

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

Servicios Legales y Profesionales

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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E.

S.

801
SUPERINTENDENCIA Y COMERCIO
Radicación : 02084184 00000002 Folios: 5
Fecha (AMB): 2004-01-29 08:53:02
Tramite : 011 PCT-PATENT 33 FASE NNCI 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref: Expediente No. 02.084.184

Solicitud de patente de invención titulada:

"COMPPUESTOS QUE CONTIENEN BENZAMIDO-
PIPERIDINA Y COMPUESTOS RELACIONADOS".

Solicitante: PFIZER PRODUCTS INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTICULO 44 DE LA DECISION 486, GACETA No. 533

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, según consta en el nuevo poder adjunto, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$177.000 pesos para cubrir la tasa correspondiente, según la Resolución 37323 del año 2003.

Aprovecho la presente oportunidad para poner en conocimiento del Despacho mi cambio de oficinas, por lo que de ahora en adelante, recibiré notificaciones en la Calle 100 No. 8A-55 Torre C, Piso 10, World Trade Center, o en la secretaría de ese Despacho.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$177.000 pesos

Poder

FTT77202/000021 040109

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**
Ante el Notario Once del Circulo de Santa Fe de Bogotá, compareció [Firma]
Quien exhibió la C.C. No. 1429
expedida en Bo y declaró que la firma y huella que aparecen en el presente memorial son suyas y que al contrario del mismo es cierto.
Memorial dirigido a _____
Santa Fe de Bogotá, D.C. **19 ENE 2004**
Firma del Notario [Firma] **HUELLA**
Autorizó la anterior Diligencia
NOTARIO ONCE DEL CIRCULO DE SANTA FE DE BOGOTA

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTA FE DE BOGOTA, D.C.
MORICA ZI BAUTISTA N
OTARIA ONCE(E)

813-212
802

HIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 02084184 00000002 Folios: 5
Fecha (AMB): 2004-01-29 00:53:02
Tramite : 011 PCT-PATENT 379 FASE NINCI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 6,399
FECHA : ENERO 28 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	13594216	27/01/2004	2,894,000.00

***** CONCEPTO *****

CANT. CONTABILITICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	177,000.00
	TOTAL :	177,000.00

SON: CIENTO SETENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

8/5 3/3

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER PRODUCTS INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb ejercía funciones de Vicepresidente de la Compañía Pfizer Products Inc., con sede en Groton, Connecticut, Estados Unidos.

Firma del notario

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

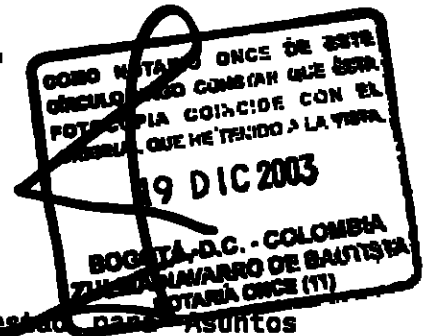
1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210435
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia para confrontación. Bogotá 25 de julio-2003.



Archivo para
Marlén Neira C.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

OLARTE RAISBECK

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Power of Attorney

The undersigned,

domiciled in

Eastern Point Road, Groton, Connecticut 06340 USA

by means of these presents hereby grants to Carlos R. Olarte, J. Ian Ralsbeck and Ana María Frieri full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

El suscrito,

Pfizer Products Inc.

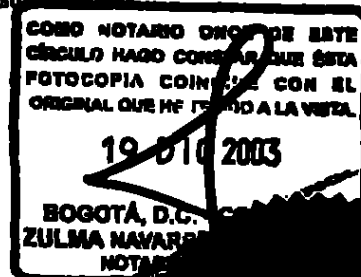
domiciliado en

por medio del presente otorga a Carlos R. Olarte, J. Ian Ralsbeck y Ana María Frieri poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha: July 14, 2003

City/Country/Ciudad,País: New York, USA



OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
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FAX: +57-1 638-6201

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Notarial Certification

Certificación Notarial

On this date,
July 14, 2003

The undersigned Notary Public certifies:

1. That *J. Trevor Lumb*
of legal age and domiciled in
NEW YORK, USA
signed the foregoing document.

2. That the grantor has executed the foregoing
document as Vice President
of Pfizer Products Inc.

3. That Pfizer Products Inc.,
having its principal place of business located in
Groton, Connecticut, U.S.A.
is duly incorporated, is currently in existence, and
that the purposes for which the Power of Attorney is
granted are within the scope of its corporate
purposes.

4. That the grantor has the authority to execute the
Power of Attorney and that his/her representation is
legal.

5. The foundation for my certifications contained in
points 2, 3 and 4 was the exhibition of the following
authentic document(s):

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido
documento en su carácter de
de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia
legal vigente y que los propósitos para los cuales
se otorga el poder se encuentra dentro de los que
comprenden su objeto social.

