



No. 13-046988-00000-0000

Fecha: 2013-03-08 15:49:25

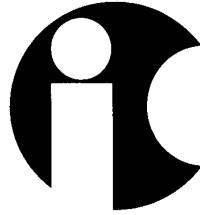
Tra. 11 PATENTE I/II

Act. 411 PRESENTACION

Dep. 2020 DIR.NUEVASCR

Eve: 378 FASE NACIONAL I

Folios: 99

**Industria y Comercio**

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

**SOLICITUD
PATENTE DE INVENCION**21. **EXPEDIENTE No.** _____54. **TÍTULO** Derivados de 6,7 -
Dihidro - 3H-Oxazolo [3,4-a]
Pirazin - 5,8 - Diona51. **CLASIFICACIÓN INTERNACIONAL** _____71. **SOLICITANTE** Biolab Sanus Farmaceutica**DOMICILIO** Sao - Paulo - Brasil74. **APODERADO** Juan Carlos Uribe Restrepo22. **BOGOTÁ, D.C.,** Marzo 8/2013

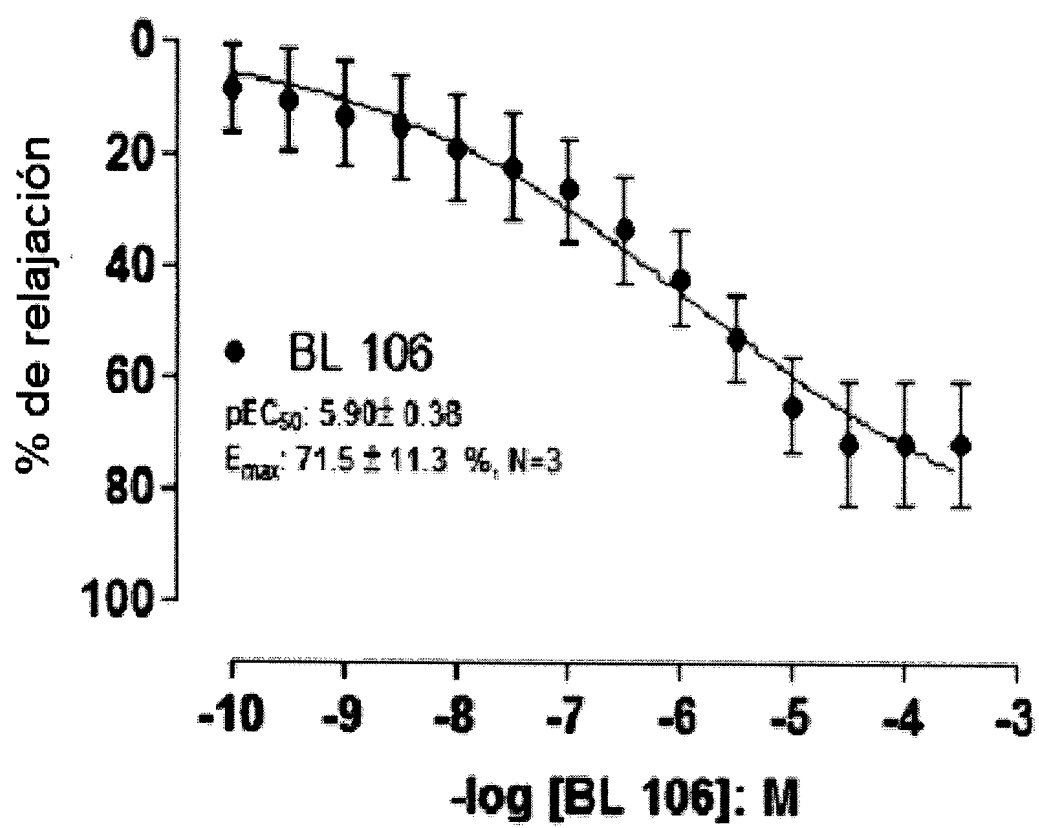
 Industria y Comercio SUPERINTENDENCIA	SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  No. 13-046988- -00000-0000 Fecha: 2013-03-08 15:49:25 Dep. 2020 DIR.NUEVASCR Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI Act. 411 PRESENTACION Folios: 99
--	--

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL -PCT

1	TIPO DE SOLICITUD	☒ Patente de invención ☒ Capítulo I	☐ Patente de Modelo de Utilidad ☐ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
Solicitud Internacional No.		PCT/ BR2011/000255	Fecha 02/08/2011
Publicación Internacional No.		WO 2012/019254 A1	Fecha 16/02/2012
3	TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)		
DERIVADOS DE 6,7-DIHIDRO-3H-OXAZOLO{3,4-a}PIRAZIN-5,8-DIONA			
4	CLASIFICACIÓN INTERNACIONAL (CIP)		
C07D 498/04 (2006.01) A61P 15/00 (2006.01) A61K 31/48 (2006.01)			
5	SOLICITANTE (S) ☐ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS O RAZÓN SOCIAL		NOMBRE	IDENTIFICACIÓN TIPO
1.	BIOLAB SANUS FARMACÊUTICA LTDA.		
6	DATOS DEL SOLICITANTE		
DIRECCIÓN AV. PAULO AYRÉS, 280, VILA LASI, TABOÃO DA SERRA, SP, 06767-220, BRASIL		No. TELÉFONO	
CIUDAD SÃO PAULO		CORREO ELECTRÓNICO	
DEPARTAMENTO/ESTADO		NACIONALIDAD O LUGAR DE CONSTITUCIÓN BRASIL	
PAÍS DE RESIDENCIA BRASIL			
7	INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS		NOMBRES	NACIONALIDAD
1. SACURAI		SÉRGIO LUIZ	BRASIL
2. ZAIM		MÁRCIO HENRIQUE	BRASIL
3. TOUZARIM		CARLOS EDUARDO DA COSTA	BRASIL
4. KEPPLER		ARTUR FRANZ	BRASIL
5. DE NUCCI		GILBERTO	BRASIL
DIRECCIÓN DE CORREO ELECTRÓNICO:			
8	DATOS INVENTOR (ES)		
PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1. BRASIL		SÃO PAULO	RUA PITANGUEIRAS, 242, APTO 122, MIRANDÓPOLIS, 04052-020 SÃO PAULO, BRASIL
2. BRASIL		SÃO PAULO	RUA DOMINGOS OLIMPIO, 119, APTO 53B, VILA SÔNIA, 05625-060 SÃO PAULO, BRASIL
3. BRASIL		SÃO PAULO	RUA GERÔNIMO SALGUERA, 49, BLOCO 22, APTO 41, PARQUE FLAMENGO, 05783-070 SÃO PAULO, BRASIL
4. BRASIL		SÃO PAULO	RUA XINGU, 245, APTO, 134, VALPARAÍSO, 09060-050 SANTO ANDRÉ, SÃO PAULO, BRASIL
5. BRASIL		SÃO PAULO	AVENIDA DR. JESUÍNO MARCONDES MACHADO, 415, 13092-108 CAMPINAS, SÃO PAULO, BRASIL
OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)			
☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.			
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS		NOMBRES	IDENTIFICACIÓN
URIBE RESTREPO		JUAN CARLOS	C.C. 79.159.313 T.P. 54.493
DIRECCIÓN CALLE 93B No. 12-48, Piso 4o. BOGOTÁ, D.C., COLOMBIA		No. TELÉFONO 6019660	
CIUDAD BOGOTÁ. D.C., COLOMBIA		CORREO ELECTRÓNICO tum@tumnet.com	
PAÍS COLOMBIA		No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL	

10	DECLARACIONES DE PRIORIDAD		☒ SI	☐ NO
(33) PAÍS DE ORIGEN		CODIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. BRASIL		BR	61/373,483	13/08/2010
2.				
3.				
11	DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS			
Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.				
☐ SI ☒ NO				
Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.				
12	DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES			
Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.				
☐ SI ☒ NO				
Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.				
13	REDUCCIÓN DE TASAS			
Declaro que carezco de medios económicos para presentar la solicitud de patente.				
☐ SI ☒ NO				
Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.				
Micro, pequeñas y medianas empresas ☐				
Universidades públicas o privadas ☐				
Entidades sin ánimo de lucro ☐				
Debe aportar los documentos que se indican en el numeral 17 de anexos				
14	AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ☐ SI ☒ NO			
Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.				
15	COMPROBANTE DE PAGO O PAGO ELECTRÓNICO	N°	Fecha	
16	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL			
Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)				
17	ANEXOS			
Documentación Técnica		Documentación Jurídica		
Solicitud Internacional en castellano				
1. ☒ Descripción N° de folios:		9. ☒ Poderes, si fuera el caso.		
2. ☒ Reivindicaciones N° Reivindicaciones: 28		10. ☒ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.		
3. ☒ Dibujos y/o figuras N° folios:		11. ☐ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.		
4. ☒ Resumen.		12. ☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.		
5. ☐ Certificado de depósito de material biológico si fuera el caso.		13. Reducción de tasas		
6. ☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.		Micro, pequeñas o medianas empresas		
7. ☒ Arte final 12 x 12.		☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.		
8. ☐ Anexo formato digital.		☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.		
9. ☐		Universidades públicas o privadas		
		☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación		
		Entidades sin ánimo de lucro		
		☐ Copia de registro vigente en Cámara de comercio.		
		☐ Hoja de información complementaria.		
		☐ Otros, especificar		
		14. ☒ Comprobante de pago de la tasa de presentación de la solicitud.		
		15. ☐ Comprobante de pago por reivindicación de prioridad.		

	16. ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación. 17. ☒ Comprobante de pago por reivindicación adicional a 10.
--	---





5

TRIANA, URIBE & MICHELSEN

REPRESENTATION AND POWER OF ATTORNEY

I (we), the undersigned in representation of **BIOLAB SANUS FARMACEUTICA Ltda.**, a corporation duly organized in accordance with the laws of Brazil, domiciled at Av. Paulo Ayres, 280, Vila Iasi, Taboão da Serra, SP, 06767-220, Brazil, enrolled at CNPJ/MF under no. 49.475.833/0001-06,

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint **FERNANDO TRIANA**, tpa. No. 45.265 c.c. No. 79.154.036; **LAURA MICHELSEN**, tpa. No. 67.897 c.c. No. 39.783.287; **JUAN CARLOS URIBE**, tpa. No. 54.493 c.c. No. 79.159.313 and **JUAN PABLO TRIANA**, tpa. 63.077 c.c. No. 79.487.222; domiciled at Calle 93 B No. 12-48 (204), Bogotá, D.C., Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property and intellectual matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second or third alternate representative is to replace the first or second one, or when the second or third is to replace the principal one. In such cases, the principal representative, shall state his intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in ceases of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second or third alternate in their turn cases, the representation can be taken again in their sequence, by the principal, the first or second or third alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first or second or third alternates in their turn shall end at such time.



REPRESENTACIÓN Y PODER

Yo (nosotros), abajo suscrito(s) en representación de **BIOLAB SANUS FARMACEUTICA Ltda.**, sociedad legalmente organizada de acuerdo con las leyes de Brazil y con domicilio en Av. Paulo Ayres, 280, Vila Iasi, Taboão da Serra, SP, 06767-220, Brazil, inscrita en el CNPJ/MF bajo el no. 49.475.833/0001-06,

por el presente nombro (nombramos) a **FERNANDO TRIANA**, tpa. No. 45.265 c.c. No. 79.154.036; **LAURA MICHELSEN**, tpa. No. 67.897 c.c. No. 39.783.287; **JUAN CARLOS URIBE**, tpa. No. 54.493 c.c. No. 79.159.313 y **JUAN PABLO TRIANA**, tpa. 63.077 c.c. No. 79.487.222; domiciliados en la Calle 93 B No. 12-48 (204), Bogotá, D.C., Colombia, en obediencia a lo dispuesto en el parágrafo 1ro. del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquel. La misma regla se aplicará cuando el segundo y tercer representantes suplentes hayan de reemplazar al primero, al segundo o al principal. En tales casos, el representante principal, o el primero, o segundo suplente, o tercer suplente en su caso, o todos ellos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo o tercer suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero o segundo o tercer suplente en su caso.



In addition, we grant a Power of Attorney in favor of the above named attorneys-at-law, to apply for registration in the following National Phase PCT Patent Application:

International Application No.:
PCT/BR2011/000255
 International Publication No.:
WO2012/019254

The attorneys are also entitled to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, in all matters concerning the following:

a) Obtainment of patents, renewal, payment of the annuity fees, assignment, license, change of name or domicile, voluntary cancellation; and the registration of commercialization agreements and licenses of use of the above rights;

b) Protection of trade secrets;
 c) Obtainment of plant variety protection;

d) Actions of repossession, of opposition, cancellation, nullity, infringement of rights, custom procedures, writ of mandamus, granting of licenses; and in general the civil, criminal and administrative suits relating to all those rights; actions and suits instituted by me (us) or against me (us).

And that in all the above matters they may substitute this Power of Attorney, compromise, execute license agreements, assignment agreements, file extraordinary remedies suches nullification and/or revision and/or supplication of court decisions, conciliate, admit the facts of the case, desist, cancel, assign, receive, resign, and ratify acts done by representatives without a Power of Attorney.

Given and Signed this/Dado y firmado hoy February 14, 2013

in/en

São Paulo, Brazil.

Signature/Firma



Dante Alario Junior
 Diretor
 CPF: 295.868.106-44

[Signature]
 Celso de Castro Marques
 Diretor
 CPF: 000.267.190-11

Ademas, confiero (conferimos) poder a los abogados arriba nombrados, para solicitar el registro en Fase Nacional de la siguiente solicitud de patente PCT.

Solicitud Internacional No.:
PCT/BR2011/000255
 Publicación Internacional No.:
WO2012/019254

Los apoderados quedan también facultados a obtener la protección de mi (nuestra) propiedad industrial e intelectual y contra la competencia desleal, a cuyo efecto autorizo(amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo concerniente a los siguientes asuntos:

a) Obtención de patentes de invención, su renovación, pago de anualidades de mantenimiento, traspaso, licencia, cambio de nombre o domicilio, cancelación voluntaria; y el registro de acuerdos de comercialización y de licencias de uso de esos derechos;

b) Protección de secretos empresariales.
 c) Obtención de la protección para variedades vegetales;

d) Las acciones reivindicatorias, de oposición, de cancelación, de nulidad, de infracción de derechos, de medidas cautelares, de medidas en frontera, de tutela, de concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso-administrativos relacionados con todos estos derechos; acciones y procesos que promovamos o se nos promuevan.

Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, suscribir contratos de licencia, contratos de cesión, presentar recursos extraordinarios de casación y/o revisión y/o suplica, conciliar, admitir los hechos del proceso, desistir, cancelar, ceder, recibir, renunciar y ratificar los actos de agentes oficiosos.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 13 - 0019068
		Bogotá D.C., Febrero 26 de 2013 - 16:13:25

RECIBIDO DE : TRIANA URIBE & MICHELSEN LTDA	NI 830.001.432
---	----------------

*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	495599226	26/02/2013	1.040.000.00

*** Conceptos Pagados ***			
CANT. RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
18 50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00	540.000.00
			\$540.000.00
=====			

SON: **QUINIENTOS CUARENTA MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-046988- -00000-0000

Fecha: 2013-03-08 15:49:25 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 99

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

	RECIBO DE CAJA	No. 13 - 0019067
		Bogotá D.C., Febrero 26 de 2013 - 16:13:25

RECIBIDO DE : TRIANA URIBE & MICHELSEN LTDA					NI 830.001.432
*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	495599226	26/02/2013	1.040.000.00

*** Conceptos Pagados ***				
CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	500.000.00	500.000.00
				\$500.000.00
=====				

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-046988- -00000-0000

Fecha: 2013-03-08 15:49:25 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 99

DERIVADOS DE 6,7-DIHIDRO-3H-OXAZOLO[3,4-a]PIRAZIN-5,8-DIONA

CAMPO DE LA INVENCION

La presente invención describe una serie de derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona, sus mezclas, sus sales farmacéuticamente aceptables, composiciones farmacéuticas que los contienen, procesos para su preparación, método de inhibición de las enzimas fosfodiesterasas, su uso como un inhibidor de las enzimas fosfodiesterasas y su uso como un inhibidor de la enzima fosfodiesterasa del tipo 5 (PDE-5). En particular, el derivado (*R*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, su enantiómero (*S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, y/o sus mezclas (en cualquier relación).

La presente invención también describe un método de tratamiento de disfunción eréctil, trastornos y/o afecciones tratables con relajación de tejido y trastornos tratables con inhibidor de PDE-5 usando derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona, sus mezclas (en cualquier relación) y/o sus sales farmacéuticamente aceptables. En particular, el derivado (*R*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, su enantiómero (*S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, y/o sus mezclas (en cualquier relación).

ANTECEDENTES DE LA INVENCION

Antes de la aparición del primer tratamiento oral, la impotencia sexual masculina se trató por medio de inyecciones intracavernosas y otros medios debidos, en particular, a dudas provenientes de reacciones adversas que podría causar la administración oral en seres humanos. Se usaban papaverina y pentoxifilina, por ejemplo, en el tratamiento de disfunción eréctil por medio de

inyecciones intracavernosas. Otros medios de tratamiento menos eficaces eran, por ejemplo, psicoterapias e implantes quirúrgicos.

El tratamiento oral es más aceptable por el hombre y emergió de la investigación clínica usando inhibidores de cGMP-PDE, más específicamente, PDE-5. El precursor de estos compuestos era 5-[2-etoxi-5-(4-metilpiperazinilsulfonil)fenil]-1-metil-3-n-propil-1,6-dihidro-7H-pirazolo[4,3-d]pirimidin-7-ona o sildenafil, con propiedades vasodilatadoras y potencia los efectos del óxido nítrico. El sildenafil es el ingrediente activo de la medicina Viagra®.

Más tarde, se desarrollaron otros compuestos inhibidores de PDE-5 y se citan en numerosas publicaciones de la literatura técnica, así como publicaciones de patente, como vardenafil, el ingrediente activo de la medicina Levitra® y tadalafil, el ingrediente activo de la medicina Cialis®.

Los compuestos de la presente invención, los derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona, también son inhibidores de la enzima fosfodiesterasa de tipo 5 (PDE-5).

DESCRIPCIÓN DE LA INVENCION

En consecuencia, es objeto de la presente invención proporcionar nuevos compuestos derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona, sus mezclas (en cualquier relación), sus sales farmacéuticamente aceptables, composiciones farmacéuticas que los contienen, que son efectivos en el tratamiento de disfunción eréctil, siendo dichos compuestos relajantes de tejidos, y/o inhibidores de las enzimas fosfodiesterasas con propiedades vasodilatadoras y efectos relajantes, en particular inhibidores de PDE-5. En particular, el derivado (R)-3-(1,3-benzodioxol-5-il)-1-(1H-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, su enantiómero (S)-3-(1,3-benzodioxol-5-il)-1-(1H-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, y/o sus mezclas (en cualquier relación).

Tames objeto de la presente invención proporcionar procesos de preparación de compuestos derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona y sus mezclas. En particular, el derivado (*R*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, su enantiómero (*S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, y/o sus mezclas (en cualquier relación).

Por otra parte, es objeto de la presente invención proporcionar composiciones farmacéuticas que comprenden una cantidad efectiva de uno de los derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona o mezclas de ellos (en cualquier relación) o sus sales farmacéuticamente aceptables y excipientes farmacéuticamente aceptables. En particular, las composiciones farmacéuticas que comprenden el derivado (*R*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, su enantiómero (*S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, y/o sus mezclas (en cualquier relación).

Un objeto adicional de la presente invención consiste en proporcionar un medicamento que comprende una cantidad terapéuticamente efectiva de uno de los derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona o sus mezclas (en cualquier relación) o sus sales farmacéuticamente aceptables. En particular, los medicamentos que comprenden el derivado (*R*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, su enantiómero (*S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, y/o sus mezclas (en cualquier relación).

Otro objeto de la presente invención es el uso de uno de los derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona o sus mezclas (en

cualquier relación) o sus sales farmacéuticamente aceptables, para el tratamiento curativo y/o preventivo de disfunción eréctil, trastornos y/o afecciones tratables con relajación de tejido y trastornos tratables con inhibidor de PDE-5 en animal. En particular, el derivado (*R*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-*a*]pirazin-5,8-diona, su enantiómero (*S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-*a*]pirazin-5,8-diona, y/o sus mezclas (en cualquier relación).

BREVE DESCRIPCIÓN DE LOS DIBUJOS

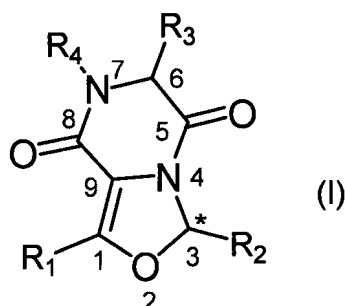
La Figura 1 muestra los efectos relajantes del compuesto 2 (BL 106) sobre tejido de uréter aislado humano.

La Figura 2 muestra los efectos relajantes del compuesto 2 (BL 106) sobre tejido arterial pulmonar aislado de conejo.

La Figura 3 muestra los efectos relajantes del compuesto 2 (BL 106) sobre tejido del cuerpo cavernoso aislado humano (Figura 3A) y tejido de cuerpo cavernoso aislado de conejo (Figura 3B).

