202080
--------------------------------	---