4. Que el otorgante tiene la representación para
suscribir el poder, y que ésta es legítima.

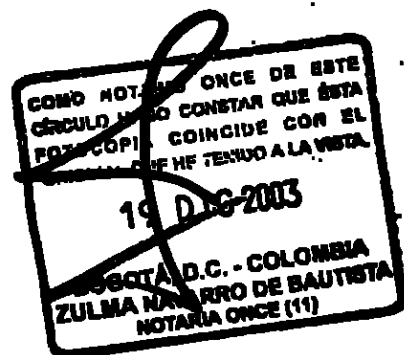
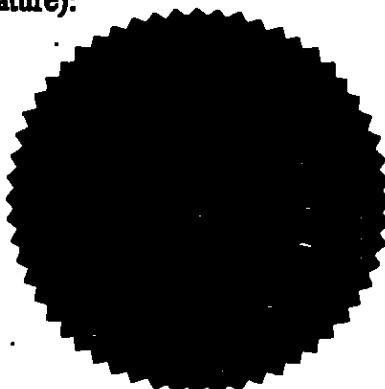
5. El fundamento de mis certificaciones
contenidas en los puntos 2, 3 y 4 fue la exhibición
de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey

This *14* Day Of *July*
2003

KENNETH GREENWOOD
NOTARY PUBLIC
HOMER ENGALL AND FRIEMAN



APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

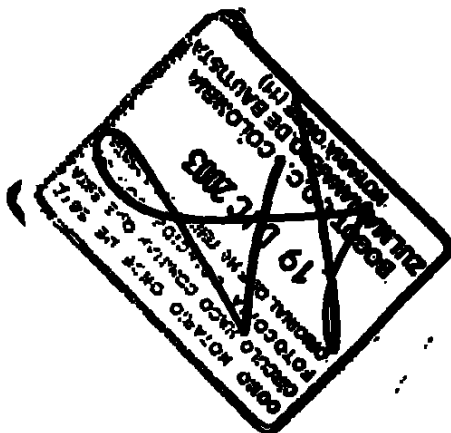
1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public
2. Has been signed by K Groszwood
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de
5. at London/A Londres
6. the/le 17 July 2003
Certified/Attesté
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth
8. Number/ous No **G210435**
9. Stamp:
timbre:
10. Signature: R. Bawden



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.



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

2020

Bogotá, D.C., 31 de octubre de 2006

Apoderado: Carlos Reinaldo Olarte

Oficio:
13607

ASUNTO

Radicación: 02-84184

Trámite 002

Evento 001

Actuación 430

Folios

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

Documentos estudiados:

- ◆Capítulo descriptivo, follos 230 a 423;
- ◆Capítulo reivindicatorio, follos 424 a 451;
- ◆Solicitud de la cual se reivindica prioridad 19 a 228, 473 a 900 ;
- ◆ Solicitud del examen de patentabilidad, follos 813 y 814.

Objeto de la Invención:

El título de la Invención "COMPUESTOS QUE CONTIENEN BENZAMIDO-PIPERIDINA Y COMPUESTOS RELACIONADOS".

El objeto de la solicitud se refiere a compuestos que al parecer una de su característica básica son dos subestructuras N-heterocíclicas no fijas, las cuales están ligadas por un puente que puede ser cíclico o no cíclico, o sea no tiene ninguna porción fija.

El campo de la invención, según la Clasificación Internacional de Patentes: C07D 401/00; A61K31/5395

Claridad de la solicitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: "Las reivindicaciones definirán la materia que se desea proteger mediante

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la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción".

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Las reivindicaciones 70 a 75 no son claras, puesto que es una mezcla de composición farmacéutica y método terapéutico. Por un lado el encabezado se refiere a una composición farmacéutica y el resto del texto a un método terapéutico, del otro lado todas estas reivindicaciones reclaman exactamente la "misma materia", por lo tanto son redundantes.

-Las reivindicaciones 19, 20, 24 y 25 no son claras, pues es una mezcla de composición farmacéutica y método terapéutico. El encabezado se refiere a una composición farmacéutica y el resto del texto a un método terapéutico. Además todas estas reivindicaciones reclaman exactamente la "misma materia", por lo tanto son redundantes y cargadas de texto no técnico, y que además no aportan características técnicas especiales o particulares.

-La reivindicación 76, no esta definida porque no presenta ninguna porción de molécula fija, pero si un número extremadamente grande de posibles compuestos, sin estar soportados enteramente en la descripción, solo se encuentra un pequeño grupo de compuestos soportados, que caen dentro de esa formula (II).

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: ***"los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"***.

Las reivindicaciones 64 a 69 se solicita proteger: un método de tratamiento terapéutico, el método consiste en la administración a dicho paciente de una composición que contiene algún compuesto de la presente solicitud.