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención describe derivados de 6,7-dihidro-3*H*-oxazolo[3,4-*a*]pirazin-5,8-diona con estructuras representadas en la fórmula (I):



y sus sales y solvatos (por ejemplo, hidratos), donde:

R¹ representa un grupo aromático, grupo condensado o no (opcionalmente sustituido con **R^B** en una o varias posiciones), un grupo heteroaromático que

contiene uno o varios heteroátomos o grupos indol (opcionalmente sustituidos con R^B en una o varias posiciones), alquenil C_{1-6} -carbonilo (opcionalmente sustituido con R^B en una o varias posiciones), aromático bicíclico (opcionalmente sustituido con R^B en una o varias posiciones) o heteroaromático bicíclico, que contiene uno o varios heteroátomos (opcionalmente sustituido con R^B en una o varias posiciones);

R^B representa halógeno, hidroxilo, nitrógeno, ciano, alquilo C_{1-6} , alquenilo C_{2-6} , alquinilo C_{2-6} , haloalquilo C_{1-6} , cicloalquilo C_{3-8} , cicloalquil C_{3-8} -alquilo C_{1-3} , arilalquilo C_{1-3} o heteroarilalquilo C_{1-3} ;

R^2 representa un grupo aromático que contiene uno o varios heteroátomos o aromático o heteroaromático bicíclico que contiene uno o varios heteroátomos o grupos metilen-3,4-dioxifenilo;

R^3 representa hidrógeno, halógeno, haloalquilo C_{1-6} , heteroalquilo C_{1-3} o alquilo C_{1-3} ;

R^4 representa hidrógeno, alquilo C_{1-6} , alquenilo C_{2-6} , alquinilo C_{2-6} , haloalquilo C_{1-6} , cicloalquilo C_{3-8} , cicloalquil C_{3-8} -alquilo C_{1-3} , arilalquilo C_{1-3} o heteroarilalquilo C_{1-3} .

En un aspecto, "alquenil C_{2-6} -carbonilo" de R^1 representa uno o varios grupos alquenilo, que contiene de 2 a 6 átomos de carbono, conjugado o no con un grupo carbonilo.

En un aspecto, "arilo" de R^B y R^4 , por ejemplo, arilalquilo C_{1-3} , representa un grupo fenilo o fenilo sustituido una o varias veces (por ejemplo 1, 2 ó 3) con halógeno, alquilo C_{1-6} , alcoxilo C_{1-6} o metilendioxilo. En otro aspecto, "heteroarilo" de R^B y R^4 , por ejemplo, heteroarilalquilo C_{1-3} , representa un grupo furilo o piridilo, opcionalmente sustituido una o varias veces con halógeno, alquilo C_{1-6} o alcoxilo C_{1-6} . En otro aspecto, "cicloalquilo C_{3-8} " de R^B y R^4 , por ejemplo, cicloalquil C_{3-8} -alquilo C_{1-3} , representa un anillo monocíclico que contiene de 3 a 8 átomos de carbono. Los ejemplos de anillos cicloalquilo

incluyen anillos cicloalquilo C_{3-6} : ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

El término “alquilo” puede representar una cadena de alquilo o cadena de alquilo ramificado. Por ejemplo, el grupo alquilo C_{1-4} puede representar metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, *s*-butilo y *t*-butilo. El término “alquenilo” incluye grupos alquenilo de cadenas lineal y ramificada, por ejemplo, grupos vinilo y alilo. El término “alquinilo” incluye grupos alquinilo de cadenas lineal y ramificada, por ejemplo, acetileno. El término “halógeno” puede representar átomos de flúor, cloro, bromo o yodo. El término “haloalquilo C_{1-6} ” puede representar un grupo alquilo que contiene de uno a diez átomos de carbono, sustituido con uno o varios (por ejemplo 1, 2 ó 3) átomos de halógeno.

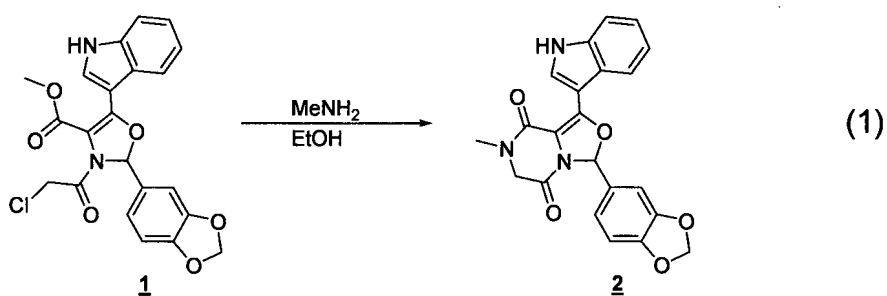
Los compuestos de la fórmula (I) pueden contener uno o varios centros asimétricos, existiendo así como enantiómeros y/o diastereómeros. Por ejemplo, en la fórmula (I), un centro quiral se indica con un asterisco. Conforme a ello, la invención incluye uno o varios enantiómeros y sus mezclas (en cualquier relación).

Los compuestos de la fórmula (I) pueden existir con diferentes formas tautoméricas y la invención incluye una o varias formas tautoméricas y sus mezclas (en cualquier relación).

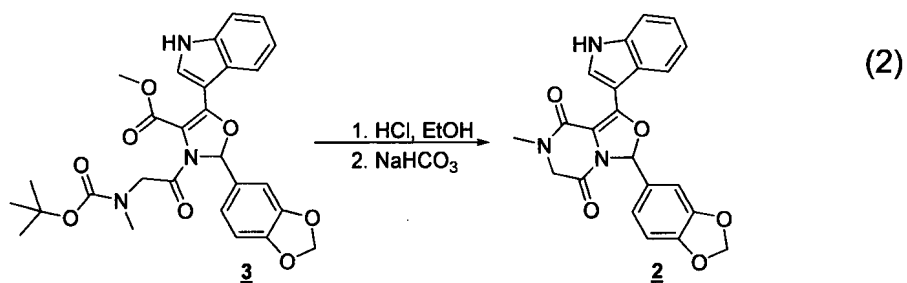
Las sales farmacéuticamente aceptables de los compuestos de la fórmula (I), que poseen un centro básico, se forman por adición de ácidos farmacéuticamente aceptables. Algunos ejemplos incluyen sales de clorhidrato, bromhidrato, sulfato o bisulfato, fosfato o hidrógeno-fosfato, acetato, benzoato, succinato, fumarato, maleato, lactato, citrato, tartarato, gluconato, metansulfonato, bencensulfonato y *p*-toluensulfonato. Los compuestos de la fórmula (I) se pueden usar en sales metálicas farmacéuticamente aceptables, en particular sales de metales alcalinos, con bases. Por ejemplo, sales de sodio y potasio.

En una forma de realización, los compuestos de esta invención tienen una estructura representada en la fórmula (I), donde R^1 representa un grupo indol, R^2 representa un grupo 3,4-metilendioxfenilo, R^3 representa hidrógeno y R^4 representa un grupo metilo. En una forma de realización preferida, los compuestos de esta invención son (*R*)-3-(benzo[d][1,3]dioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro-3*H*-oxazolo[3,4-*a*]pirazin-5,8-diona, y/o su enantiómero (*S*)-3-(benzo[d][1,3]dioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro-3*H*-oxazolo[3,4-*a*]pirazin-5,8-diona.

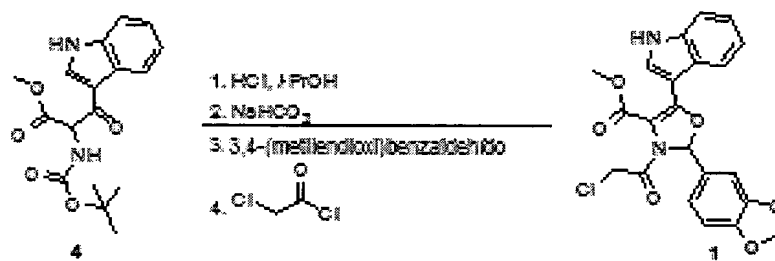
El compuesto (*R,S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-*a*]pirazin-5,8-diona (**2**), de acuerdo con la presente invención, se puede preparar a partir de la reacción del compuesto **1** en presencia de metilamina, usando etanol como solvente, de acuerdo con el esquema 1:



Un enfoque alternativo para la preparación del compuesto **2** es a través de la reacción de **3** con ácido en etanol, de acuerdo con el esquema 2:



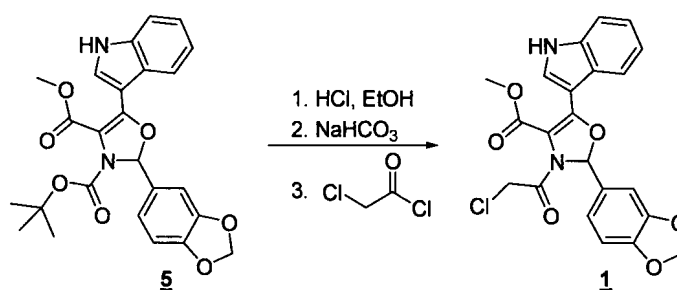
El compuesto **1** se puede preparar de acuerdo con el esquema 3:



(3)

El compuesto **4** se trata con ácido en isopropanol. Después de neutralizar con bicarbonato de sodio, se añade 4-(metilendioxi)benzaldehído. La última etapa de este enfoque es la adición de cloruro de cloroacetilo.

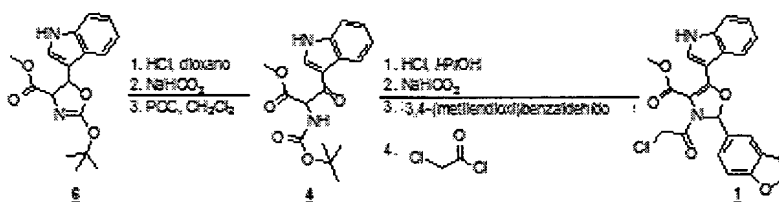
De modo alternativo, el compuesto **1** se puede preparar de acuerdo con el esquema 4:



(4)

En este enfoque, el compuesto **5** se trata con ácido en etanol. Después de neutralizar con bicarbonato de sodio, se añade cloruro de cloroacetilo.

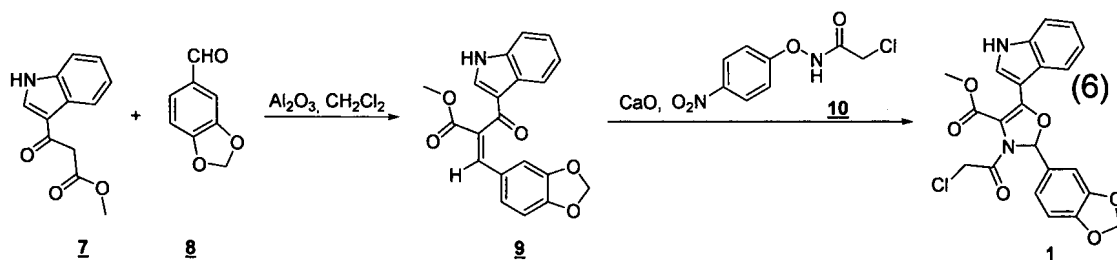
El compuesto **1** also se puede preparar de acuerdo con el esquema 5:



(5)

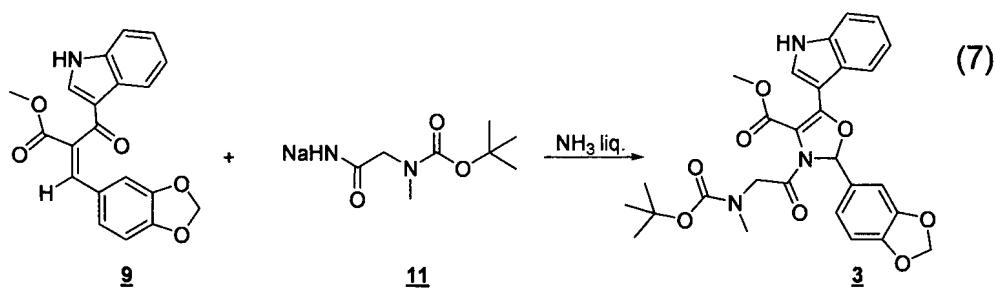
En este enfoque, el compuesto **6** se trata con ácido en dioxano. Después de neutralizar con bicarbonato de sodio, se hace una reacción de oxidación con clorocromato de piridina (PCC), llevando a la formación del intermediario **4**, que se trata con ácido en isopropanol. Después de neutralizar con bicarbonato de sodio, se añade 3,4-(metilendioxi)benzaldehído. La última etapa de este enfoque es la adición de cloruro de cloroacetilo.

Otro enfoque para la preparación del compuesto **1** se da en el esquema 6:



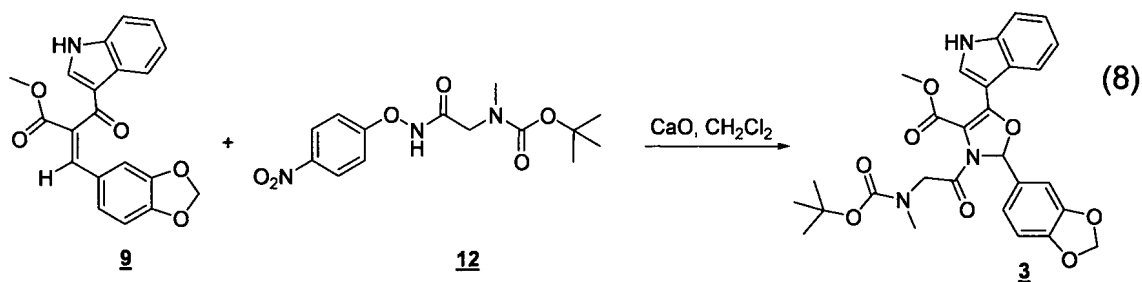
En este enfoque, la reacción de **7** y **8** en presencia de óxido de aluminio (Al_2O_3) en diclorometano lleva a la formación del intermediario **9**, que reacciona con **10** en presencia de óxido de calcio (CaO).

El compuesto **3** se puede preparar de acuerdo con el esquema 7:



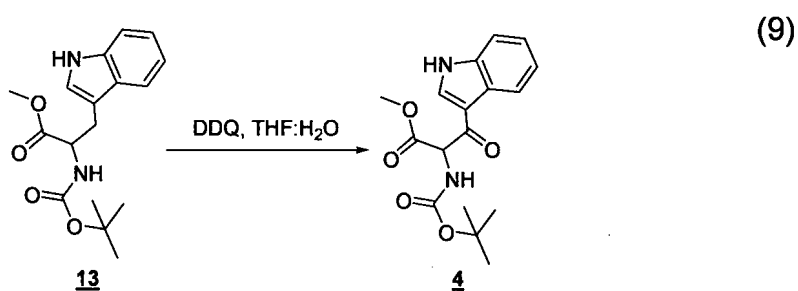
En este enfoque, el intermediario **9** reacciona con el compuesto **11**, usando amoníaco líquido como solvente.

De modo alternativo, el compuesto **3** se puede preparar de acuerdo con el esquema 8:



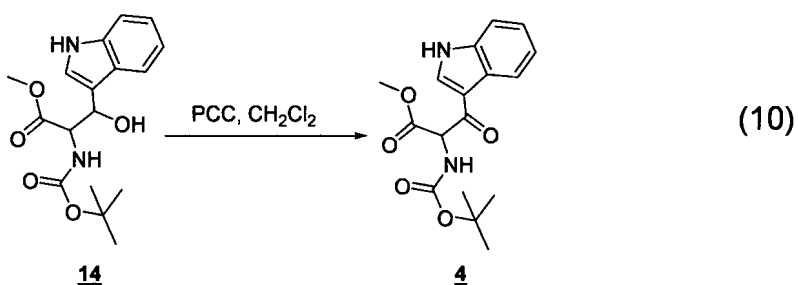
En este enfoque, en presencia de óxido de calcio (CaO), el intermediario **9** reacciona con el compuesto **12**.

El compuesto **4** se puede preparar de acuerdo con el esquema 9:



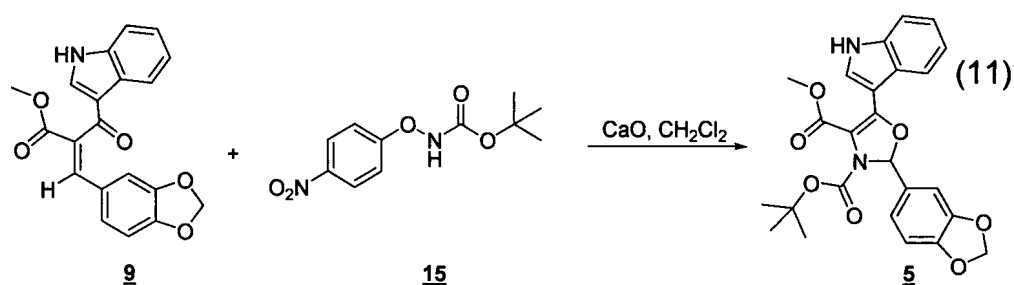
En este enfoque, el compuesto **13** se trata con (2,3)-dicloro-5,6-diciano-1,4-benzoquinona (DDQ), usando una mezcla de tetrahidrofurano:agua como solvente para la reacción.

Otro enfoque para la preparación del compuesto **4** se da en el esquema 10:



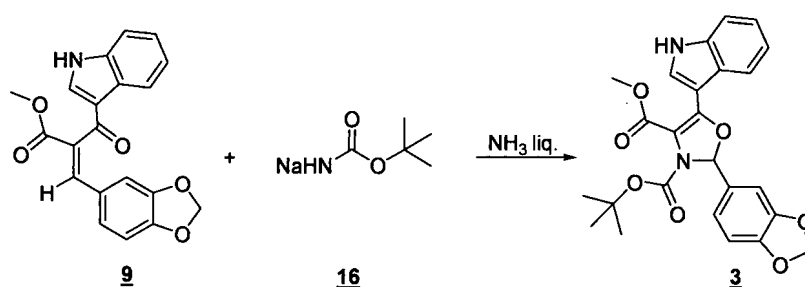
En este enfoque, el compuesto **14** se trata con cloruro de clorocromato de piridina (PCC), usando cloruro de metileno como solvente para la reacción.

El compuesto **5** se puede preparar de acuerdo con el esquema 11:



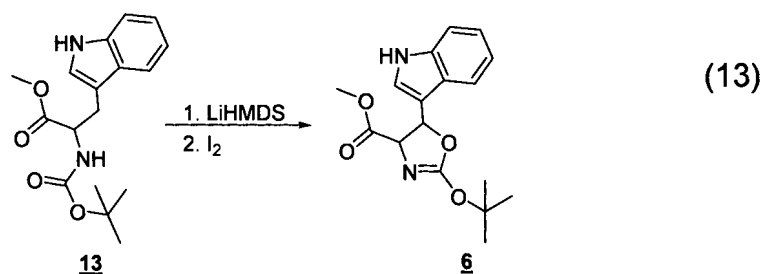
En este enfoque, en presencia de óxido de calcio (CaO), el intermediario **9** reacciona con el compuesto **15**.

De modo alternativo, el compuesto **5** se puede preparar de acuerdo con el esquema 12:



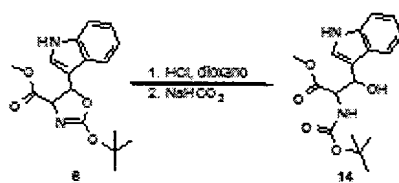
En este enfoque, el intermediario **9** reacciona con el compuesto **16**, usando amoníaco líquido como solvente.

El compuesto **6** se puede preparar de acuerdo con el esquema 13:



En este enfoque, el compuesto **13** se trata con hexametildisilazida de litio (LiHDMS). La última etapa de este enfoque es la adición de yodo (I_2).

El compuesto **14** se puede preparar de acuerdo con el esquema 14.

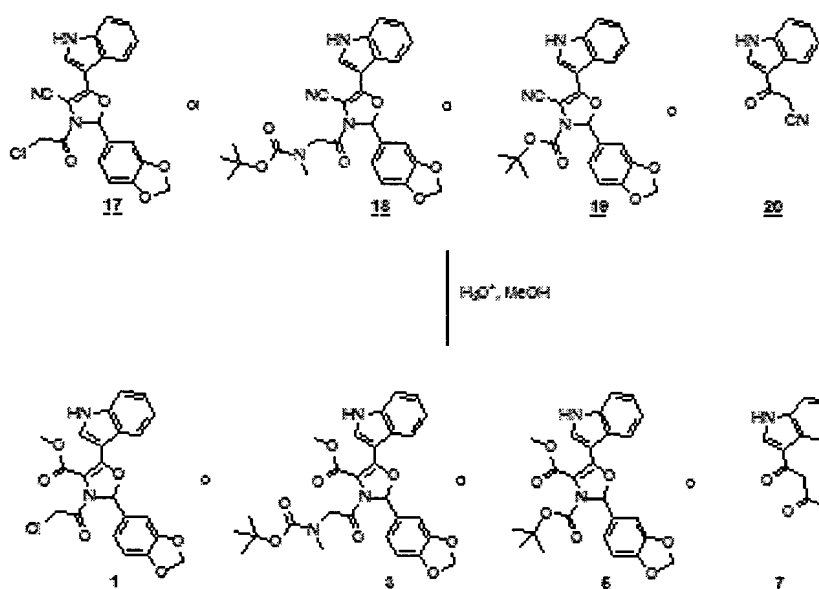


(14)

En este enfoque, el compuesto 6 se trata con ácido en dioxano.

Todos los compuestos que contienen el grupo carboximetilo, en particular 1, 3, 5 y 7, se puede preparar a partir de (sus) derivados que contienen el grupo nitrilo, por ejemplo, de acuerdo con el esquema 15.

(15)



Por ejemplo, el compuesto 17 se trata con ácido en metanol. Este enfoque también se puede usar individualmente con compuestos 18, 19 y 20 a fin de preparar los intermediarios 3, 5 y 7 respectivamente.

La presente invención también proporciona una composición farmacéutica, por ejemplo, una forma de dosificación apropiada, en donde dicha composición comprende una cantidad efectiva de uno o varios compuestos de la fórmula (1) o una de sus sales farmacéuticamente aceptables y un excipiente farmacéuticamente aceptable.

En una forma de realización, la composición farmacéutica también comprende otros inhibidores de PDE-5, tales como sildenafil, vardenafil y tadalafil; o una de sus sales farmacéuticamente aceptables. En otra forma de realización, la composición farmacéutica también comprende uno o varios compuestos que tratan la disfunción eréctil o el trastorno tratable con el inhibidor de PDE-5.

En una forma de realización, la composición farmacéutica se administra con una segunda composición farmacéutica que comprende otros inhibidores de PDE-5, por ejemplo sildenafil, vardenafil y tadalafil; o una de sus sales farmacéuticamente aceptables. En otra forma de realización, dicha segunda composición farmacéutica comprende uno o varios compuestos que tratan la disfunción eréctil o el trastorno tratable con el inhibidor de PDE-5. La administración puede ser la coadministración o la administración secuencial.

Las composiciones farmacéuticas se pueden preparar por medio de métodos bien conocidos en el estado del arte. De forma apropiada, se pueden usar Remington's Pharmaceutical Sciences o fuentes de información similares para preparar una formulación apropiada de acuerdo con la invención.

Las composiciones farmacéuticas para administración oral se pueden presentar como unidades discretas tales como cápsulas, comprimidos, tabletas efervescentes, tabletas masticables, píldoras, polvos, gránulos y geles o formas farmacéuticas similares. Otras formas de formulación oral incluyen suspensiones o emulsiones en un portador acuoso o no acuoso.

En formas de dosificación sólidas, los compuestos de la fórmula (I) se pueden mezclar con un portador farmacéuticamente aceptable que comprende al menos un componente seleccionado del grupo que comprende diluyentes, aglutinante, desintegrantes, lubricantes, agentes colorantes y agentes saborizantes. Los diluyentes inertes de ejemplo son carbonato de calcio, fosfato de calcio dibásico, fosfato de calcio tribásico, sulfato de calcio, celulosa

microcristalina, celulosa en polvo, dextratos, dextrinas, ciclodextrinas, excipientes de dextrosa, fructosa, caolín, lactitol, lactosa, manitol, sorbitol, almidón, almidón pregelatinizado, sacarosa, azúcar compresible y azúcar en polvo. Como aglutinantes se pueden usar una o varias sustancias, por ejemplo, metilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, gelatina, goma arábiga, etilcelulosa, alcohol polivinílico, pululano, almidón pregelatinizado, agar, tragacanto, alginato de sodio, propilenglicol y alginato. Como desintegrante se pueden usar una o varias sustancias seleccionadas de hidroxipropilcelulosa de baja sustitución, carboximetilcelulosa, carboximetilcelulosa de calcio, carboximetilcelulosa de sodio, croscarmelosa sódica, almidón, celulosa cristalina, hidroxipropilalmidón y almidón parcialmente pregelatinizado y croscarmelosa sódica. Los lubricantes de ejemplo son ácido esteárico, estearato de magnesio, estearato de calcio, talco, aceite de ricino hidrogenado y sacarosa.

En el caso de cápsulas, comprimidos, tabletas efervescentes y píldoras, las formas de dosificación también pueden comprender agentes tampón. Las cápsulas de gelatina blanda se pueden preparar para contener una mezcla de los compuestos de la fórmula (I) y aceite vegetal. Las cápsulas de gelatina dura pueden contener gránulos de los compuestos de la fórmula (I) en combinación con un portador sólido pulverulento tales como lactosa, sacarosa, sorbitol, manitol, almidón de papa, almidón de maíz, amilopectina, derivados celulósicos de gelatina. Además, los comprimidos y las píldoras se pueden preparar con recubrimientos entéricos.

En una forma de realización, las formas de dosificación son un tipo de liberación controlada / retardada / modulada, que se basan en portadores o matrices que incluyen, pero sin limitación, polímeros biocompatibles, matrices poliméricas farmacéuticamente aceptables, liposomas, PEG-liposomas o una matriz de ciclodextrina o una matriz derivada de ciclodextrina.

Las composiciones farmacéuticas se pueden administrar por medio de una variedad de rutas de administración que incluyen, pero sin limitación, oral, inyección intracavernosa, tópica y suministro transdérmico a través de la piel en varios sitios o vías parenterales. El modo particular seleccionado dependerá de los compuestos presentes en la composición, la gravedad de la disfunción eréctil, trastornos y/o afecciones tratables con relajación de tejido o trastorno tratable con el inhibidor de PDE-5 en tratamiento y la dosificación requerida para eficacia terapéutica. Con preferencia, las composiciones de la invención son en forma de administración oral debido a la conveniencia del paciente y el esquema de dosificación.

Los relajantes de tejidos se usaron para promover la relajación en diversos tejidos para tratar o actuar como adyuvante del tratamiento, procedimiento o cirugía relacionada con litiasis (Korkes, F. et al, J Bras Nefrol. (2009) 31(1): 55), engrosamiento de próstata (por ejemplo, hiperplasia benigna de próstata, prostatitis) (documento WO 9911279) y constricción de uréter (Van der Werf et al., BJU International (2002) 90:588). Se conocen otros trastornos y/o afecciones tratables con relajación de tejido y se describen en la técnica.

Se usaron inhibidores de PDE-5 para bloquear la degradación de cGMP para prolongar los efectos de óxido nítrico (NO) sobre diversos tejidos, por ejemplo, para mantener la relajación de vías aéreas y vasos inducida por NO (Barnes, P. J., et al., (1995) y para mantener la protección de tejidos inducida por NO (Duffin, R., et. al., Br J Pharmacol. (2008) 153(4): 623). Estas acciones sobre tejidos se mostraron beneficiosas para el tratamiento de varios trastornos —en la presente, trastornos tratables con inhibidor de PDE-5— incluyendo hipertensión pulmonar (tratada comercialmente con citrato de sildenafil); bronquitis, asma crónica, hipertensión (documentos EP 758653, US 7569572); fenómeno de Raynaud (Ghofrani H.A., et. al., Nat Rev Drug Discov. 2006, 5:689); insuficiencia cardíaca derecha incipiente (Ghofrani et al. (2003)

AJRCCM 167(8): 1139); neurogénesis y recuperación funcional después de accidente cerebrovascular (Zhang et al. (2002) Stroke 33: 2675–2680); relajación arterial coronaria (Halcox et al. (2002) J Am Coll Cardiol 40: 1232); trastornos de la excitación sexual femenina (Nehra et al. (2001) World J Urol. 19(1): 115); angina e insuficiencia cardíaca congestiva (Reffellmann et al., Circ. (2003) 108(2): 239). Se conocen otros trastornos tratables con inhibidor de PDE–5 y se describen en el arte.

Una cantidad terapéuticamente efectiva para el tratamiento de disfunción eréctil es una que es suficiente para lograr una mejora en la función eréctil o un alivio de los síntomas de disfunción eréctil o incluso restaurar la capacidad eréctil. Una cantidad terapéuticamente efectiva para el tratamiento de trastornos tratables con inhibidor de PDE–5 es una que es suficiente para lograr una mejora en dicho trastorno o un alivio de los síntomas de dicho trastorno. Las cantidades efectivas dependerán de la condición específica en tratamiento y su gravedad; características individuales del paciente, incluyendo la edad, condición física, tamaño y peso; tratamiento concurrente; y el modo de administración. Estos factores son bien conocidos por los expertos en el arte y se pueden establecer sin experimentación indebida. En general, las dosis de compuestos de la fórmula (I) variarán de aproximadamente 0,01 mg/kg de peso corporal por día a 100 mg/kg de peso corporal por día, con preferencia de 0,1 mg/kg de peso corporal por día a 10 mg/kg de peso corporal por día. Se pueden contemplar múltiples dosis por día para lograr niveles sistémicos apropiados de ingredientes activos presentes en la composición de la invención.

Los siguientes ejemplos describen la presente invención con mayor detalle. Se notará que la invención no está limitada por la siguiente descripción.

EJEMPLO 1

Preparación del compuesto 2, (R,S)–3–(1,3–benzodioxol–5–il)–1–

(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-*a*]pirazin-5,8-diona.

Preparación del compuesto intermediario 4

A una solución de DDQ (228,0 g; 1,0 mol) en una mezcla de 1000 mL de THF:H₂O (9:1), se añadió 2-[(*ter*-butoxicarbonil)amino]-3-(1*H*-indol-3-il)propanoato de metilo (80,0 g; 0,251 mol). La mezcla de reacción se mezcló durante 3 horas. Alícuotas adicionales de DDQ se añadieron hasta que todo el material de partida se hubiera consumido (TLC). Después de ello, la mezcla de reacción se lavó con una solución saturada de NaHCO₃ y el producto se extrajo con cloruro de metileno. Las fases orgánicas se combinaron y se secaron con MgSO₄. El solvente se eliminó parcialmente y a esta mezcla se añadieron 3 g de carbón activado. Esta mezcla se mezcló durante 30 minutos y, después de equilibrar hasta temperatura ambiente, se filtró. El solvente se eliminó por rotoevaporación hasta sequedad. El aceite resultante se solubilizó en caliente en acetona (70,0 mL). La solución se enfrió y se colocó en un baño de hielo, produciendo la precipitación de 2-[(*tert*-butoxicarbonil)amino]-3-(1*H*-indol-3-il)-3-oxopropanoato de metilo que se filtró y se secó en un calentador a 60 °C.

Preparación del compuesto intermediario 1

A una suspensión de 2-[(*ter*-butoxicarbonil)amino]-3-(1*H*-indol-3-il)-3-oxopropanoato de metilo (6,23 g; 19,0 mmol) **4** en 200 mL de isopropanol, se añadieron 2,0 mL de HCl al 36%. La mezcla de reacción se mezcló durante 3 horas. Alícuotas adicionales de HCl al 36% se añadieron hasta consumir todo el material de partida. Después de completar la reacción, la mezcla de reacción se enfrió hasta temperatura ambiente. Se añadieron alícuotas de NaHCO₃ para neutralizar la solución. 3,4-(Metilendioxi)benzaldehído (2,86 g; 19 mmol) se añadió luego a la solución y la mezcla de reacción resultante se mezcló bajo agitación magnética durante 24 horas, llevando a la precipitación de 2-[(*E*)-(1,3-benzodioxol-5-ilmetiliden)amino]-3-(1*H*-indol-3-il)-3-oxopropanoato de metilo, que se filtró y se secó en un calentador a 60 °C.

Metil 2-[(*E*)-(1,3-benzodioxol-5-ilmetiliden)amino]-3-(1*H*-indol-3-il)-3-oxopropanoato (5,46 g; 15,0 mmol) se añadió a una solución de piridina (10 mL) en 50 mL de cloruro de metileno seco. Esta suspensión se mezcló bajo agitación magnética con un tubo de secado CaCO_3 durante 30 minutos. Se disolvió cloruro de cloroacetilo (2,3 mL; 30,0 mmol) en 2,5 mL de cloruro de metileno seco. Esta solución se añadió gota a gota a la mezcla de reacción, durante un período de 30 minutos. Después de un período adicional de 3 horas, se añadieron 100 mL de una solución acuosa saturada de CuSO_4 a la mezcla de reacción. La fase orgánica se extrajo en un embudo de separación y se aisló. La fase acuosa se lavó con 50 mL de cloruro de metileno y la fase orgánica se aisló. Las fases orgánicas se combinaron. Este procedimiento de lavado se repitió dos veces más. La fase orgánica se lavó con una solución acuosa saturada de NaCl. La fase orgánica se aisló y se secó con MgSO_4 . El solvente se eliminó por rotoevaporación, llevando al aislamiento de 3-(cloroacetil)-5-(1*H*-indol-3-il)-2-fenil-2,3-dihidro-1,3-oxazol-4-carboxilato de metilo 1.

Preparación del compuesto 2

A una solución de 3-(cloroacetil)-5-(1*H*-indol-3-il)-2-fenil-2,3-dihidro-1,3-oxazol-4-carboxilato de metilo (5,46 g; 12,4 mmol) 1 en 100 mL de etanol, se añadieron 10 mL de una solución acuosa del 40% de metilamina. Esta mezcla de reacción se mezcló bajo agitación magnética durante 24 horas, llevando a la precipitación de (*R,S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-*a*]pirazin-5,8-diona 2. El producto obtenido presentaba las siguientes características: P. f. 279–281 °C. HRMS (EI): *m/z* calc. para $[\text{C}_{22}\text{H}_{18}\text{N}_3\text{O}_5]$ 404,1246; exp.: 404,1239. IV (KBr): 3322, 1647, 1613, 1467 cm^{-1} . RMN ^1H (300MHz, $\text{DMSO}-d_6$): δ = 11,87 (s, 1H); 9,00 (s, 1H); 7,87 (d, 1H, J = 9,0 Hz); 7,48 (d, 1H, J = 9,0 Hz); 7,14 (m, 5H); 7,00 (d, 1H, J = 9,0 Hz); 6,06 (s, 2H); 4,20 (s, 2H); 2,94 (s, 3H). RMN ^{13}C (125MHz,

DMSO–d6): δ = 158,3; 156,7; 148,2; 147,5; 147,3; 135,7; 130,9; 130,7; 125,1; 122,0; 121,2; 120,4; 120,2; 112,0; 108,1; 106,4; 104,7; 102,2; 101,3; 90,1; 52,7; 32,2.

EJEMPLO 2

Efecto del compuesto 2 en cuerpo cavernoso y uréter humanos y cuerpo cavernoso y arteria pulmonar de conejo

Tejido

Se obtuvieron cuerpo cavernoso y uréter humanos de tejidos descartados de cirugías, que se colocaron en solución helada de Krebs para un transporte rápido al laboratorio.

Se usaron conejos blancos machos de Nueva Zelanda (2–2,5 kg) para tejidos de pene y arteria pulmonar, que se seccionaron y se transfirieron a solución helada de Krebs. Se obtuvieron dos tiras y cuatro anillos de cada cuerpo cavernoso (CC) y arteria pulmonar, respectivamente.

Registro de tensión isométrica

Se montaron tiras cavernosas, arteria pulmonar y uréter en cámaras con 10 ml de órganos que contenían solución de Krebs a 37 °C, pH 7,4 burbujeando de forma continua una mezcla de 95% de O₂ y 5% de CO₂. Los tejidos se estiraron con una fuerza en reposo de 5 mN y se dejó compensar durante 60 min. Se registraron los cambios en la fuerza isométrica usando un sistema de adquisición de datos PowerLab 4/30 (software Chart, versión 7.0; ADInstruments, Colorado Springs, CO). Se obtuvieron curvas acumulativas de concentración–respuesta del compuesto 2 (denominado BL 106 en las Figuras 1, 2 y 3) (0,001–10 μ M) en tiras cavernosas, anillos de la arteria pulmonar y uréter contraídos con noradrenalina (NOR 10 μ M) (Sigma, St. Louis, MO). Se construyeron curvas de concentración– respuesta del compuesto 2 (designado BL 106 en las Figuras 1, 2 y 3) para cada muestra. Para la arteria pulmonar, también se construyeron las curvas de concentración–respuesta del compuesto

2 en presencia o ausencia del inhibidor soluble de guanilatociclasa 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-ona (ODQ 10 μ M) (Sigma, St. Louis, MO). También se corrientes en paralelo anillos de control (tratados con 40 mM de DMSO) con tiras y anillos experimentales.

Relajación de uréter humano

La noradrenalina causó una contracción sostenida en el tejido de uréter humano. El compuesto **2** (BL 106) (0,0001–1 μ M) produjo relajaciones dependientes de la concentración en tejido de uréter (pEC₅₀: 6,29 y Emáx 49 %, n = 3) (Figura 1).

Relajación de arteria pulmonar de conejo

La noradrenalina (3 ó 10 μ M) causó una contracción sostenida en la arteria pulmonar de conejo (17,4 mN). El compuesto **2** (BL 106) (0,001–10 μ M) produjo relajaciones dependientes de la concentración en anillos de arteria pulmonar (pEC₅₀: 6,23 [588 nM] y Emáx 62 %, n = 3) (Figura 2).

Relajación en cuerpo cavernoso humano

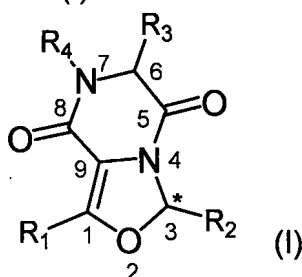
La noradrenalina causó una contracción sostenida en el cuerpo cavernoso humano. El compuesto **2** (BL 106) (0,0001–1 μ M) produjo relajaciones dependientes de la concentración en el cuerpo cavernoso (pEC₅₀: 7,65 y Emáx 71 %, n = 3) (Figura 3A).

Relajación del cuerpo cavernoso de conejo

La noradrenalina (3 ó 10 μ M) causó una contracción sostenida en el cuerpo cavernoso de conejo (13,8 mN). El compuesto **2** (BL 106) produjo relajaciones dependientes de la concentración en el cuerpo cavernoso (pEC₅₀: 5,92 [1,2 μ M] y Emáx: 91 %, n = 3) (Figura 3B).

REIVINDICACIONES

1. Un compuesto de la fórmula (I):



o sus sales, solvatos o hidratos; en donde:

R¹ es un grupo aromático, opcionalmente condensado, opcionalmente sustituido con **R^B** en una o varias posiciones; un grupo heteroaromático que contiene uno o varios heteroátomos, opcionalmente sustituido con **R^B** o un grupo indol en una o varias posiciones; un alquenil C₁₋₆-carbonilo, opcionalmente sustituido con **R^B** en una o varias posiciones; un aromático bicíclico, opcionalmente sustituido con **R^B** en una o varias posiciones o un heteroaromático bicíclico que contiene uno o varios heteroátomos, opcionalmente sustituido con **R^B** en una o varias posiciones;

R^B es un halógeno, hidroxilo, nitrógeno, ciano, alquilo C₁₋₆, alquenilo C₂₋₆, alquinilo C₂₋₆, haloalquilo C₁₋₆, cicloalquilo C₃₋₈, cicloalquil C₃₋₈-alquilo C₁₋₃, arilalquilo C₁₋₃ o heteroarilalquilo C₁₋₃;

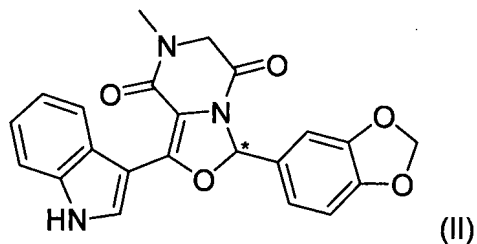
R² es un grupo aromático que contiene uno o varios heteroátomos, un grupo heteroaromático que contiene uno o varios heteroátomos o grupos metilen-3,4-dioxifenilo o a aromático bicíclico que contiene uno o varios heteroátomos o grupos metilen-3,4-dioxifenilo;

R³ es hidrógeno, halógeno, haloalquilo C₁₋₆, heteroalquilo C₁₋₃ o alquilo C₁₋₃; y

R⁴ es hidrógeno, alquilo C₁₋₆, alquenilo C₂₋₆, alquinilo C₂₋₆, haloalquilo C₁₋₆, cicloalquilo C₃₋₈, cicloalquil C₃₋₈-alquilo C₁₋₃, arilalquilo C₁₋₃ o heteroarilalquilo C₁₋₃.

2. El compuesto de acuerdo con la reivindicación 1 o sus sales o

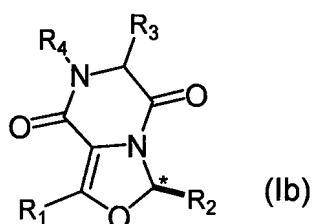
solvatos, en donde dicho compuesto está representado por la fórmula (II):



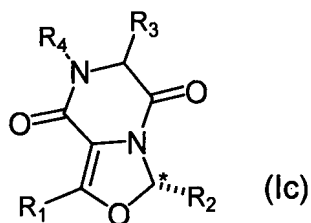
3. El compuesto de acuerdo con la reivindicación 2 o sus sales o solvatos, en donde el compuesto es un isómero (R).

4. El compuesto de acuerdo con la reivindicación 2 o sus sales o solvatos, en donde el compuesto es un isómero (S).

5. El compuesto de acuerdo con la reivindicación 1 o sus sales o solvatos, en donde el compuesto es un isómero (R) y está representado por la fórmula (Ib):



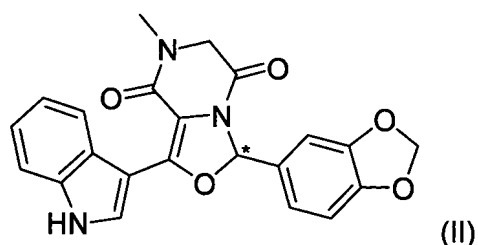
6. El compuesto de acuerdo con la reivindicación 1 o sus sales o solvatos, en donde el compuesto es un isómero (S) y está representado por la fórmula (Ic):



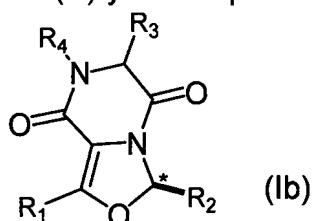
7. Una composición farmacéutica que comprende una cantidad efectiva de uno o varios compuestos de acuerdo con la reivindicación 1 o una de sus sales o solvatos farmacéuticamente aceptables; y un excipiente farmacéuticamente aceptable.

8. La composición farmacéutica de acuerdo con la reivindicación 7, en

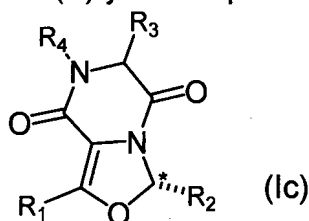
donde la composición comprende un compuesto de la fórmula (II):



9. La composición farmacéutica de acuerdo con la reivindicación 8, en donde el compuesto es un isómero (R) y está representado por la fórmula (Ib):



10. La composición farmacéutica de acuerdo con la reivindicación 8, en donde el compuesto es un isómero (S) y está representado por la fórmula (Ic):



11. Un método de inhibición de las enzimas fosfodiesterasas en un paciente, que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 7 a dicho paciente.