Por lo tanto, se indica que tales reivindicaciones, se encuentran dentro de las excepciones a la patentabilidad, del artículo 20 de la Decisión 486.

Evaluación de la Unidad de Invención:

Esta solicitud de patente comprende solamente una invención o un grupo de invenciones relacionadas entre sí, de manera que se integra un único concepto inventivo conforme al artículo 25 de la Decisión 486 de la Comisión de la Comunidad Andina.

Para el presente caso existen los siguientes grupos de invenciones:

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- i) Los compuestos de fórmulas I y II en las cuales Q es C=NH;
- ii) Los compuestos de fórmulas I y II en las cuales Q es C=CH₂
- iii) Los compuestos de fórmulas I y II en las cuales Q se selecciona de C=S, C=O, Y y Z son carbono;
- iv) Los compuestos de fórmulas I y II en las cuales Q se selecciona de C=S, C=O; con Y y Z que se seleccionan de NH y C no siendo ambos iguales,
- v) Los compuestos de fórmulas I y II en las cuales Q es SO, o SO₂;
- vi) Los compuestos de fórmula T-NH₂.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizó la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la presente solicitud 2003-01-22. Consultada la fuente de información con que cuenta este despacho se encontró muchos documentos solo se adjuntaron algunos:

No.	Documento No.	Título	Fecha de Publicación
D1	WO9703066	Substituted Benzolactam compounds as sunstance P antagonists	30-ene-1997

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D2	US3539584	5-Substituted-2,1-benzisothiazolines	10-nov-1970
D3	US5604252	Azanorbomane derivatives	18-feb-1997
D4	WO9206079	Fused ring analogs of nitrogen containing nonaromatic Heterocycles	16-abr-1992
D5	WO9958500	Method stereochemycally controled production of isomerically pure highly substituted azacyclic compounds	18-nov-1999
D6	EP0122494	Triazine derivatives, processes for preparation thereof and pharmaceutical composition the same	24-oct-1984

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: ***"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."***

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

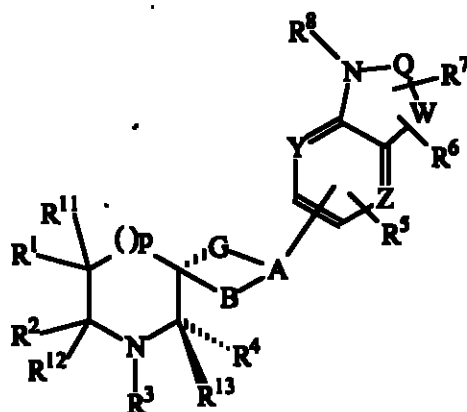
Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: ***"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica." "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."***

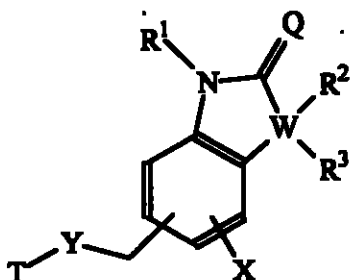
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha

de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Las reivindicaciones de la presente solicitud reclaman como nuevo los compuestos que caen bajo el alcance de la formula Marckush (I):



-Los documentos que se citaron como D1 compuestos de fórmula (I),



métodos de síntesis y composiciones que los comprenden, caen dentro de los compuestos reclamados con la fórmula Marckush (I) de la solicitud en estudio, especialmente cuando miramos los ejemplos y las reivindicaciones de esta anterioridad, donde están definidos compuestos específicos, que son reclamados como nuevos en la presente solicitud, mediante una formula que no tiene ninguna porción fija.

-Las anterioridades D2 y D6 comprenden derivados de anillos nitrogenados que son

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reclamados como nuevos en la presente solicitud en la reivindicación 76.

-Las anterioridades D3, D4 y D5, describen compuestos con anillos nitrógeno fusionados que son reclamados por la solicitud en estudio mediante la reivindicación 78.

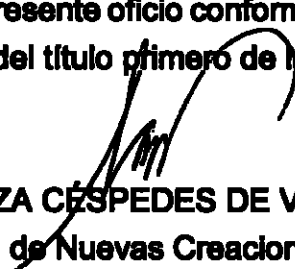
Cuando una solicitud esta afectada su novedad, obviamente no posee nivel inventivo.