12. Un método de inhibición de las enzimas fosfodiesterasas en un paciente, que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 8 a dicho paciente.

13. Un método de inhibición de la enzima fosfodiesterasa de tipo 5 en un paciente, que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 7 a dicho paciente.

14. Un método de inhibición de la enzima fosfodiesterasa de tipo 5 en un paciente, que comprende la administración de la composición farmacéutica de

acuerdo con la reivindicación 8 a dicho paciente.

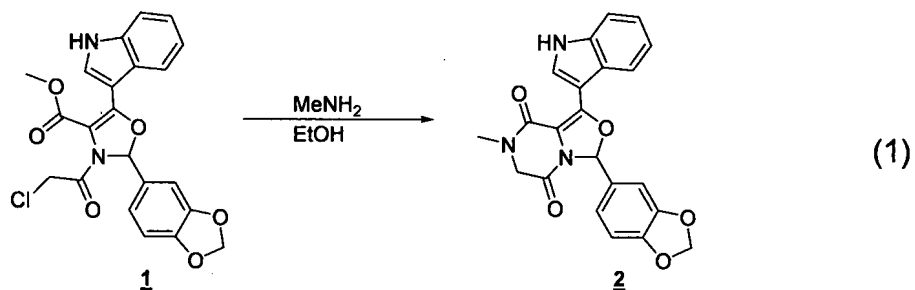
15. Un método para el tratamiento o la prevención de disfunción eréctil en el hombre, que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 7 a dicho animal.

16. Un método para el tratamiento o la prevención de disfunción eréctil en el hombre, que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 8 a dicho animal.

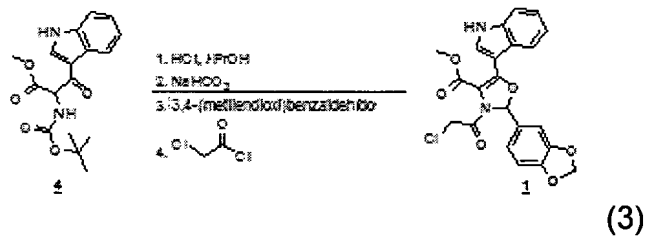
17. Un método para el tratamiento o la prevención de litiasis, hiperplasia de próstata, hipertensión pulmonar, constricción de uréter, disfunción sexual femenina y/o disfunción sexual masculina que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 7 a dicho animal.

18. Un método para el tratamiento o la prevención de litiasis, hiperplasia de próstata, hipertensión pulmonar, constricción de uréter, disfunción sexual femenina y/o disfunción sexual masculina que comprende la administración de la composición farmacéutica de acuerdo con la reivindicación 8 a dicho animal.

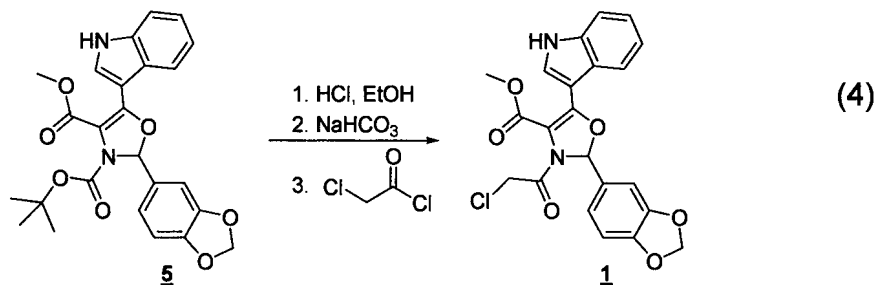
19. Un método de preparación del compuesto de acuerdo con la reivindicación 2, que comprende la preparación del compuesto 2 a partir del compuesto 1, usando opcionalmente metilamina y etanol.



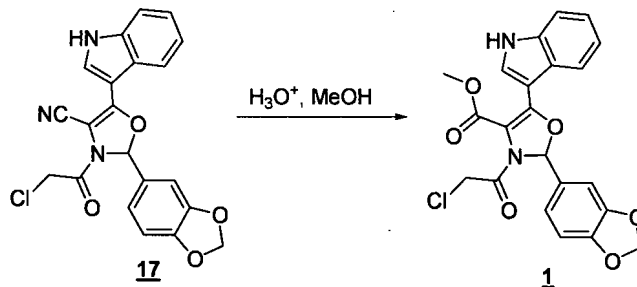
20. El método de acuerdo con la reivindicación 19, que también comprende la preparación del compuesto 1 a partir del compuesto 4, usando opcionalmente ácido en isopropanol, bicarbonato de sodio, 3,4-(metilendioxi)benzaldehído y cloruro de cloroacetilo.



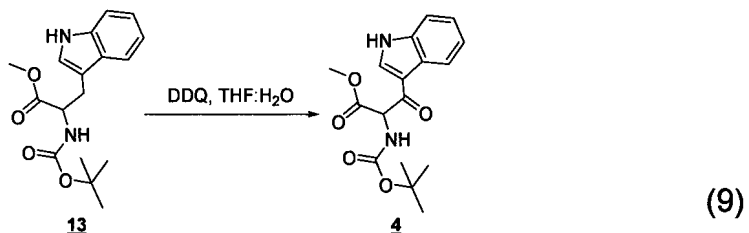
21. El método de acuerdo con la reivindicación 20, que también comprende la preparación del compuesto 1 a partir del compuesto 5, usando opcionalmente ácido en etanol, bicarbonato de sodio y cloruro de cloroacetilo.



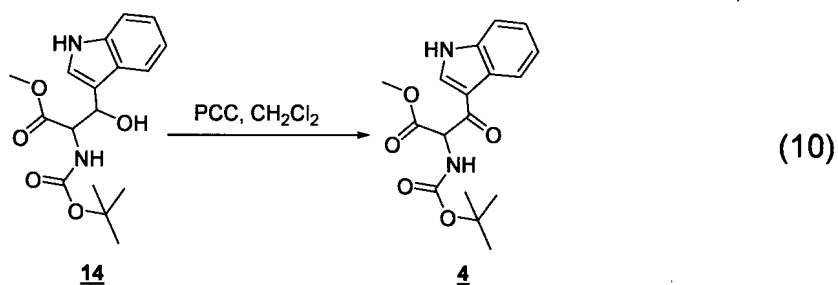
22. El método de acuerdo con la reivindicación 21, que también comprende la preparación del compuesto 1 a partir del compuesto 17, usando opcionalmente metanol e ion hidronio.



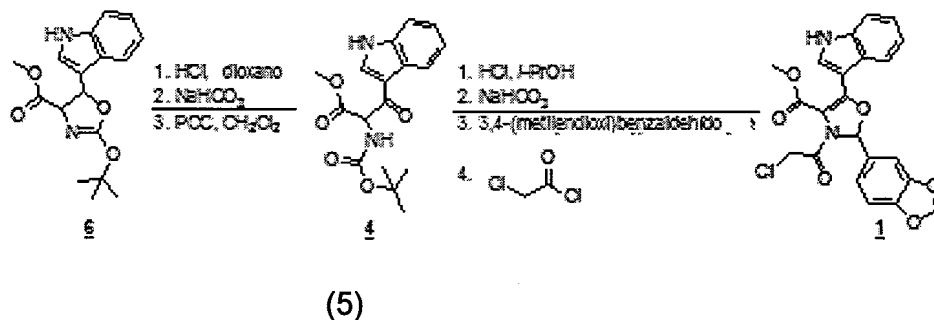
23. El método de acuerdo con la reivindicación 20, que también comprende la preparación del compuesto 4 a partir del compuesto 13, usando opcionalmente (2,3)-dicloro-5,6-diciano-1,4-benzoquinona y una mezcla de tetrahidrofurano:agua.



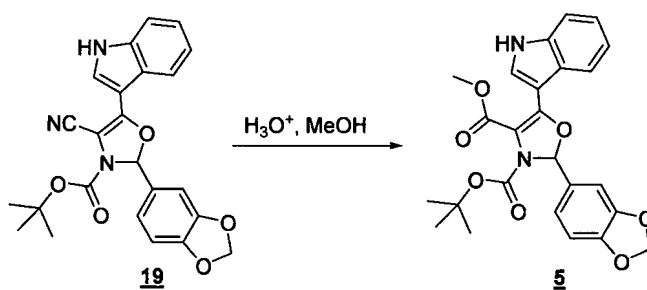
24. El método de acuerdo con la reivindicación 20, que también comprende la preparación del compuesto 4 a partir del compuesto 14, usando opcionalmente clorocromato de piridina (PCC) y cloruro de metileno.



25. El método de acuerdo con la reivindicación 19, que también comprende la preparación del compuesto 4 a partir del compuesto 6, usando opcionalmente ácido en dioxano, bicarbonato de sodio, clorocromato de piridina (PCC) y cloruro de metileno.

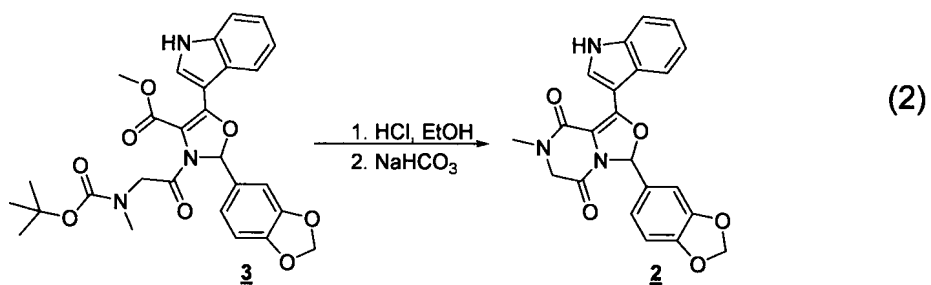


26. El método de acuerdo con la reivindicación 21, que también comprende la preparación del compuesto 5 a partir del compuesto 19, usando opcionalmente metanol e ion hidronio

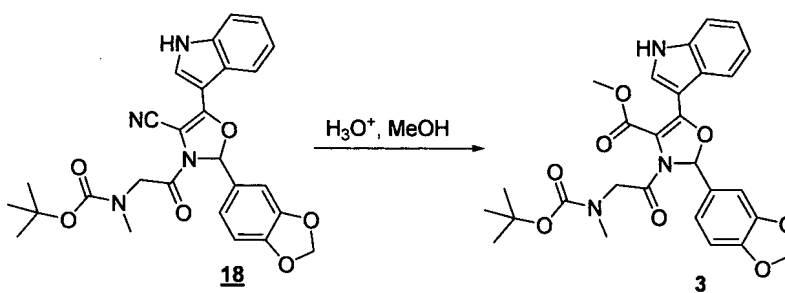


27. Un método de preparación del compuesto de acuerdo con la reivindicación 2, que comprende la preparación del compuesto 2 a partir del

compuesto 3, usando opcionalmente ácido en etanol y bicarbonato de sodio.



28. El método de acuerdo con la reivindicación 27, que también comprende la preparación del compuesto 3 a partir del compuesto 18, usando opcionalmente metanol e ion hidronio.



RESUMEN

DERIVADOS DE 6,7-DIHIDRO-3H-OXAZOLO[3,4-A]PIRAZIN-5,8-DIONA

La presente invención describe una serie de derivados de 6,7-dihidro-3H-oxazolo[3,4-a]pirazin-5,8-diona, sus mezclas, sus sales farmacéuticamente aceptables, que son inhibidores de PDE-5, que poseen propiedades vasodilatadoras y efectos de relajación. En particular, el derivado (*R*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona, su enantiómero (*S*)-3-(1,3-benzodioxol-5-il)-1-(1*H*-indol-3-il)-7-metil-6,7-dihidro[1,3]oxazolo[3,4-a]pirazin-5,8-diona.

La presente invención describe, además, procesos para la preparación de dichos compuestos, composiciones farmacéuticas que los contienen, así como usos como inhibidores de la enzima fosfodiesterasa de tipo 5 (PDE-5) en el tratamiento de la disfunción eréctil y trastornos tratables con inhibidor de PDE-5.

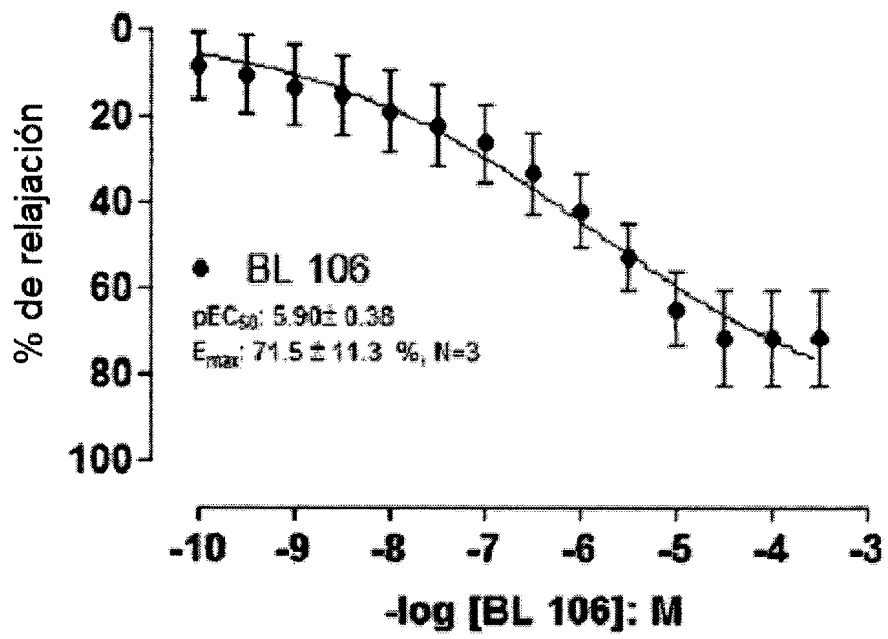


Figura 1. Curva de concentración y respuesta de BL 106 en uréter aislado de ser humano. Los datos son la media $\pm$ SEM, experimentos n = 3.

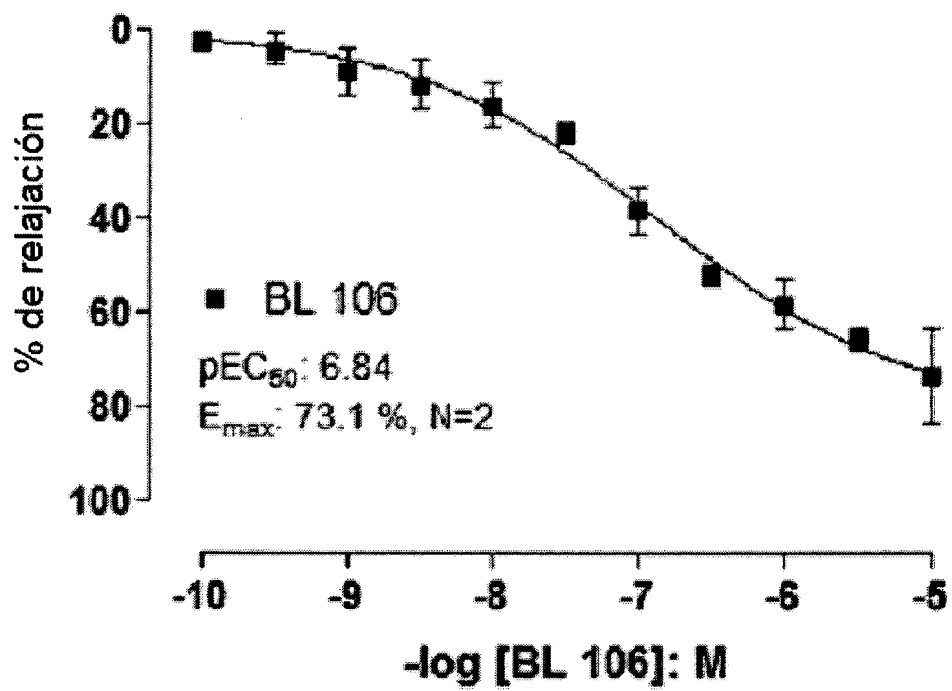


Figura 2. Curva de concentración y respuesta de BL 106 en arteria pulmonar aislada de conejo.

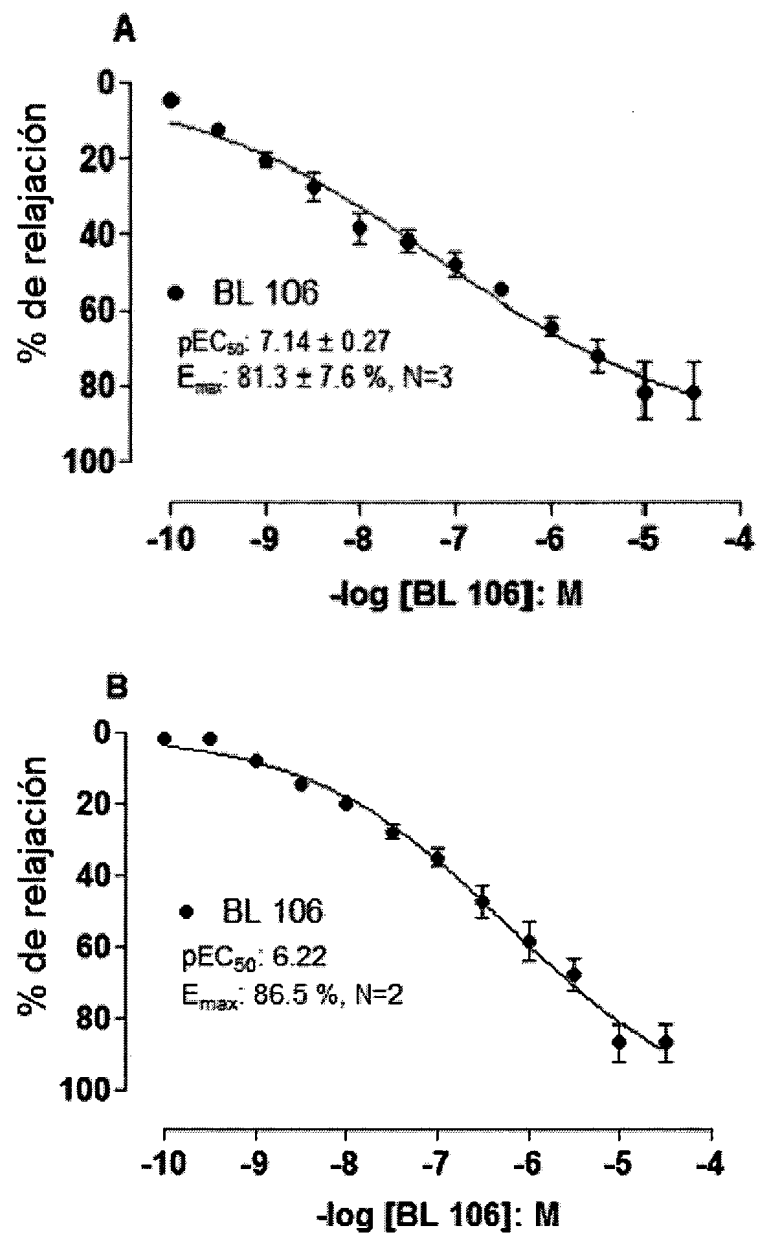


Figura 3. Curva de concentración y respuesta de BL 106 en cuerpo cavernoso aislado de humano (A) y conejo (B). Los datos son la media $\pm$ SEM, experimentos $n = 3$.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION,
OBTENTION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

WEGMANN, Ana Cristina Almeida Müller
Avenida Almirante Barroso, 52 - 33º
Centro
20031-000 Rio de Janeiro - RJ
BRÉSIL

Date of mailing (day/month/year) 22 August 2011 (22.08.2011)	
Applicant's or agent's file reference P2010-ANA	IMPORTANT NOTIFICATION
International application No. PCT/BR2011/000255	International filing date (day/month/year) 02 August 2011 (02.08.2011)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 13 August 2010 (13.08.2010)
Applicant BIOLAB SANUS FARMACÊUTICA LTDA. et al	

The applicant is hereby notified of the date of receipt (or of obtaining by the International Bureau) of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to the date of receipt, **the priority document concerned was submitted or transmitted to or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-bis)**. This Form replaces any previously issued notification concerning submission, transmittal or obtaining of priority documents.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
13 August 2010 (13.08.2010)	61/373,483	US	16 August 2011 (16.08.2011)

The letters "NR" denote a priority document which, on the date of mailing of this Form, had not yet been received or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-bis). Where the applicant has failed to either submit, request to prepare and transmit or obtain and transmit, or to request the International Bureau to obtain the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

An asterisk "*" next to a date of receipt, denotes a priority document submitted or transmitted to or obtained by the International Bureau but not in compliance with Rule 17.1(a), (b) or (b-bis) (the priority document was received after the time limit prescribed in Rule 17.1(a); the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b) or the request to the receiving Office or the International Bureau to obtain the priority document was made after the applicable time limit under Rule 17.1(b-bis)). Even though the priority document was not furnished in compliance with Rule 17.1(a), (b) or (b-bis), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Simin Baharlou e-mail pt09.pct@wipo.int Telephone No. +41 22 338 74 09
Facsimile No. +41 22 338 71 30	

44



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
61/373,483	08/13/2010		220	030014-00011		

CONFIRMATION NO. 1236

4372
ARENT FOX LLP
1050 CONNECTICUT AVENUE, N.W.
SUITE 400
WASHINGTON, DC 20036

FILING RECEIPT



0000000043139815

Date Mailed: 08/25/2010

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Sérgio Luiz SACURAI, Sao Paulo - SP, BRAZIL;
Márcio Henrique ZAIM, Sao Paulo - SP, BRAZIL;
Carlos Eduardo, da Costa TOUZARIM, Sao Paulo - SP, BRAZIL;
Artur Franz KEPPLER, Sao Paulo - SP, BRAZIL;
Gilberto DE NUCCI, Campinas - SP, BRAZIL;

Power of Attorney:

Richard Berman--39107

If Required, Foreign Filing License Granted: 08/20/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 61/373,483**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Derivatives of 6,7-dihydro-3H-oxazolo[3,4- α]pyrazine-5,8-dione

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same

effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with

respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

P2010-ANA

1/5

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	PCT/BR 2011 / 000255
0-2	International Filing Date	02 AGO 2011 020811
0-3	Name of receiving Office and "PCT International Application"	IMPI/BRAZIL-PCT INTERNATIONAL APPLICATION
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.51.044.220 MT/FOP 20100101/0.20.5.18
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	National Institute of Industrial Property (Brazil) (RO/BR)
0-7	Applicant's or agent's file reference	P2010-ANA
I	Title of Invention	"DERIVATIVES OF 6,7-DIHYDRO-3H-OXAZOLO[3,4-a]PYRAZINE-5, 8-DIONE"
II	Applicant	
II-1	This person is	Applicant only
II-2	Applicant for	All designated States except US
II-4	Name	Biolab Sanus Farmacêutica Ltda.
II-5	Address	Rua das Olimpíadas, 242 - 3° andar Vila Olímpia 04551-000 São Paulo - SP Brazil
II-6	State of nationality	BR
II-7	State of residence	BR
III-1	Applicant and/or inventor	
III-1-1	This person is	Applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	SACURAI, Sérgio Luiz
III-1-5	Address	Rua Pitangueiras, 242 - Apto. 122 Mirandópolis 04052-020 São Paulo - SP Brazil
III-1-6	State of nationality	BR
III-1-7	State of residence	BR

P2010-ANA

2/5

PCT REQUEST

Original (for SUBMISSION)

III-2	Applicant and/or inventor	
III-2-1	This person is	Applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ZAIM, Márcio Henrique
III-2-5	Address	Rua Domingos Olímpio, 119 - Apto. 53B Vila Sônia 05625-060 São Paulo - SP Brazil
III-2-6	State of nationality	BR
III-2-7	State of residence	BR
III-3	Applicant and/or inventor	
III-3-1	This person is	Applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	TOUZARIM, Carlos Eduardo da Costa
III-3-5	Address	Rua Gerônimo Salguera, 49, Bloco 22 - Apto. 41 Parque Flamengo 05783-070 São Paulo - SP Brazil
III-3-6	State of nationality	BR
III-3-7	State of residence	BR
III-4	Applicant and/or inventor	
III-4-1	This person is	Applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	KEPPLER, Artur Franz
III-4-5	Address	Rua Xingu, 245 - Apto. 134 Valparaíso 09060-050 Santo André - SP Brazil
III-4-6	State of nationality	BR
III-4-7	State of residence	BR
III-5	Applicant and/or inventor	
III-5-1	This person is	Applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	DE NUCCI, Gilberto
III-5-5	Address	Avenida Dr. Jesuíno Marcondes Machado, 415 13092-108 Campinas - SP Brazil
III-5-6	State of nationality	BR
III-5-7	State of residence	BR

PCT/BR 2011 / 000255

P2010-ANA

3/5

PCT REQUEST

Original (for SUBMISSION)

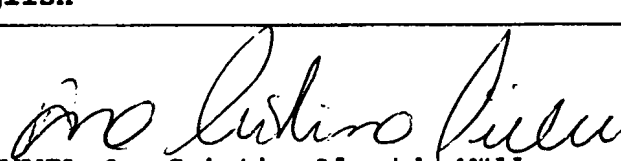
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	Agent
IV-1-1	Name (LAST, First)	WEGMANN, Ana Cristina Almeida Müller
IV-1-2	Address	Avenida Almirante Barroso, 52 - 33° Centro 20031-000 Rio de Janeiro - RJ Brazil
IV-1-3	Telephone No.	55 21 3824-5757
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	13 August 2010 (13.08.2010)
VI-1-2	Number	61/373,483
VI-1-3	Country	US
VI-2	Incorporation by reference : where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.	
VII-1	International Searching Authority Chosen	National Institute of Industrial Property (Brazil) (ISA/BR)

P2010-ANA

4/5

PCT REQUEST

Original (for SUBMISSION)

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	23	-
IX-3	Claims	8	-
IX-4	Abstract	1	✓
IX-5	Drawings	2	-
IX-7	TOTAL	39	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-18	PCT-SAFE physical media	-	✓
IX-19	Other	Inventor's assignment	
IX-19	Other	Priority document	
IX-20	Figure of the drawings which should accompany the abstract	3A	
IX-21	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	 WEGMANN, Ana Cristina Almeida Müller	
X-1-1	Name (LAST, First)		
X-1-2	Name of signatory		
X-1-3	Capacity		

P2010-ANA

5/5

PCT REQUEST

Original (for SUBMISSION)

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	02 AGO 2011 020811
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/BR
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

BIOLAB SANUS Farmacêutica Ltda /
Rua das Olimpíadas, 242 - 3º andar,
Vila Olímpia , São Paulo / SP , BR, Tel:
 , Fax: , CEP 04551-000

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference		Date of mailing (day/month/year) 181011
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/BR2011/000255	International Filing Date (day/month/year) 02/08/2011	Priority Date(day/month/year) 13/08/2010
International Patent Classification (IPC) or both national classification and IPC C07D498/04 (2006.01), A61K 31/48 (2006.01), A61P 15/00 (2006.01)		
Applicant BIOLAB SANUS Farmacêutica Ltda		

1. This opinion contains indications relating to the following items:

- | | |
|---|--|
| ☒ Box No. I | Basis of the opinion |
| ☐ Box No. II | Priority |
| ☒ Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ Box No. IV | Lack of unity of invention |
| ☒ Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ Box No. VI | Certain documents cited |
| ☒ Box No. VII | Certain defects in the international application |
| ☐ Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/BR: INPI INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL Rua Mayrink Veiga nº 9, 18º andar Facsimile Nº +55 21 3037-3663	Date of completion of this opinion	Authorized officer Jaqueline Mendes Soares Telephone No +55 21 3037-3686/3742
---	------------------------------------	---

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application N°
PCT/BR2011/000255

Box No. 1	Basis of this opinion
	1. With regard to the language, this opinion has been established on the basis of: ☒ the international application in the language in which it was filed. ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)). 2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)) 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of: a. (means) ☐ on paper ☐ in electronic form b. (time) ☐ in the international application as filed ☐ together with the international application in electronic form ☐ subsequently to this Authority for the purposes of search 4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished. 5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application N°
PCT/BR2011/000255

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-18

because:

☒ the said international application, or the said claims Nos. 11-18
relate to the following subject matter which does not require an international search (*specify*):

Claims 11 to 18 refer to a subject that the current Administration considers being addressed by PCT Rule 39.1 (iv), that covers methods for treatment of the human or animal body by surgery or therapy; diagnostic methods practiced on the human or animal body. Thereby, no opinion will be submitted concerning novelty, inventive step and industrial applicability of the subject presented by this/these claims (PCT Article 17.2(a)(i)).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b)

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application N°
PCT/BR2011/000255

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-10 and 19-28</u>	YES
	Claims	<u>None</u>	NO
Inventive step (IS)	Claims	<u>1-10 and 19-28</u>	YES
	Claims	<u>None</u>	NO
Industrial applicability (IA)	Claims	<u>1-10 and 19-28</u>	YES
	Claims	<u>None</u>	NO

2. Citations and explanations:

D1: WO02098877 (Lilly Icos LLC [US]), 12 December 1997;
D2: WO9703675 (Laboratoire Glaxo Wellcome S. A. [FR]), 06 February 1997;
D3: WO03000691 (Lilly Icos LLC [US]), 03 January 2003).

The present application describes derivatives of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione, their preparation and their use in the treatment of erectile dysfunction and PDE-5 inhibitor treatable disorders.

D1 describe derivatives of pyrazino 1', 2': 1,6 pyrido 3,4-b indole 1,4-dione derivatives and their use in the treatment of sexual dysfunction.
D2 describe derivatives of (3,4-methylenedioxyphenyl)-pyrazino[2', 1': 6,1]pyrido[3,4-b]indole-1,4-dione and their use in the treatment of sexual dysfunction.
D3 describe derivatives of carboline and their use in the treatment of sexual dysfunction.

Since none of the cited documents discloses the special compounds according to the present application, claims 1-10 and 19-28 are novel in the sense of Article 33(2) PCT.

Since the structural modification to be carried out to the compounds of in order to arrive at the compounds of the present application cannot be regarded as obvious, claims 1-10 and 19-28 are considered to involve an inventive step (Article 33(3) PCT). Industrial applicability is given (Article 33(4) PCT).

The cited documents only disclose the general prior art, and are not considered of relevance. Thus, is considered that the subject matter claimed meet the requirements of novelty, inventive step and industrial application.

57

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application N°
PCT/BR2011/000255

Box No. VII **Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

The description does not indicate the background art which, as far as known to the applicant, can be regarded as useful for the understanding, searching and examination of the invention (PCT Rule 5.1 (a) (ii)).

The claims does not contain a characterizing portion according to the PCT Rule 6.3 (b) (ii)).

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 February 2012 (16.02.2012)

(10) International Publication Number
WO 2012/019254 A1

(51) International Patent Classification:
C07D 498/04 (2006.01) A61P 15/00 (2006.01)
A61K 31/48 (2006.01)

(BR). DE NUCCI, Gilberto [BR/BR]; Avenida Dr. Jesuino Marcondes Machado, 415, 13092-108 Campinas - SP (BR).

(21) International Application Number:
PCT/BR2011/000255

(74) Agent: WEGMANN, Ana Cristina Almeida Müller; Avenida Almirante Barroso, 52 - 33º, Centro, 20031-000 Rio de Janeiro - RJ (BR).

(22) International Filing Date:
2 August 2011 (02.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/373,483 13 August 2010 (13.08.2010) US

(71) Applicant (for all designated States except US): BIO-LAB SANUS FARMACÊUTICA LTDA. [BR/BR]; Rua das Olimpíadas, 242 - 3º andar, Vila Olímpia, 04551-000 São Paulo - SP (BR).

(72) Inventors; and

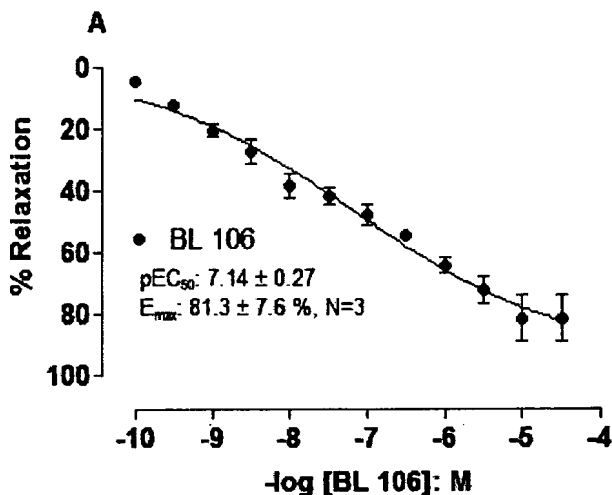
(75) Inventors/Applicants (for US only): SACURAI, Sérgio Luiz [BR/BR]; Rua Pitangueiras, 242 - Apto. 122, Mirandópolis, 04052-020 São Paulo - SP (BR). ZAIM, Márcio Henrique [BR/BR]; Rua Domingos Olímpio, 119 - Apto. 53B, Vila Sônia, 05625-060 São Paulo - SP (BR). TOUZARIM, Carlos Eduardo da Costa [BR/BR]; Rua Gerônimo Salguera, 49, Bloco 22 - Apto. 41, Parque Flamengo, 05783-070 São Paulo - SP (BR). KEPPLER, Artur Franz [BR/BR]; Rua Xingu, 245 - Apto. 134, Valparaíso, 09060-050 Santo André - SP

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: DERIVATIVES OF 6, 7-DIHYDRO-3H-OXAZOLO [3, 4-A] PYRAZINE-5, 8- DIONE



(57) Abstract: The present invention describes a series of derivatives of 6, 7-dihydro-3H-oxazolo [3, 4-a] pyrazine-5, 8-dione, mixtures thereof, their pharmaceutically acceptable salts, which are inhibitors of PDE-5, possessing vasodilator properties and relaxing effects. In particular, the derivative (3R)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6, 7-dihydro [1, 3] oxazolo [3, 4-a] pyrazine-5, 8-dione, its enantiomer (S)-3-(1, 3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6, 7-dihydro [1,3] oxazolo [3, 4-a] pyrazine-5, 8-dione. The present invention describes, additionally, processes for the preparation of said compounds, pharmaceutical compositions containing them, as well as uses as inhibitors of the enzyme phosphodiesterase type 5 (PDE-5) in the treatment of the erectile dysfunction and PDE-5 inhibitor treatable disorders.

WO 2012/019254 A1



Published:

— with international search report (Art. 21(3))

"DERIVATIVES OF 6,7-DIHYDRO-3H-OXAZOLO[3,4-a]PYRAZINE-5,8-DIONE"

FIELD OF THE INVENTION

5

The present invention describes a series of derivatives of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione, mixtures thereof, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, processes of their preparation, method of inhibiting the enzymes phosphodiesterases, their use as an inhibitor of the enzymes phosphodiesterases, and their use as an inhibitor of the enzyme phosphodiesterase of type 5 (PDE-5). In particular, the derivative (R)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, its enantiomer (S)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, and/or mixtures thereof (in any ratio).

The present invention also describes a method of treatment of erectile dysfunction, tissue relaxation treatable disorders and/or conditions and PDE-5 inhibitor treatable disorders using derivatives of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione, mixtures thereof (in any ratio) and/or their pharmaceutically acceptable salts. In particular, the derivative (R)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, its enantiomer (S)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, and/or mixtures thereof (in any ratio).

BACKGROUND OF THE INVENTION

Before the appearance of the first oral treatment, male sexual impotence was treated by intracavernous injections and other means, due to, in particular, doubts stemming from adverse reactions that oral administration could cause in humans. Papaverine and pentoxifylline, for example, were used in the treatment of erectile dysfunction by intracavernous injections. Other means of treatment, less efficient, were, for example, psychotherapies and surgical implants.

Oral treatment is most acceptable by man, and it emerged from clinical research using inhibitors of cGMP-PDE, more specifically, PDE-5. The precursor of these compounds was 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl) phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, or sildenafil, with vasodilator properties and potentiates the effects of nitric oxide. Sildenafil is the active ingredient of the medicine Viagra®.

20

Later, other inhibitor compounds of PDE-5 were developed and are cited in numerous publications of technical literature, as well as patent publications, such as vardenafil, the active ingredient of the medicine Levitra®, and tadalafil, the active ingredient of the medicine Cialis®.

25

The compounds of the present invention, the derivatives of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione, are also inhibitors of the enzyme phosphodiesterase type 5 (PDE-5).

30

DESCRIPTION OF THE INVENTION

It is, therefore, the objective of the present invention to provide new derivative compounds of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione, mixtures thereof (in any ratio), their pharmaceutically acceptable salts, pharmaceutical compositions containing them, that are effective in the treatment of erectile dysfunction, said compounds being tissue relaxants, and/or inhibitors of the enzymes phosphodiesterases possessing vasodilator properties and relaxing effects, particularly inhibitors of PDE-5. In particular, the derivative (R)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, its enantiomer (S)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, and/or mixtures thereof (in any ratio).

It is also the objective of the present invention to provide processes preparation of derivative compounds of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione, and mixtures thereof. In particular, the derivative (R)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, its enantiomer (S)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione, and/or mixtures thereof (in any ratio).

Furthermore, it is the objective of the present invention to provide pharmaceutical compositions comprising an effective amount of one of the derivatives of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione or mixtures thereof (in any ratio) or their pharmaceutically acceptable salts, and pharmaceutically acceptable excipients. In particular, pharmaceutical compositions comprising the derivative (R)-3-

(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione, its enantiomer (*S*)-3-(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione, and/or mixtures thereof (in any ratio).

An additional objective of the present invention is to provide a medicament comprising a therapeutically effective amount of one of the derivatives of 6,7-dihydro-3*H*-oxazolo[3,4-*a*]pyrazine-5,8-dione or mixtures thereof (in any ratio) or their pharmaceutically acceptable salts. In particular, medicaments comprising the derivative (*R*)-3-(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione, its enantiomer (*S*)-3-(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione, and/or mixtures thereof (in any ratio).

Another objective of the present invention is the use of one of the derivatives of 6,7-dihydro-3*H*-oxazolo[3,4-*a*]pyrazine-5,8-dione, or mixtures thereof (in any ratio), or their pharmaceutically acceptable salts, for curative and/or prophylactic treatment of erectile dysfunction, tissue relaxation treatable disorders and/or conditions, and PDE-5 inhibitor treatable disorders in animal. In particular, the derivative (*R*)-3-(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione, its enantiomer (*S*)-3-(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione, and/or mixtures thereof (in any ratio).

BRIEF DESCRIPTION OF THE DRAWINGS

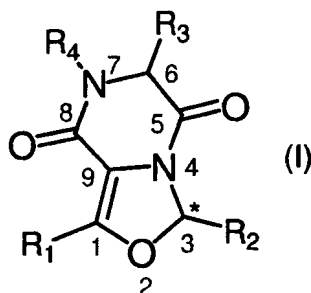
Figure 1 shows the relaxing effects of compound 2 (BL 106) on human isolated urether tissue. Figure 1 represents the concentration response curve to BL 106 in isolated urether from human. Data are the mean $\pm$ SEM, n=3 experiments.

Figure 2 shows the relaxing effects of compound 2 (BL 106) on rabbit isolated pulmonary artery tissue. Figure 2 represents the concentration response curve to BL 106 in isolated pulmonary artery from rabbit.

Figure 3 shows the relaxing effects of compound 2 (BL 106) on human isolated corpus cavernosum tissue (Figure 3A) and rabbit isolated corpus cavernosum tissue (Figure 3B). Figure 3 represents concentration response curve to BL 106 in isolated corpus cavernosum from human (A) and rabbit (B). Data are the mean $\pm$ SEM, n=3 experiments.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes derivatives of 6,7-dihydro-3H-oxazolo[3,4-a]pyrazine-5,8-dione with structures represented in formula (I):



and salts and solvates (for example, hydrates) thereof, where:

- R^1 represents an aromatic group, condensed group or not, (optionally substituted with R^B in one or more positions), a heteroaromatic group containing one or more heteroatoms or indol groups (optionally substituted with R^B in one or more positions), C_{1-6} alkenylcarbonyl (optionally substituted with R^B in one or more positions), bicyclic aromatic (optionally substituted with R^B in one or more positions), or bicyclic heteroaromatic, containing one or heteroatoms (optionally substituted with R^B in one or more positions);
- 10 R^B represents halogen, hydroxyl, nitrogen, cyano, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl, aryl C_{1-3} alkyl or heteroaryl C_{1-3} alkyl;
- R^2 represents an aromatic group containing one or heteroatoms, or bicyclic aromatic or heteroaromatic containing one or more heteroatoms or methylene-3,4-dioxyphenyl groups;
- 15 R^3 represents hydrogen, halogen, C_{1-6} haloalkyl, C_{1-3} heteroalkyl, or C_{1-3} alkyl;
- R^4 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-3} alkyl, aryl C_{1-3} alkyl or heteroaryl C_{1-3} alkyl.
- 20

In one aspect, " C_{2-6} alkenylcarbonyl" of R^1 represents one or more alkenyl groups, containing from 2 to 6 carbon atoms, conjugated or not with a carbonyl group.

25

- In one aspect, "aryl" of R^B and R^4 , e.g., aryl C_{1-3} alkyl, represents a phenyl group or phenyl substituted one or more times (e.g. 1, 2 or 3) by halogen, C_{1-6} alkyl, C_{1-6} alkoxy or methylenedioxy. In another aspect, "heteroaryl" of R^B and R^4 , e.g., heteroaryl C_{1-3} alkyl, represents a furil group or pyridyl, optionally substituted one or more times with halogen, C_{1-6} alkyl or C_{1-6} alkoxy. In another aspect, " C_{3-8} cycloalkyl" of R^B and R^4 , e.g., C_{3-8} cycloalkyl C_{1-3} alkyl, represents a monocyclic
- 30

ring containing from 3 to 8 carbon atoms. Examples of cycloalkyl rings include C₃₋₆ cycloalkyl rings: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

5 The term "alkyl" can represent an alkyl chain or branched alkyl chain. For example, the C₁₋₄ alkyl group can represent methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl and *t*-butyl. The term "alkenyl" includes alkenyl groups of straight and branched chains, e.g., vinyl and allyl groups. The term
10 "alkynyl" includes alkynyl groups of straight and branched chains, e.g., acetylene. The term "halogen" can represent atoms of fluorine, chlorine, bromine or iodine. The term "halo C₁₋₆alkyl" can represent an alkyl group containing from one to six carbon atoms, substituted with one or more (e.g. 1, 2 or
15 3) atoms of halogen.

The compounds of formula (I) can contain one or more asymmetrical centers, thus existing as enantiomers and/or diastereomers. For example, in formula (I), a chiral center is
20 indicated with an asterisk. Accordingly, the invention includes one or more enantiomers, and mixtures thereof (in any ratio).