En conclusión los requisitos de Patentabilidad de la presente solicitud están afectadas así:

Documento	Reivindicaciones	Requisito que afecta
D1	1 a 77	Novedad
D2	76 -77	Novedad
D3	78	Novedad
D4	78	Novedad
D5	78	Novedad
D6	76-77	Novedad

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2,literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
24 NOV. 2008

CONCEPTO TÉCNICO No. 1770	EXAMINADOR TÉCNICO Código No.202012
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D1

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PCT

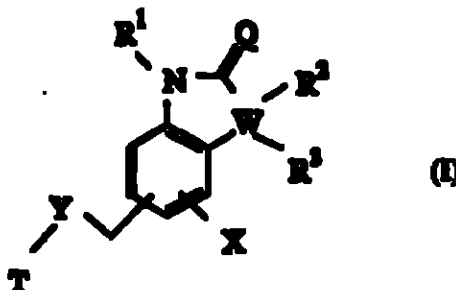
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(31) International Patent Classification 6 : C07D 401/12, A61K 31/40, 31/47, C07D 471/08, 453/02, 265/18, 265/28, 279/08, 279/10	A1	(11) International Publication Number: WO 97/03066 (43) International Publication Date: 30 January 1997 (30.01.97)
(21) International Application Number: PCT/IB96/00434 (22) International Filing Date: 9 May 1996 (09.05.96) (30) Priority Data: PCT/JP95/01359 7 July 1995 (07.07.95) WO (34) Country for which the regional or international application was filed: JP (71) Applicant (for JP only): PFIZER PHARMACEUTICALS INC. [JP/JP]; Mitsui Building, 1-1, Nishi-shinjuku 2-chome, Shinjuku-ku, Tokyo 163 (JP). (71) Applicant (for AT BE CA CH DE DK ES FI FR GB GR IE IT LU MC MX NL PT SE only): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): WAKABAYASHI, Hiroaki [JP/JP]; 3-1, Sumiyoshi-cho, Kariya-shi, Aichi-ken 448 (JP). IKUNAKA, Masaya [JP/JP]; 1-1-2, Sakuragoken, Taketoyo-cho, Chita-gun, Aichi-ken 470-23 (JP). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).	(81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.	

(54) Title: SUBSTITUTED BENZOLACTAM COMPOUNDS AS SUBSTANCE P ANTAGONISTS**(57) Abstract**

This invention provides a compound of general formula (I) and its pharmaceutically acceptable salts, wherein: W is methylene, ethylene, propylene, vinylene, -CH₂-O-, -O-CH₂-, -CH₂-S- or -S-CH₂-; R¹, R² and R³ are independently hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy or halo C₁-C₃ alkyl, provided that when W is methylene, both R² and R³ are not hydrogen; X is halo, C₁-C₃ alkoxy, C₁-C₃ alkyl, halo C₁-C₃ alkoxy or C₁-C₃ alkanyl; Y is imino or oxy; Q is oxygen or sulfur; and T is (2S,3S)-2-diphenylmethylquinolidin-3-yl, (2S,3S)-2-phenylpiperidin-3-yl or (2S,3S)-2-diphenylmethyl-1-azabornan-3-yl. These compounds are useful in the treatment of treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases, emesis, urinary incontinence, pain, migraine, angiogenesis or the like in a mammalian subject, especially humans. Also, intermediates of the above compounds are disclosed.

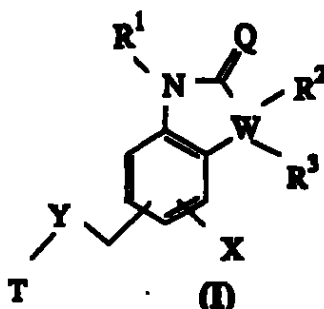


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binding affinity).

Brief Description of the Invention

The present invention provides substituted benzolactam and cyclichioamide compounds of the following chemical formula (I):



and its pharmaceutically acceptable salts, wherein

W is methylene, ethylene, propylene, vinylene, $-\text{CH}_2\text{-O}-$, $-\text{O-CH}_2-$, $-\text{CH}_2\text{-S-}$ or $-\text{S-CH}_2-$;

R^1 , R^2 and R^3 are independently hydrogen, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ alkoxy or halo $\text{C}_1\text{-C}_3$ alkyl, provided that when W is methylene, both R^2 and R^3 are not hydrogen;

X is halo, $\text{C}_1\text{-C}_3$ alkoxy, $\text{C}_1\text{-C}_3$ alkyl, halo $\text{C}_1\text{-C}_3$ alkoxy or $\text{C}_1\text{-C}_3$ alkenyl;

Y is imino or oxy;

Q is oxygen or sulfur; and

T is (2*S*,3*S*)-2-diphenylmethylquinuclidin-3-yl, (2*S*,3*S*)-2-phenylpiperidin-3-yl or (2*S*,3*S*)-2-diphenylmethyl-1-azanobornan-3-yl.

Also, this invention includes an intermediate compound useful for preparation of the compounds of formula (I), which is (2*S*,3*S*)-3-amino-1-(*tert*-butoxycarbonyl)-2-phenylpiperidine.

The compounds of the present invention of formula (I) exhibit good antagonist activity toward Substance P, particularly good activity against CNS disorders with decreased side effects (e.g., Ca^{2+} channel affinity), and are thus useful for treatment of a gastrointestinal disorder, a central nervous system disorder, an inflammatory disease, emesis, urinary incontinence, pain, migraine or angiogenesis in a mammalian subject, especially human.