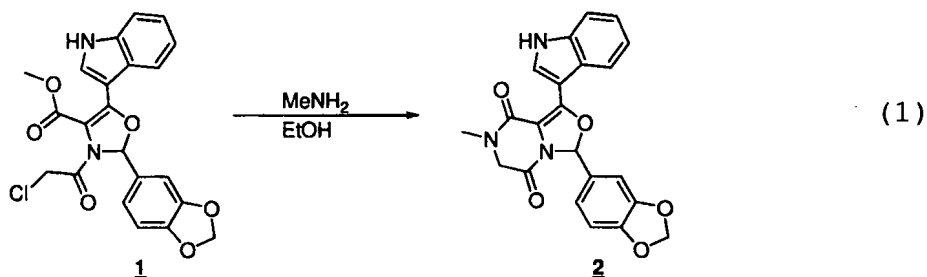
The compounds of formula (I) can exist with different
25 tautomeric forms, and the invention includes one or more tautomeric forms, and mixtures thereof (in any ratio).

Pharmaceutically acceptable salts of the compounds of formula (I), which possess a basic center, are formed by the
30 addition of pharmaceutically acceptable acids. Some examples include salts of hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartarate,

gluconate, methanesulfonate, benzenesulfonate and *p*-toluenesulfonate. The compounds of formula (I) can be used in pharmaceutically acceptable metal salts, in particular salts of alkaline metals, with bases. For example, salts of sodium and potassium.

In one embodiment, the compounds of this invention have a structure represented in formula (I), where **R¹** represents an indol group, **R²** represents an 3,4- methylenedioxyphenyl group, **R³** represents hydrogen and **R⁴** represents a methyl group. In a preferred embodiment, the compounds of this invention are (*R*)-3-(benzo[d][1,3]dioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro-3*H*-oxazolo[3,4-*a*]pyrazine-5,8-dione, and/or its enantiomer (*S*)-3-(benzo[d][1,3]dioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro-3*H*-oxazolo[3,4-*a*]pyrazine-5,8-dione.

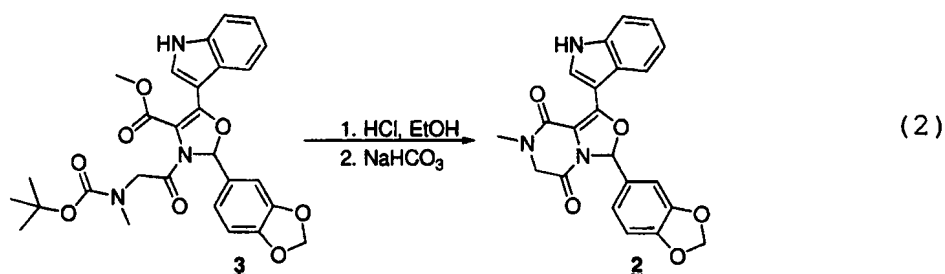
The compound (*R,S*)-3-(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione (**2**), according to the present invention, can be prepared from the reaction of compound **1** in the presence of methylamine, using ethanol as solvent, according to Scheme 1:



An alternative approach for the preparation of compound **2** is via the reaction of **3** with acid in ethanol, according to Scheme 2:

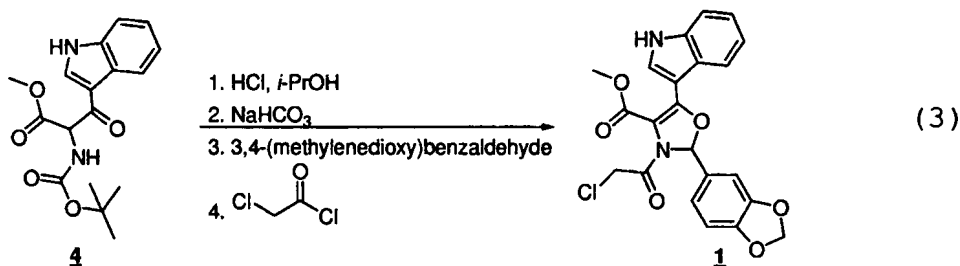
9

5



Compound 1 can be prepared according to Scheme 3:

10



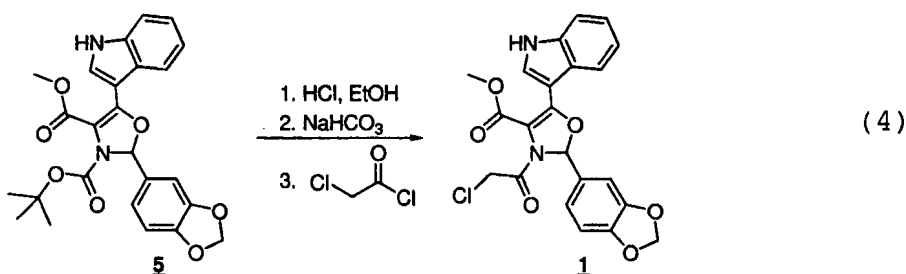
15

Compound 4 is treated with acid in isopropanol. After neutralization with sodium bicarbonate, 3,4-(methylenedioxy)benzaldehyde is added. The last step of this approach is addition of chloroacetyl chloride.

20

Alternatively, compound 1 can be prepared according to Scheme 4:

25

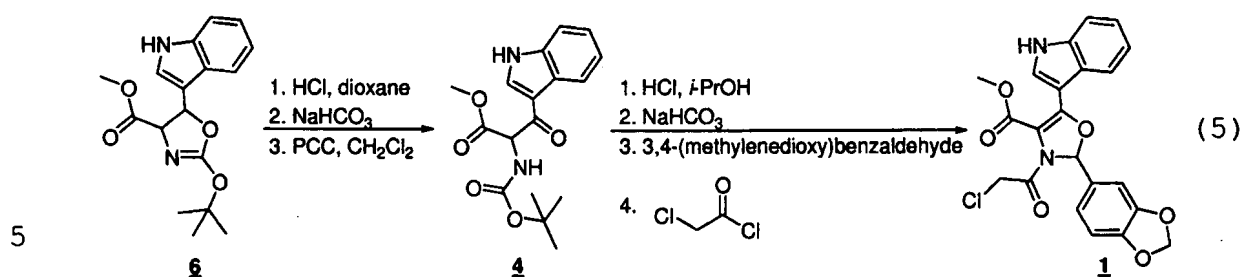


30

In this approach, compound 5 is treated with acid in ethanol. After neutralization with sodium bicarbonate, chloroacetyl chloride is added.

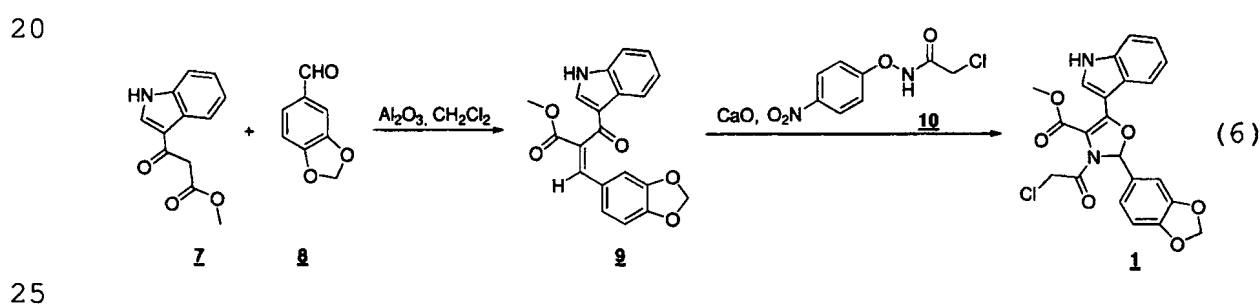
Compound 1 also can be prepared according to Scheme 5:

10



In this approach, compound 6 is treated with acid in dioxane. After neutralization with sodium bicarbonate, an oxidation reaction is made with pyridine chlorochromate (PCC), leading to formation of intermediate 4, that is treated with acid in isopropanol. After neutralization with sodium bicarbonate, 3,4-(methylenedioxy)benzaldehyde is added. The last step of this approach is addition of chloroacetyl chloride.

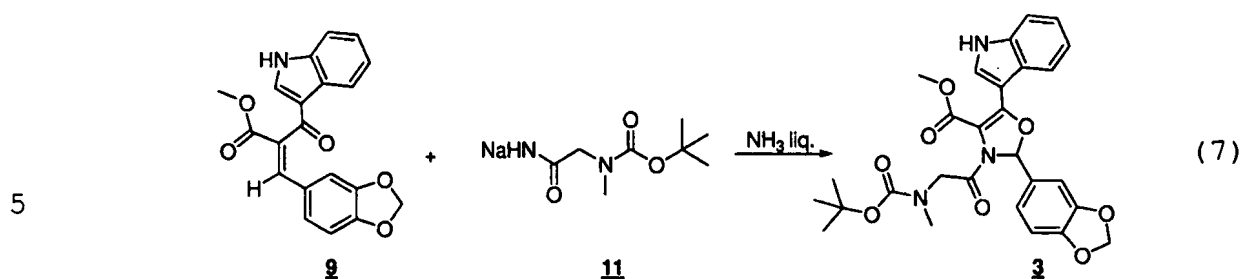
Another approach for preparation of compound 1 is given in Scheme 6:



In this approach, the reaction of 7 and 8 in presence of aluminum oxide (Al_2O_3) in dichloromethane leads to the formation of intermediate 9, which reacts with 10 in the presence of calcium oxide (CaO).

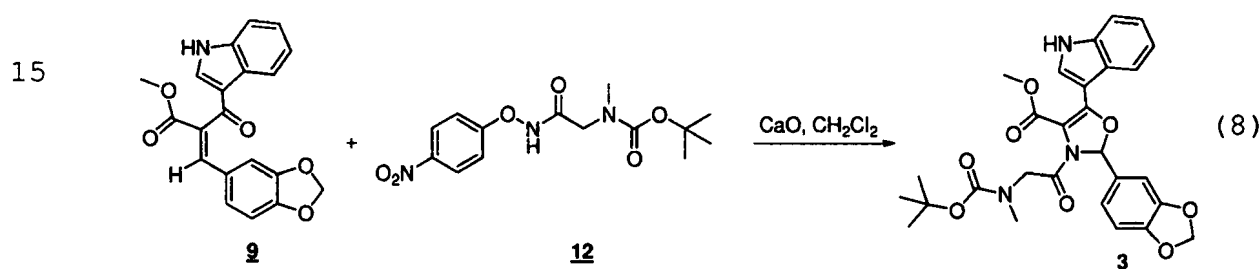
Compound 3 can be prepared according to Scheme 7:

11



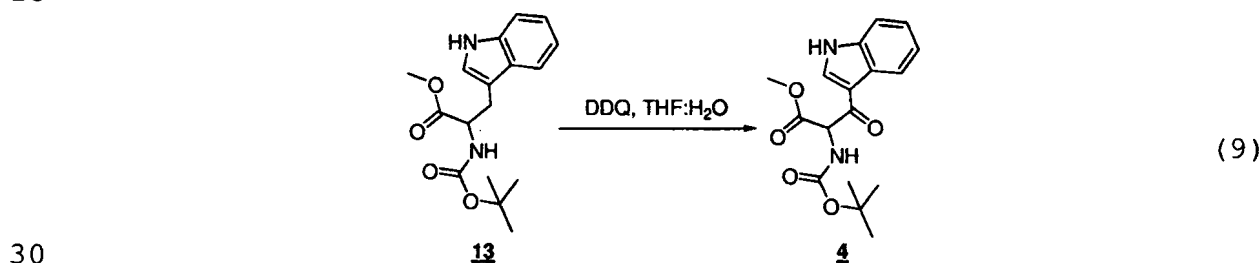
In this approach, intermediate **9** reacts with compound **11**, using liquid ammonia as a solvent.

Alternatively, compound **3** can be prepared according to Scheme 8:



In this approach, in the presence of calcium oxide (CaO), intermediate **9** reacts with compound **12**.

Compound **4** can be prepared according to Scheme 9:

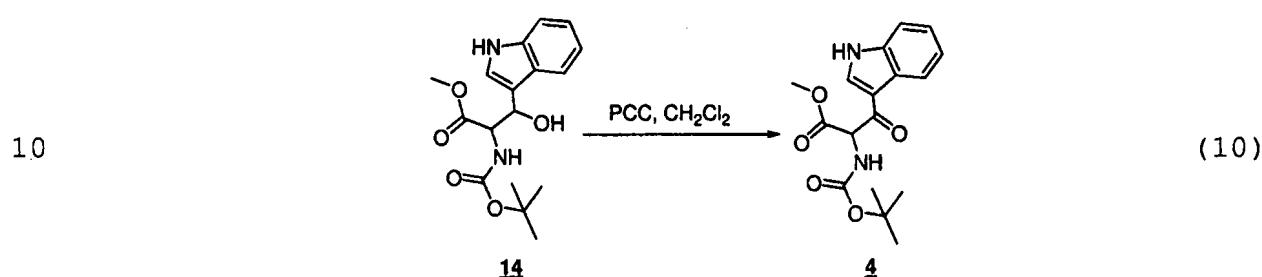


30

12

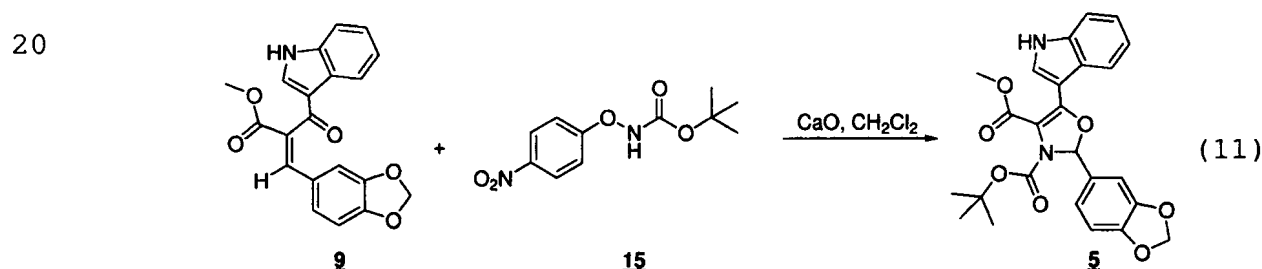
In this approach, compound **13** is treated with (2,3)-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), using a mixture of tetrahydrofuran:water as solvent for the reaction.

5 Another approach for preparation of compound **4** is given in Scheme 10:



15 In this approach, compound **14** is treated with chloride of pyridine chlorochromate (PCC), using methylene chloride as solvent for the reaction.

Compound **5** can be prepared according to Scheme 11:



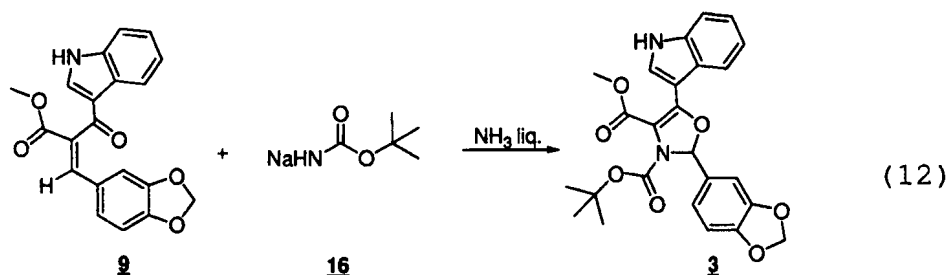
25

In this approach, in the presence of calcium oxide (CaO), intermediate **9** reacts with compound **15**.

30 Alternatively, compound **5** can be prepared according to Scheme 12:

13

5

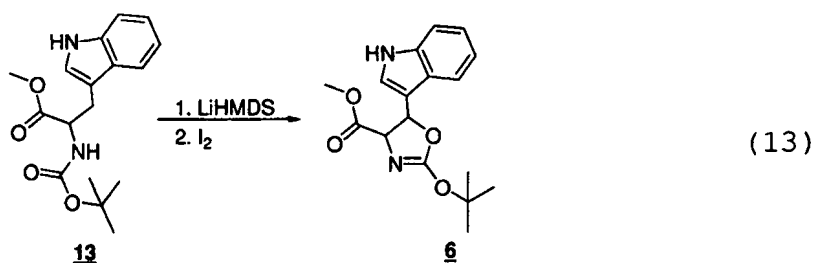


In this approach, intermediate **9** reacts with compound **16**, using liquid ammonia as solvent.

10

Compound **6** can be prepared according to Scheme 13:

15

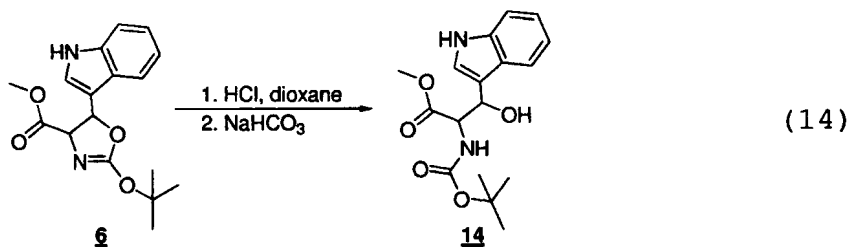


In this approach, compound **13** is treated with lithium hexamethyldisilazide (LiHMDS). The last step of this approach is iodine addition (I_2).

20

Compound **14** can be prepared according to Scheme 14:

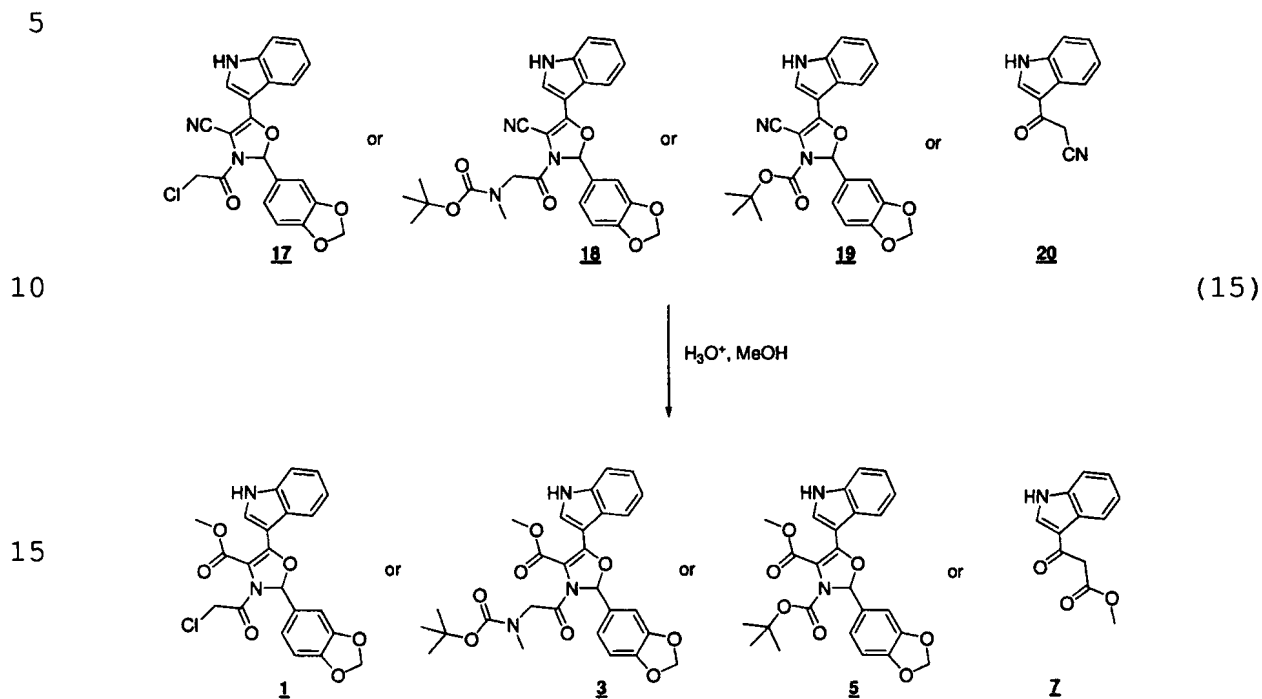
25



30

In this approach, compound **6** is treated with acid in dioxane.

All compounds containing the carboxymethyl group, particularly 1, 3, 5 and 7, can be prepared from (their) derivatives containing the nitrile group, e.g., according to Scheme 15.



For example, compound 17 is treated with acid in methanol. This approach can also be used, individually, with compounds 18, 19 and 20 in order to prepare intermediates 3, 5 and 7 respectively.

The present invention also provides a pharmaceutical composition, e.g. an appropriate dosage form, wherein said composition comprises an effective amount of one or more compounds of formula (1) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In one embodiment, the pharmaceutical composition further comprises other PDE-5 inhibitors, such as sildenafil, vardenafil and tadalafil; or a pharmaceutically acceptable salt thereof. In another embodiment, the pharmaceutical

composition further comprises one or more compounds that treat erectile dysfunction or the PDE-5 inhibitor treatable disorder.

5 In one embodiment, the pharmaceutical composition is administered with a second pharmaceutical composition comprising other PDE-5 inhibitors, for example sildenafil, vardenafil and tadalafil; or a pharmaceutically acceptable salt thereof. In another embodiment, said second
10 pharmaceutical composition comprises one or more compounds that treat erectile dysfunction or the PDE-5 inhibitor treatable disorder. The administration may be co-administration or sequential administration.

15 Pharmaceutical compositions may be prepared by methods well known in the state of the art. Appropriately, Remington's Pharmaceutical Sciences or similar information sources may be used to prepare a suitable formulation according to the invention.

20

Pharmaceutical compositions for oral administration may be presented as discrete units such as capsules, tablets, effervescent tablets, chewable tablets, pills, powders, granules and gels or similar pharmaceutical forms. Other oral
25 formulation forms include suspensions or emulsions in an aqueous or non-aqueous carrier.

In solid dosage forms, the compounds of formula (I) can be admixed with a pharmaceutically acceptable carrier comprising
30 at least one component selected from the group comprising diluents, binders, disintegrants, lubricants, coloring agents, and flavoring agents. Exemplary inert diluents are calcium carbonate, calcium phosphate-dibasic, calcium phosphate-

tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrans, cyclodextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, 5 sugar compressible, and sugar confectioners. As binders may be used one or more substances, e.g., methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, 10 tragacanth, sodium alginate, propylene glycol, and alginate. As disintegrant may be used one or more substances selected from low substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium, starch, 15 crystalline cellulose, hydroxypropyl starch, and partially pregelatinized starch, and croscarmellose sodium. Exemplary lubricants are stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, and sucrose.

20 In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the compounds of formula (I) and vegetable oil. Hard gelatin capsules may contain granules of the compounds of 25 formula (I) in combination with a solid, pulverulent carrier such as, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. In addition, tablets and pills can be prepared with enteric coatings.

30

In one embodiment, the dosage forms are a controlled/retarded/modulated release type, which are based on carriers or matrices including, but not being limited to,

biocompatible polymers, pharmaceutically acceptable polymeric matrices, liposomes, PEG-liposomes, or a cyclodextrin or a cyclodextrin derivative matrix.

5 Pharmaceutical compositions may be administered by a variety of administration routes, including, but not being limited to, oral, intracavernosal injection, topically and transdermally delivered through the skin into various sites or parenteral routes. The particular mode selected will depend on
10 the compounds present in the composition, the severity of the erectile dysfunction, tissue relaxation treatable disorders and/or conditions, or PDE-5 inhibitor treatable disorder being treated and the dosage required for therapeutic efficacy. Preferably, the compositions of the invention are in oral
15 administration form because of convenience of the patient and the dosing schedule.

Tissue relaxants have been used to promote relaxation on various tissues to treat or act as adjuvant of the treatment,
20 procedure or surgery related with lithiasis (Korkes, F. et al, J Bras Nefrol. (2009) 31(1): 55), prostate enlargement (e.g., benign prostatic hyperplasia, prostatitis) (WO 9911279) and urether constriction (Van der werf et al, BJU International (2002) 90:588). Other tissue relaxation treatable disorders
25 and/or conditions are known and described in the art.

PDE-5 inhibitors have been used to block cGMP degradation to prolong the effects of nitric oxide (NO) on various tissues, e.g., to maintain NO-induced relaxation of airways
30 and vessels (Barnes, P. J., et al., (1995), and to maintain NO-induced protection of tissue (Duffin, R., et. al., Br J Pharmacol. (2008) 153(4): 623). Such actions on tissues have been shown beneficial for treatment of several disorders -

herein, PDE-5 inhibitor treatable disorders - including pulmonary hypertension (commercially treated with sildenafil citrate); bronchitis, chronic asthma, hypertension (EP 758653, US 7569572); Raynaud's phenomenon (Ghofrani H.A., et. al., Nat Rev Drug Discov. 2006, 5:689); commencing right-heart failure (Ghofrani et al. (2003) AJRCCM 167(8): 1139); neurogenesis and functional recovery after stroke (Zhang et al. (2002) Stroke 33: 2675-2680); coronary artery relaxation (Halcox et al. (2002) J Am Coll Cardiol 40: 1232); female sexual arousal disorders (Nehra et al. (2001) World J Urol. 19(1): 115); angina and congestive heart failure (Reffellmann et al., Circ. (2003) 108(2): 239). Other PDE-5 inhibitor treatable disorders are known and described in the art.

15 A therapeutically effective amount for treatment of erectile dysfunction is one that is sufficient to achieve improvement in erectile function or an alleviation of the symptoms of erectile dysfunction, or even to restore the erectile capacity. A therapeutically effective amount for
20 treatment of PDE-5 inhibitor treatable disorders is one that is sufficient to achieve improvement in said disorder or an alleviation of the symptoms of said disorder. Effective amounts will depend on the specific condition being treated and the severity thereof; individual patient characteristics,
25 including age, physical condition, size and weight; concurrent treatment; and the mode of administration. These factors are well known to those skilled in the art and can be established without undue experimentation. Generally, doses of compounds of formula (I) will range from about 0.01 mg/kg body weight
30 per day to 100 mg/kg body weight per day, preferably from 0.1 mg/kg body weight per day to 10 mg/kg body weight per day. Multiple doses per day may be contemplated to achieve

appropriate systemic levels of active ingredients present in the composition of the invention.

The following Examples describe the present invention in more detail. It should be noted that the invention is not limited by the following description.

EXAMPLE 1

Preparation of Compound 2, (R,S)-3-(1,3-benzodioxol-5-yl)-1-(1H-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-a]pyrazine-5,8-dione.

Preparation of intermediate compound 4

To a solution of DDQ (228.0g; 1.0mol) in a mixture 1000mL of THF:H₂O (9:1), was added methyl 2-[(tert-butoxycarbonyl)amino]-3-(1H-indol-3-yl)propanoate (80.0g; 0.251mol). The reaction mixture was mixed for 3 hours. Additional aliquots of DDQ were added until all the starting material was consumed (TLC). Afterwards, the reaction mixture was washed with a saturated solution of NaHCO₃ and the product was extracted with methylene chloride. The organic phases were combined and dried with MgSO₄. The solvent partially was removed and to this mixture was added 3g of activated carbon. This mixture was mixed for 30 minutes and, after equilibrating to ambient temperature, was filtered. The solvent was removed by rotoevaporation until dryness. The resulting oil was heat solubilized in acetone (70.0mL). The solution was cooled and placed in ice bath, leading to the precipitation of methyl 2-[(tert-butoxycarbonyl)amino]-3-(1H-indol-3-yl)-3-oxopropanoate, which was filtered and dried in a heater at 60°C.

Preparation of intermediate compound 1

To a suspension of methyl 2-[(*tert*-butoxycarbonyl)amino]-3-(1*H*-indol-3-yl)-3-oxopropanoate (6.23g; 19.0mmol) **4** in 200mL of isopropanol, was added 2.0mL of 36% HCl. The reaction mixture was mixed for 3 hours. Additional aliquots of 36% HCl were added until all the starting material was consumed. After completion of the reaction, the reaction mixture was cooled to ambient temperature. Aliquots of NaHCO₃ were added to neutralize the solution. 3,4-(Methylenedioxy)benzaldehyde (2.86g; 19mmol) was then added to the solution and the resultant reaction mixture was mixed under magnetic agitation for 24 hours, leading to the precipitation of methyl 2-[(*E*)-(1,3-benzodioxol-5-ylmethylidene)amino]-3-(1*H*-indol-3-yl)-3-oxopropanoate, which was filtered and dried in a heater at 60°C.

Methyl 2-[(*E*)-(1,3-benzodioxol-5-ylmethylidene)amino]-3-(1*H*-indol-3-yl)-3-oxopropanoate (5.46g; 15.0mmol) was added to a solution of pyridine (10mL) in 50mL of dry methylene chloride. This suspension was mixed under magnetic agitation with a drying tube of CaCO₃ for 30 minutes. Chloroacetyl chloride (2.3mL; 30.0mmol) was dissolved in 2.5mL of dry methylene chloride. This solution was added drop wise to the reaction mixture, over a period of 30 minutes. After an additional period of 3 hours, 100mL of a saturated aqueous solution of CuSO₄ was added to the reaction mixture. The organic phase was extracted in a separation funnel and isolated. The aqueous phase was washed with 50mL of methylene chloride and organic phase was isolated. The organic phases were combined. This procedure of washing was repeated two more times. The organic phase was washed with a saturated aqueous solution of NaCl. The organic phase was isolated and dried with MgSO₄. The solvent was removed by rotoevaporation, leading

to the isolation of methyl 3-(chloroacetyl)-5-(1*H*-indol-3-yl)-2-phenyl-2,3-dihydro-1,3-oxazole-4-carboxylate 1.

Preparation of compound 2

5 To a solution of methyl 3-(chloroacetyl)-5-(1*H*-indol-3-yl)-2-phenyl-2,3-dihydro-1,3-oxazole-4-carboxylate (5.46g; 12.4mmol) 1 in 100 mL of ethanol, was added 10 mL of an aqueous solution of 40% methylamine. This reaction mixture was mixed under magnetic agitation for 24 hours, leading to the
10 precipitation of (R,S)-3-(1,3-benzodioxol-5-yl)-1-(1*H*-indol-3-yl)-7-methyl-6,7-dihydro[1,3]oxazolo[3,4-*a*]pyrazine-5,8-dione 2. The obtained product presented the following characteristics: M.P. 279-281°C. HRMS (EI): *m/z* cal. for [C₂₂H₁₈N₃O₅] 404,1246; found: 404,1239. IR (KBr): 3322, 1647, 1613, 1467 cm⁻¹. NMR ¹H (300MHz, DMSO-*d*₆): δ = 11.87 (s, 1H); 9.00 (s, 1H); 7.87 (d, 1H, *J* = 9.0 Hz); 7.48 (d, 1H, *J* = 9.0 Hz); 7.14 (m, 5H); 7.00 (d, 1H, *J* = 9.0 Hz); 6.06 (s, 2H); 4.20 (s, 2H); 2.94 (s, 3H). NMR ¹³C (125MHz, DMSO-*d*₆): δ = 158.3; 156.7; 148.2; 147.5; 147.3; 135.7; 130.9; 130.7; 125.1;
15 122.0; 121.2; 120.4; 120.2; 112.0; 108.1; 106.4; 104.7; 102.2;
20 101.3; 90.1; 52.7; 32.2.

EXAMPLE 2

Effect of Compound 2 on Human Corpus Cavernosum and Urether,
25 **and Rabbit Corpus Cavernosum and Pulmonary Artery**

Tissue

Human corpus cavernosum and urether were obtained from discarded tissues from surgeries, which were placed in ice-cold Krebs solution for rapid transport to the laboratory.
30

Male New Zealand White rabbits (2-2.5 kg) were used for penis and pulmonary artery tissues, which were excised and

transferred to ice-cold Kreb's solution. Two strips and four rings were obtained from each corpus cavernosum (CC) and pulmonary artery, respectively.

5 Isometric Tension Recording

Cavernosal strips, pulmonary artery, and urether were mounted in 10 ml organ chambers containing Kreb's solution at 37°C, pH 7.4 continuously bubbled with a mixture of 95% O₂ and 5% CO₂. The tissues were stretched to a resting force of 5 mN and allowed to equilibrate for 60 min. Changes in isometric force were recorded using a PowerLab 4/30 data acquisition system (Chart software, version 7.0; ADInstruments, Colorado Springs, CO). Cumulative concentration-response curves to compound 2 (named BL 106 in Figures 1, 2 and 3) (0.001-10 µM) were obtained in cavernosal strips, pulmonary artery rings, and urether contracted with noradrenaline (NOR 10 µM) (Sigma, St. Louis, MO). Concentration response curves to compound 2 (denoted BL 106 in Figures 1, 2 and 3) were constructed for each sample. For pulmonary artery, concentration response curves to compound 2 were also constructed in the presence or absence of the soluble guanylate cyclase inhibitor 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one (ODQ 10 µM) (Sigma, St. Louis, MO). Control rings (treated with 40 mM DMSO) were also ran in parallel with experimental strips and rings.

25 Relaxation of Human Urether

Noradrenaline caused a sustained contraction in the human urether tissue. Compound 2 (BL 106) (0.0001-1 µM) produced concentration dependent relaxations in urether tissue (pEC50: 30 6.29 and Emax 49 %, n=3) (Figure 1).

Relaxation of Rabbit Pulmonary Artery

Noradrenaline (3 or 10 μM) caused a sustained contraction in the rabbit pulmonary artery (17.4 mN). The compound 2 (BL 106) (0.001-10 μM) produced concentration-dependent relaxations in pulmonary artery rings (pEC50: 6.23 [588 nM] and Emax 62 %, n=3) (Figure 2).

Relaxation of Human Corpus Cavernosum

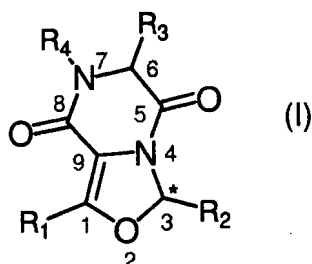
Noradrenaline caused a sustained contraction in the human corpus cavernosum. The compound 2 (BL 106) (0.0001-1 μM) produced concentration-dependent relaxations in corpus cavernosum (pEC50: 7.65 and Emax 71 %, n=3) (Figure 3A).

Relaxation of Rabbit Corpus Cavernosum

Noradrenaline (3 or 10 μM) caused a sustained contraction in rabbit corpus cavernosum (13.8 mN). Compound 2 (BL 106) produced concentration dependent relaxations in corpus cavernosum (pEC50: 5.92 [1.2 μM] and Emax: 91 %, n=3) (Figure 3B).

CLAIMS

1. A compound of formula (I):

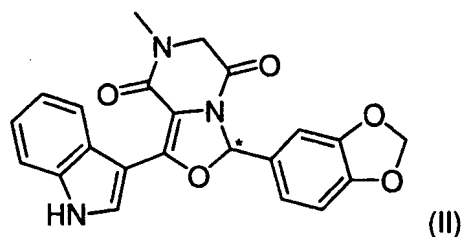


- 5 or salts, solvates, or hydrates thereof; wherein:
- R¹** is an aromatic group, optionally condensed, optionally substituted with **R^B** in one or more positions; a heteroaromatic group containing one or more heteroatoms, optionally substituted with **R^B** or an indol group in one or more positions;
- 10 a C₁₋₆ alkenylcarbonyl, optionally substituted with **R^B** in one or more positions; a bicyclic aromatic, optionally substituted with **R^B** in one or more positions, or a bicyclic heteroaromatic containing one or heteroatoms, optionally substituted with **R^B** in one or more positions;
- 15 **R^B** is a halogen, hydroxyl, nitrogen, cyano, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkylC₁₋₃ alkyl, arylC₁₋₃ alkyl or heteroararylC₁₋₃ alkyl;
- R²** is an aromatic group containing one or heteroatoms, a heteroaromatic containing group containing one or heteroatoms
- 20 or methylene-3,4-dioxyphenyl groups, or a bicyclic aromatic containing one or heteroatoms or methylene-3,4-dioxyphenyl groups;
- R³** is hydrogen, halogen, C₁₋₆ haloalkyl, C₁₋₃ heteroalkyl, or C₁₋₃ alkyl; and
- 25 **R⁴** is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkylC₁₋₃ alkyl, arylC₁₋₃ alkyl or heteroarylC₁₋₃ alkyl,

25

2. The compound of claim 1, or salts or solvates thereof, wherein said compound is represented by formula (II):

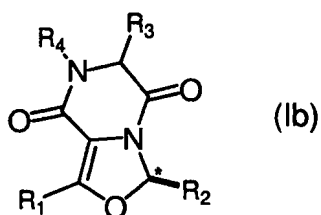
5



3. The compound of claim 2, or salts or solvates thereof, wherein the compound is an (*R*)-isomer.

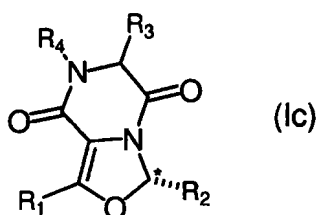
4. The compound of claim 2, or salts or solvates thereof, wherein the compound is an (*S*)-isomer.

5. The compound of claim 1, or salts or solvates thereof, wherein the compound is an (*R*)-isomer and represented by formula (Ib):



20

6. The compound of claim 1, or salts or solvates thereof, wherein the compound is an (*S*)-isomer and represented by formula (Ic):



25

85

85

85



85



85



85



12. A method of inhibiting the enzymes phosphodiesterases in a patient, the method comprising administering the pharmaceutical composition of claim 8 to said patient.

5 13. A method of inhibiting the enzyme phosphodiesterase type 5 in a patient, the method comprising administering the pharmaceutical composition of claim 7 to said patient.

10 14. A method of inhibiting the enzyme phosphodiesterase type 5 in a patient, the method comprising administering the pharmaceutical composition of claim 8 to said patient.

15 15. A method for treatment or prevention of erectile dysfunction in man, the method comprising administering the pharmaceutical composition of claim 7 to said animal.

16. A method for treatment or prevention of erectile dysfunction in man, the method comprising administering the pharmaceutical composition of claim 8 to said animal.

20

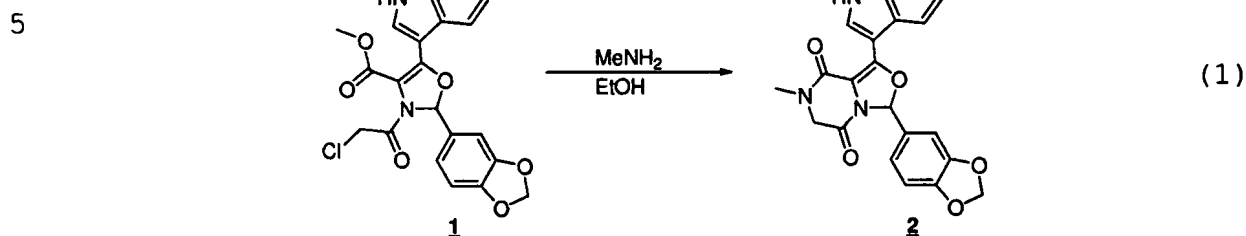
17. A method for treatment or prevention of lithiasis, prostatic hyperplasia, lung hypertension, urether constriction, female sexual dysfunction and/or male sexual dysfunction comprising administering the pharmaceutical composition of claim 7 to said animal.

25

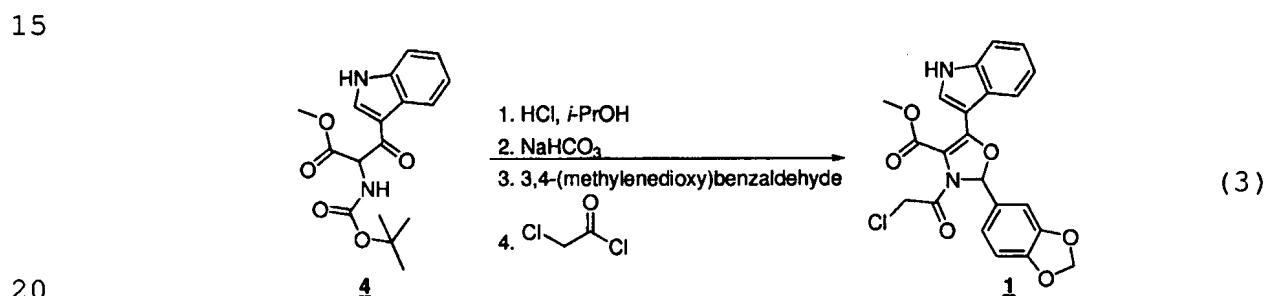
18. A method for treatment or prevention of lithiasis, prostatic hyperplasia, lung hypertension urether constriction, female sexual dysfunction and/or male sexual dysfunction comprising administering the pharmaceutical composition of claim 8 to said animal.

30

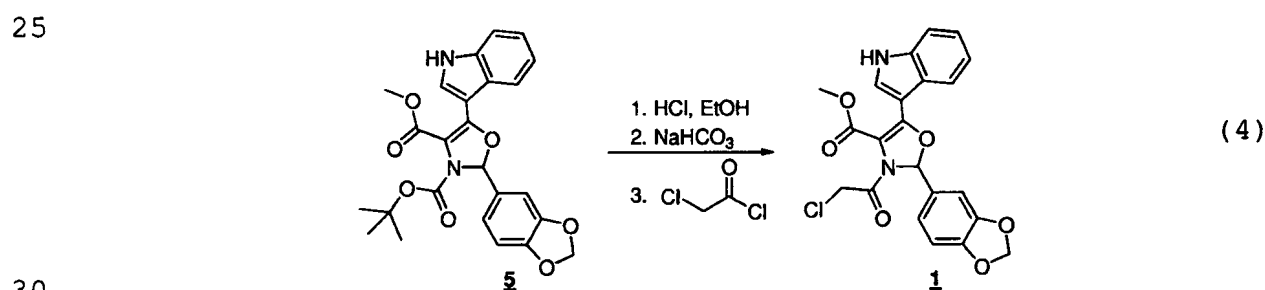
19. A method of preparing the compound of claim 2, the method comprising preparing compound **2** from compound **1**, optionally using methylamine and ethanol.



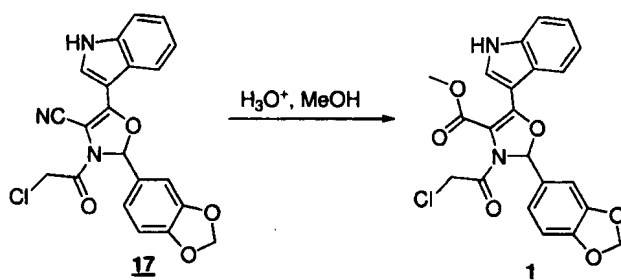
20. The method of claim 19, the method further comprising preparing compound **1** from compound **4**, optionally using acid in isopropanol, sodium bicarbonate, 3,4-(methylenedioxy)benzaldehyde, and chloroacetyl chloride.



21. The method of claim 20, the method further comprising preparing compound **1** from compound **5**, optionally using acid in ethanol, sodium bicarbonate and chloroacetyl chloride.