Accordingly, the present invention provides a pharmaceutical composition for the treatment of a gastrointestinal disorder, a central nervous system disorder, an

inflammatory disease, emesis, urinary incontinence, pain, migraine or angiogenesis in a mammalian subject, which comprises a therapeutically effective amount of a compound of the formula (I) together with a pharmaceutically acceptable carrier.

Detailed Description of the Invention

5 In this specification,

the term "halo C₁-C₃ alkyl" is used herein to mean a C₁-C₃ alkyl radical substituted with one or more halogens (e.g., Cl, F, I or Br) including, but not limited to, chloromethyl, trifluoromethyl, 2,2,2-trichloroethyl and the like; and

the term "halo C₁-C₃ alkoxy" is used herein to mean a C₁-C₃ alkoxy radical
10 substituted with one or more halogens (e.g., Cl, F, I or Br) including, but not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy and the like.

A preferred group of compounds of this invention includes the compounds of formula (I) wherein R¹, R² and R³ are independently hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy or halo C₁-C₃ alkyl, provided that when W is methylene, both R² and R³ are
15 not hydrogen; X is C₁-C₃ alkoxy or halo C₁-C₃ alkoxy; Y is imino; and T is (2S,3S)-2-diphenylmethylquinuclidin-3-yl or (2S,3S)-2-phenylpiperidin-3-yl.

A particularly preferred group of compounds of the invention includes the compounds of formula (I), wherein R¹ is methyl, isopropyl, methoxy or 2,2,2-trifluoroethyl; R² and R³ are independently hydrogen, methyl or trifluoromethyl,
20 provided that when W is methylene, both R² and R³ are not hydrogen; and X is methoxy, isopropoxy, difluoromethoxy or trifluoromethylmethoxy. When W is methylene, T-Y-CH₂- and X are preferably at 5- or 6-position on the benzolactam ring. When W is ethylene or vinylene, T-Y-CH₂- and X are preferably at 6- or 7- position on the benzolactam ring. When W is -CH₂-O-, -O-CH₂-, -CH₂-S- or -S-CH₂-, X and
25 T-Y-CH₂- are preferably at 6- or 7- position on the benzoxadine and benzothiadine ring. When W is propylene, X and T-Y-CH₂- are preferably 7- or 8- position on the benzazepin ring, respectively.

Preferred individual compounds of this invention are the following:

(2S,3S)-3-(6-methoxy-1,3,3-trimethyloxindol-5-yl)methylamino-2-
30 phenylpiperidine or its salts;

(2S,3S)-3-(6-methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylamino-2-phenylpiperidine or its salts;

(2*S*,3*S*)-3-(6-isopropoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylamino-2-phenylpiperidine or its salts;

(2*S*,3*S*)-3-(1-isopropyl-6-methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylamino-2-phenylpiperidine or its salts;

5 (2*S*,3*S*)-3-[(6-methoxy-1-methyl-2-thioxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino-2-phenylpiperidine dihydrochloride or its salts;

(2*S*,3*S*)-3-[(7-methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino-2-phenylpiperidine dihydrochloride or its salts; and

(2*S*,3*S*)-3-[(6-methoxy-1-methyl-2-oxo-4*H*-3,1-benzothiazin-7-yl)methyl]amino-
10 2-phenylpiperidine dihydrochloride or its salts.

Particularly preferred individual compounds of this invention are the following:

(2*S*,3*S*)-2-diphenylmethyl-3-(6-methoxy-1,3,3-trimethyloxindol-5-yl)methylamino-1-azabicyclo[2.2.2]octane or its salts;

(2*S*,3*S*)-2-diphenylmethyl-3-(6-methoxy-1-methyl-2-oxo-1,2,3,4-
15 tetrahydroquinolin-7-yl)methylamino-1-azabicyclo[2.2.2]octane or its salts;

(2*S*,3*S*)-2-diphenylmethyl-3-(6-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-7-yl)methylamino-1-azabicyclo[2.2.2]octane or its salts;

(2*S*,3*S*)-3-[(6-methoxy-1-methyl-2-thioxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino-2-phenylpiperidine dihydrochloride or its salts; and

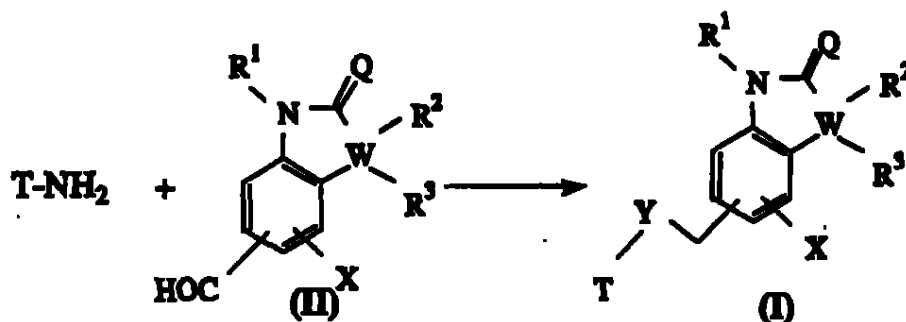
20 (2*S*,3*S*)-3-[(6-methoxy-1-methyl-2-oxo-4*H*-3,1-benzothiazin-7-yl)methyl]amino-2-phenylpiperidine dihydrochloride or its salts.

General Synthesis

The compounds of the formula (I) of this invention may be prepared as described in the following reaction schemes.

25 Unless otherwise indicated, in the reaction schemes that follow, R¹, R², R³, X, Y, Z, W, Q and T are defined as above.

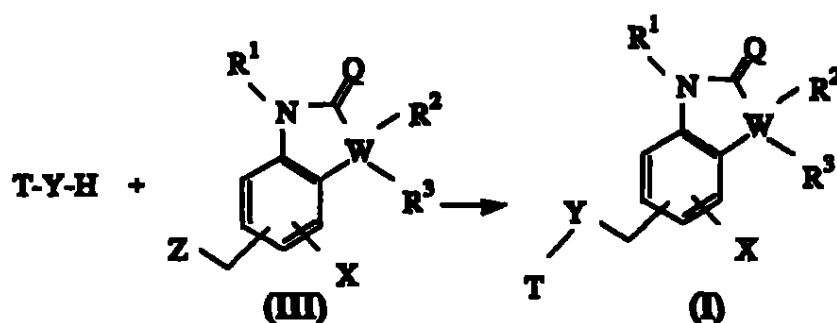
Scheme A-I



Scheme A-I illustrates a method for preparing compounds of the formula (I) by reductive amination of a compound of the formula (II) with a compound of the formula: $T-NH_2$ ($Y=NH$). The reduction can be carried out by catalytic hydrogenation, or with several hydride reagents in a reaction-inert solvent. The catalytic hydrogenation may be carried out in the presence of a metal catalyst such as palladium or Raney nickel. Suitable hydride reagents include borohydrides such as sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaBH_3CN$) and sodium triacetoxyborohydride ($NaB(OAc)_3H$), boranes, aluminum-based reagents and trialkylsilanes. Suitable solvents include polar solvents such as methanol, ethanol, methylene chloride, tetrahydrofuran (THF), dioxane and ethylacetate. This reaction is typically carried out at a temperature from $-78^\circ C$ to reflux temperature of the solvent, preferably from $0^\circ C$ to $25^\circ C$ for 5 minutes to 48 hours, preferably from 0.5 to 12 hours.

Alternatively, the compounds of the formula (I) of this invention may be prepared as shown in the following scheme A-II.

Scheme A-II



(wherein Z is a leaving group such as halo or sulfonate including tosylate or mesylate)

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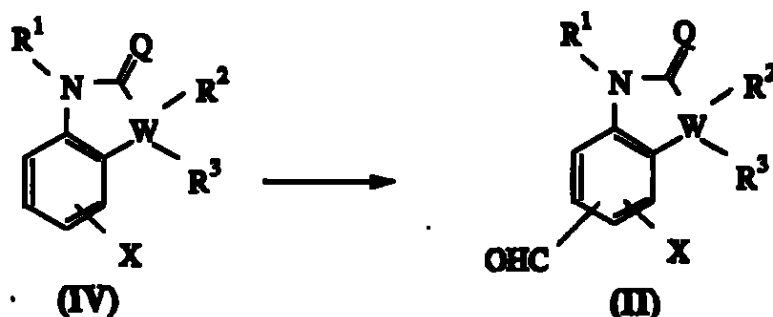
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may be prepared by a reaction of a compound of the formula (III) with a compound of the formula: T-Y-H. When Y is NH, the compound (III) may be treated with T-NH₂ in the presence of a base (e.g., K₂CO₃ or Na₂CO₃) in a polar solvent (e.g., methanol, ethanol, isopropylalcohol, THF, dioxane, dimethylformamide (DMF) or dimethylsulfoxide (DMSO)). When Y is O, the compound (III) may be treated with T-OH in the presence of a base (e.g., NaH or KH) in a polar solvent (e.g., THF, dioxane, DMF or DMSO). This reaction is typically carried out at a temperature from -78°C to reflux temperature of the solvent, preferably from 0°C to 25°C for 5 minutes to 48 hours, preferably from 0.5 to 12 hours.