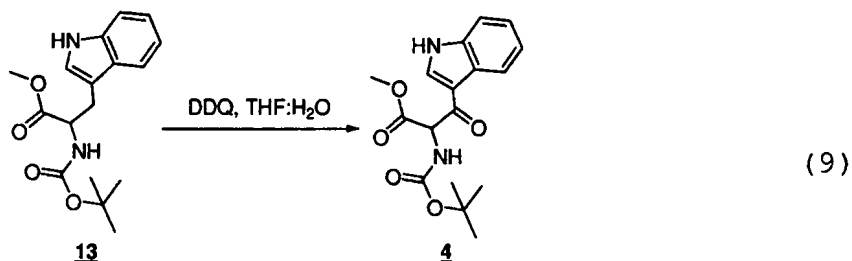


22. The method of claim 21, the method further comprising preparing compound **1** from compound **17**, optionally using methanol and hydronium ion.



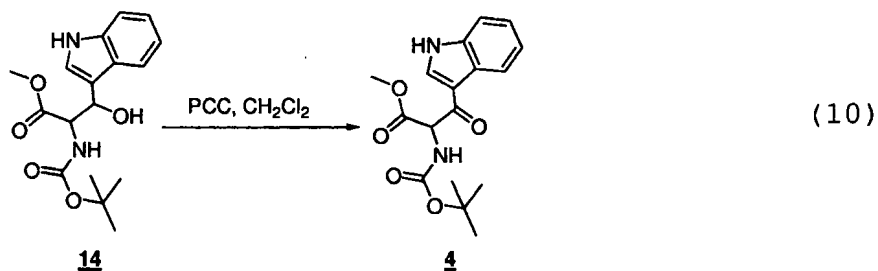
10

23. The method of claim 20, the method further comprising preparing compound **4** from compound **13**, optionally using (2,3)-dichloro-5,6-dicyano-1,4-benzoquinone and a tetrahydrofuran:water mixture.



20

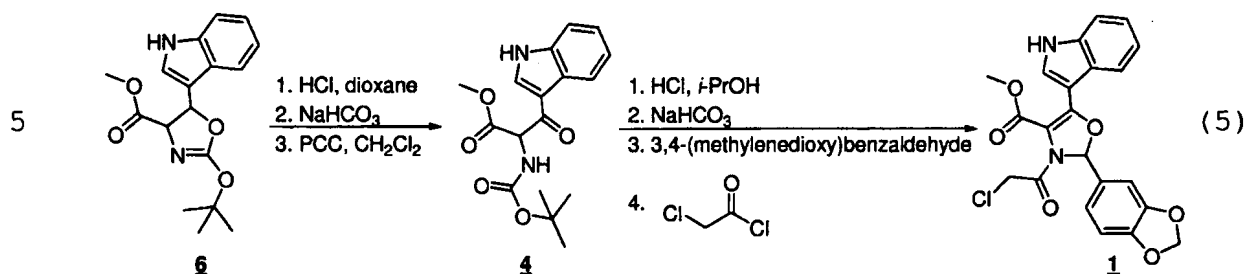
24. The method of claim 20, the method further comprising preparing compound **4** from compound **14**, optionally using pyridine chlorochromate (PCC) and methylene chloride.



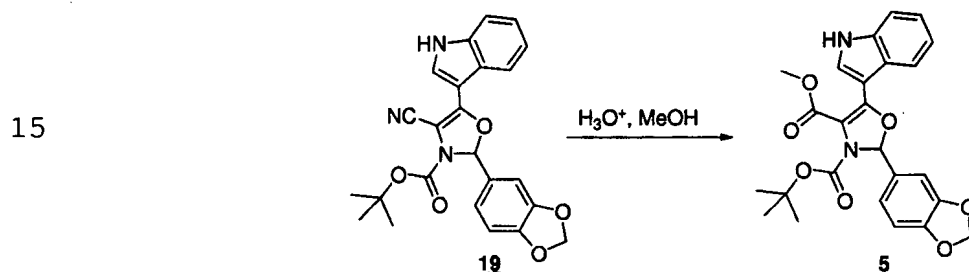
30

25. The method of claim 19, the method further comprising preparing compound **4** from compound **6**, optionally using acid in

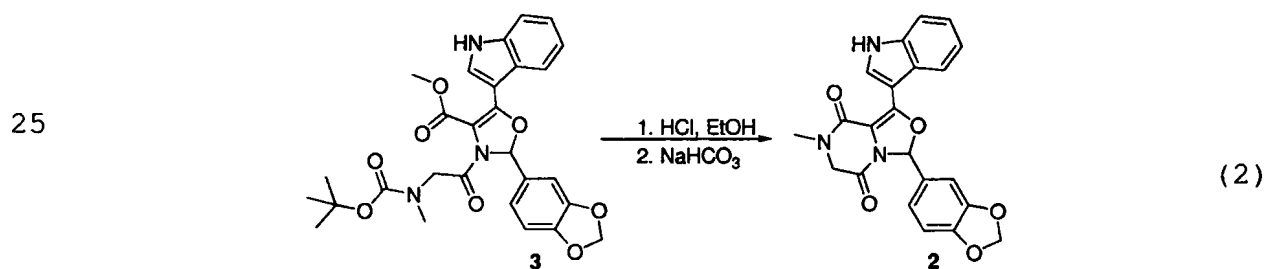
dioxane, sodium bicarbonate, pyridine chlorochromate (PCC), and methylene chloride.



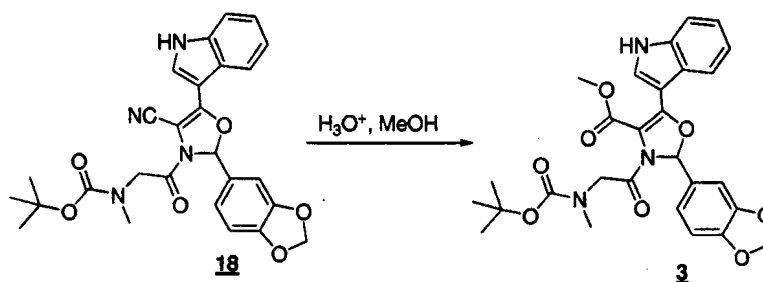
- 10 26. The method of claim 21, the method further comprising preparing compound 5 from compound 19, optionally using methanol and hydronium ion.



- 20 27. A method of preparing the compound of claim 2, the method comprising preparing compound 2 from compound 3, optionally using acid in ethanol and sodium bicarbonate.



28. The method of claim 27, the method further comprising preparing compound **3** from compound **18**, optionally using methanol and hydronium ion.



1/2

FIG. 1

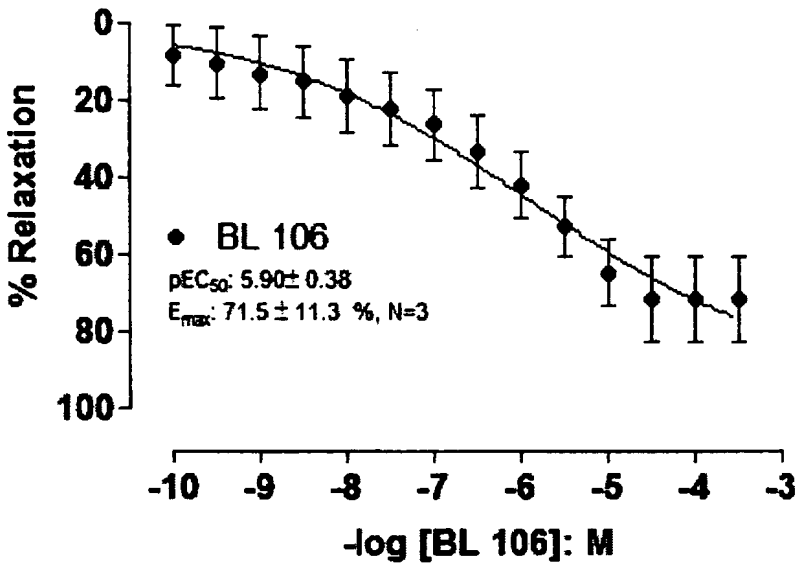
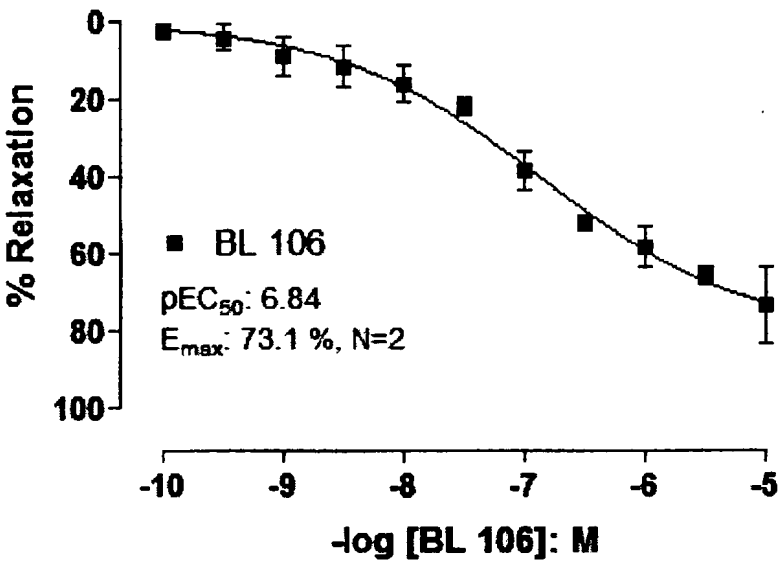
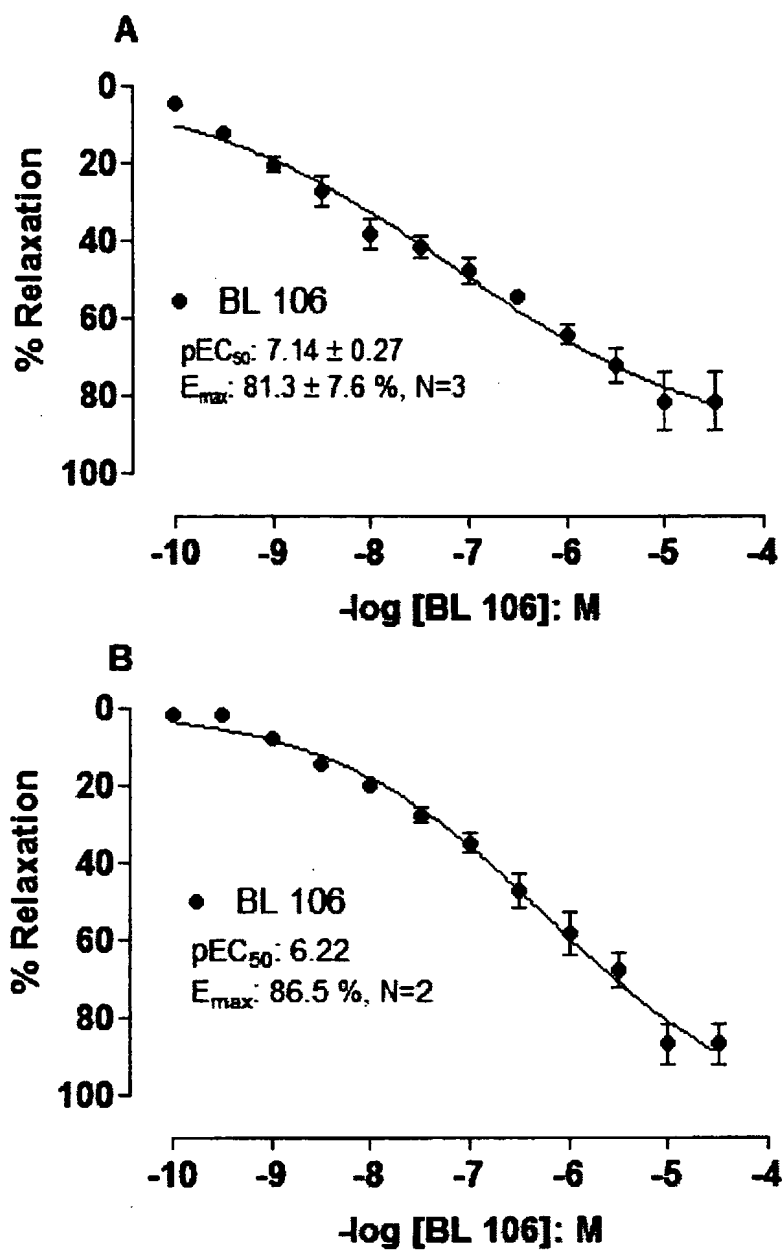


FIG. 2



2/2

FIG. 3



INTERNATIONAL SEARCH REPORT

International application N°
PCT/BR2011/000255

A. CLASSIFICATION OF SUBJECT MATTER
C07D498/04 (2006.01), A61K 31/48 (2006.01), A61P 15/00 (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D: A61K: A61P
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
INPI/BR
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPODOC: Derwent Chemistry Resource: IMS R&D Focus: IMS Patente Focus: Index Chemicus: Drug Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claims N°
A	WO 9703675 A1 (DAUGAN ALAIN CLAUDE MARIE [FR]) 06 February 1997 (1997-02-06) the whole document	1-10 and 19-28
A	WO 02098877 A1 (CHULTZE LISA M [US]) 12 December 2002 (2002-12-12) the whole document	1-10 and 19-28
A	WO 03000691 A1 (GOSMINI ROMAIN LUC MARIE [FR]) 03 January 2003 (2003-01-03) the whole document;	1-10 and 19-28
P, A	BR 09038032 (BIOLAB SANUS FARMACÊUTICA LTDA [BR]) 07 June 2011(2011-06-07) the whole document;	1-10 and 19-28

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 23 September 2011	Date of mailing of the international search report 18 10 11
Name and mailing address of the ISA/BR INPI INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL Rua Marink Veiga nº 9, 18º andar Facsimile N°: +55 21 3037-3663	Authorized officer Jaqueline Mendes Soares Telephone N°: +55 21 3037-3493/3742

INTERNATIONAL SEARCH REPORT

International application N°

PCT/BR2011/000255

Box No II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 11 to 18 refer to a subject that the current Administration considers being addressed by PCT Rule 39.1 (iv), that covers methods for treatment of the human or animal body by surgery or therapy; diagnostic methods practiced on the human or animal body (PCT Article 17.2(a)(i)).

2. ☐ Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application N°

PCT/BR2011/000255

Patent documents cited in search report	Publication date	Patent family members	Publication date
WO 9703675 A1	1997-02-06	AP 9500712 D0	1995-01-31
		AP 556 A	1996-11-07
		AT 169018 T	1998-08-15
		AT 216997 T	2002-05-15
		AT 327756 T	2006-06-15
		AU 1574895 A	1995-08-08
		AU 689205 B2	1998-03-26
		AU 702324 B2	1999-02-18
		AU 704955 B2	1999-05-13
		AU 7391298 A	1998-08-20
		AU 707055 B2	1999-07-01
		AU 5785699 A	2000-04-03
		AU 6419196 A	1997-02-18
		AU 6419296 A	1997-02-18
		BG 100727 A	1997-02-28
		BG 62733 B1	2000-06-30
		BR 9506559 A	1997-10-28
		BR 9609758 A	1999-01-26
		BR 9609780 A	1999-03-09
		BR 9913824 A	2001-06-19
		CA 2181377 A1	1995-07-27
		CA 2226761 A1	1997-02-06
		CA 2226784 A1	1997-02-06
		CA 2340636 A1	2000-03-23
		CN 1143963 A	1997-02-26
		CN 1045777 C	1999-10-20
		CN 1195349 A	1998-10-07
		CN 1069318 C	2001-08-08
		CN 1224720 A	1999-08-04
		CN 1070492 C	2001-09-05
		CN 1195290 A	1998-10-07
		CN 1112928 C	2003-07-02
		CN 1513452 A	2004-07-21
		CN 1311828 C	2007-04-25
		CO 4340684 A1	1996-07-30
		CO 4700455 A1	1998-12-29
		CY 2563 B1	2008-07-02
		CZ 9602116 A3	1997-06-11
		CZ 286566 B6	2000-05-17
		CZ 9800033 A3	1998-05-13
		CZ 289686 B6	2002-03-13
		CZ 289832 B6	2002-04-17
		CZ 9800032 A3	1998-06-17
		DE 10399006 I1	2003-07-31
		DE 69503753 D1	1998-09-03
		DE 69621026 D1	2002-06-06
		DE 69636193 D1	2006-07-06
		DK 740668 T3	1999-05-03
		DK 0839040 T3	2006-09-25
		EE 03231 B1	1999-10-15
		EP 0740668 A1	1996-11-06
		EP 0839040 A1	1998-05-06
		EP 0846118 A1	1998-06-10

INTERNATIONAL SEARCH REPORT
 Information on patent family members

International application N°

PCT/BR2011/000255

Patent documents cited in search report	Publication date	Patent family members	Publication date
		EP 1113800 A1	2001-07-11
		EP 2036560 A1	2009-03-18
		EP 2327408 A1	2011-06-01
		ES 2122543 T3	1998-12-16
		ES 2176471 T3	2002-12-01
		ES 2267111 T3	2007-03-01
		FI 962927 A	1996-07-19
		FI 113176 B1	2004-03-15
		GB 9401090 D0	1994-03-16
		GB 9514464 D0	1995-09-13
		GB 9514465 D0	1995-09-13
		GB 9514474 D0	1995-09-27
		HK 1005363 A1	2006-12-01
		HK 1013286 A1	2000-05-19
		HR 950023 A2	1998-04-30
		HR 960321 A2	1998-08-31
		HU 9601982 D0	1996-09-30
		HU T74943 A	1997-03-28
		HU 222494 B1	2003-07-28
		HU 9900006 A2	1999-04-28
		HU 9900065 A2	1999-05-28
		IL 112384 D0	1995-03-30
		IL 122870 D0	1998-08-16
		IL 122923 D0	1998-08-16
		IL 127776 D0	1999-10-28
		IN 183942 A1	2000-05-20
		IS 4252 A	1995-07-22
		IS 1888 B	2003-09-01
		JP 9508113 T	1997-08-19
		JP 3808095 B2	2006-08-09
		JP 4150818 B2	2008-09-17
		JP 11509221 T	1999-08-17
		JP 4169365 B2	2008-10-22
		JP 2004217674 A	2004-08-05
		JP 4347125 B2	2009-10-21
		JP 11509535 T	1999-08-24
		JP 2002524516 A	2002-08-06
		JP 2009102386 A	2009-05-14
		LU 91017 A9	2003-05-26
		LV 11690 A	1997-02-20
		MA 23433 A1	1995-10-01
		MX 9602904 A	1997-12-31
		MX 9800411 A	1998-04-30
		MX 9800414 A	1998-06-28
		MX PA02009987 A	2003-02-28
		NL 300124 I1	2003-07-01
		NO 963015 D0	1996-07-19
		NO 306465 B1	1999-11-08
		NO 980153 D0	1998-01-13
		NO 314685 B1	2003-05-05
		NO 980154 D0	1998-01-13
		NO 2003002 I2	2005-03-21
		NZ 279199 A	1998-01-26
		OA 10584 A	2002-08-26

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application N°
PCT/BR2011/000255

Patent documents cited in search report	Publication date	Patent family members	Publication date
		PL 315559 A1	1996-11-12
		PL 179744 B1	2000-10-31
		PL 324495 A1	1998-05-25
		PL 185737 B1	2003-07-31
		PL 185999 B1	2003-09-30
		PL 324527 A1	1998-06-08
		PT 839040 E	2006-09-29
		RO 117794 B1	2002-07-30
		RU 2142463 C1	1999-12-10
		RU 2181288 C2	2002-04-20
		SG 49184 A1	1998-05-18
		SI 0740668 T1	1999-02-28
		SI 0839040 T1	2006-10-31
		SK 3898 A3	1998-11-04
		SK 3998 A3	1998-07-08
		SK 284141 B6	2004-10-05
		SK 94096 A3	1997-04-09
		SK 280879 B6	2000-08-14
		SK 284494 B6	2005-05-05
		SV 1995000002 A	1995-10-04
		TW 378210 B	2000-01-01
		US 5859006 A	1999-01-12
		US 5981527 A	1999-11-09
		US 6025494 A	2000-02-15
		US 6127542 A	2000-10-03
		US 6140329 A	2000-10-31
		US 6143746 A	2000-11-07
		US 6369059 B1	2002-04-09
		US 6608065 B1	2003-08-19
		US 2002119976 A1	2002-08-29
		US 6784179 B2	2004-08-31
		WO 0015228 A1	2000-03-23
		WO 9519978 A1	1995-07-27
		WO 9703985 A1	1997-02-06
		ZA 9500424 A	1995-09-27
		ZA 9605934 A	1997-02-03
WO 02098877 A1	2002-12-12	AT 397606 T	2008-06-15
		CA 2445625 A1	2002-12-12
		DE 60226970 D1	2008-07-17
		EP 1392688 A1	2004-03-03
		ES 2307758 T3	2008-12-01
		JP 2004532889 A	2004-10-28
		JP 4217605 B2	2009-02-04
		MX PA03011082 A	2004-07-08
		US 2004152705 A1	2004-08-05
		US 7098209 B2	2006-08-29
WO 03000691 A1	2003-01-03	AT 335742 T	2006-09-15
		CA 2445189 A1	2003-01-03
		DE 60213798 D1	2006-09-21
		EP 1397361 A1	2004-03-17
		ES 2269679 T3	2007-04-01
		JP 2005500316 A	2005-01-06

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application N°
PCT/BR2011/000255

Patent documents cited in search report	Publication date	Patent family members	Publication date
		JP 4339679 B2	2009-10-07
		MX PA03011167 A	2004-02-26
		US 2004171830 A1	2004-09-02
		US 6984641 B2	2006-01-10
BR 09038032	--	None	



No. 13-046988-00000-0000

Fecha: 2013-03-08 15:49:25 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 99

PATENTE DE INVENCION ☐

MODELO DE UT

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

PATENTE DE INVENCION PCT ☒

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

☒	Indicación que se solicita una PCT
☒	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☒	Dibujos de ser estos pertinentes
☒	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☒	Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐	Indicación que se solicita Diseño industrial
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