10 The compounds (III) may be prepared by reduction of an aldehyde of the formula (II), followed by conversion of a hydroxy group of the resultant compound into a leaving group, Z. Reduction of the aldehyde (II) may be accomplished using a variety of reducing agents in a reaction-inert solvent. Suitable reducing agent/solvent systems include sodium tetrahydroborate (NaBH₄) in methanol or ethanol; lithium tetrahydroborate (LiBH₄) in THF or diethyl ether; lithium tetrahydroaluminium (LiAlH₄), lithium triethoxyhydroaluminium (LiAl(OEt)₃H) lithium *tert*-butoxyhydroaluminium (LiAl(OBu)₃H) or aluminium trihydride (AlH₃) in THF or diethyl ether; and *iso*-buthyl aluminium hydride(*i*-BuAlH₂) or diisopropyl aluminum hydride (DIBAL-H) in dichloromethane, THF or *n*-hexane. This reaction is generally carried out at a temperature from -20°C to 25°C for 5 minutes to 12 hours. Then, the hydroxy group of the resultant compound is converted to a leaving group, Z (e.g., halo such as chloro, bromo, iodo or fluoro, or sulfonate including tosylate or mesylate). Conversion of the hydroxy group into the leaving group, Z may be accomplished according to methods known to those skilled in the art. For example, when Z is sulfonate such as tosylate or mesylate, the hydroxy compound is reacted with sulfonate in the presence of pyridine or triethylamine in dichloromethane. When Z is halo such as chloro or bromo, the hydroxy compound may be treated with SOX₂ (X is Cl or Br) in the presence of pyridine.

25 The compounds of the formula (II) can be prepared as illustrated in the following scheme B.

Scheme B



The compounds of the formula (II) may be prepared by direct or indirect formylation of a compound of the formula (IV). Any formylation methods known to those skilled in the art may be used, to introduce a formyl group into a benzene ring.

- 5 For example, direct formylation may be accomplished by contacting the compound (IV) with a suitable formylating agent in the presence of a suitable catalyst. Suitable formylating agent/catalyst systems include dichloromethyl methyl ether / titanium (IV) chloride ($\text{Cl}_2\text{CHOCH}_3/\text{TiCl}_4$), trifluoroacetic acid ($\text{CF}_3\text{CO}_2\text{H}$) / hexamethylenetetramine (modified Duff's conditions) and phosphoryl trichloride (POCl_3) / DMF (Vilsmeier's
- 10 conditions). Indirect formylation may be achieved by halogenating the compound (IV), displacing the halogen atom introduced with a cyano group, and then subjecting the resultant cyano-substituted compound to reduction. The halogenation as used herein may be carried out according to the procedure reported in G. A. Olah et. al., *J. Org Chem*, **58**, 3194 (1993). The displacement of the halogen atom with a cyano group
- 15 may be performed according to the methods reported in D. M. Tschaem et. al., *Synth Commun*, **24**, 887 (1994), K. Takagi et. al., *64 Bull Chem. Soc. Jpn.*, **64**, 1118 (1991). The reduction as used herein may be performed in the presence of diisopropyl aluminiumhydride (DIBAL-H) in dichloromethane or Raney nickel in formic acid.

In addition, the compound (II) wherein W is vinylene can be prepared by 20 dehydrogenation of the formula (II) wherein W is ethylene in a suitable solvent such as dioxane.

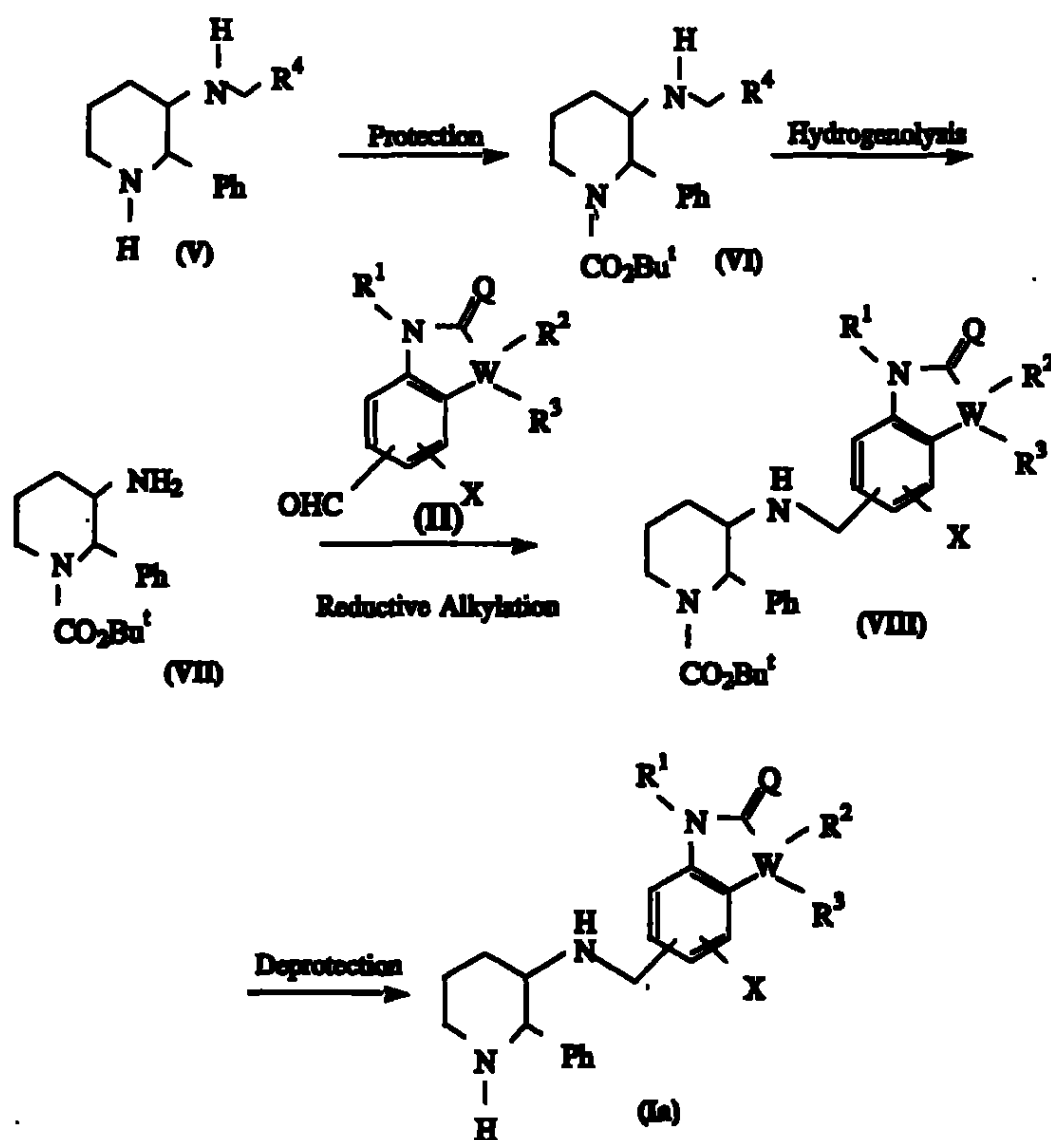
The starting materials of the formula (IV) are known compounds which are commercially available, or can be prepared by known methods. For example, compounds of the formula (IV) wherein R^1 is alkyl can be prepared by *N*-alkylation

25 of the corresponding compounds (IV) wherein R^1 is hydrogen, in the presence of a base (e.g., NaH or KH) in a suitable solvent (e.g., DMSO, DMF and THF).

Compounds of the formula (IV) wherein R^2 or R^3 is not hydrogen, can be also prepared from the corresponding compounds (IV) wherein R^2 or R^3 is hydrogen, using similar techniques as described above. Compounds (IV) can be also prepared by other methods as described in European Patent No. 385662 and C. Crestini. et. al., *Synth. Commun.* **24** 2853 (1994) or G. W. Rewcastle et. al., *J. Med. Chem.* **37**, 2033 (1994). Compound (IV) wherein Q is S, can be prepared by thionation of the corresponding compound (IV) wherein Q is O. Suitable thionation agents are Lawesson reagent (*Tetrahedron*, **41**, 5061 (1985)) and P_4S_{10} (*Chem. Pharm. Bull.*, **10**, 647 (1962)).

Alternatively, compounds of the formula (I) wherein T is 2-phenylpiperidinyl and Y is NH, may be prepared as shown in the following Scheme A-III.

Scheme A-III



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Scheme A-III illustrates the preparation of compounds of the formula (Ia) (corresponding to Compound (I) wherein T is 2-phenylpiperidinyI and Y is NH).

Referring to Scheme A-III, N-protection of a compound of the formula (V) (R^4 is phenyl or the like) may be carried out by treatment with (*t*-BuOCO)₂O (Boc₂O) in the presence of a base such as sodium bicarbonate (NaHCO₃) or triethylamine (Et₃N) to obtain a compound of the formula (VI). Compound (VI) is subjected to hydrogenolysis to obtain a compound of the formula (VII) (wherein R^5 is phenyl; and R^6 is *t*-butoxycarbonyl). An alternative route for N-protection of a compound of the formula (V) may be carried out by treatment with carbobenzoxy chloride (Cbz-Cl) in the presence of a base such as sodium bicarbonate (NaHCO₃) or triethylamine (Et₃N), wherein R^5 is phenyl; and R^6 is benzyloxycarbonyl. The hydrogenolysis may be carried out by treatment with H₂ or ammonium formate (HCO₂NH₄) in the presence of a metal catalyst such as a palladium on charcoal (e.g. 20% palladium on charcoal) in a suitable solvent. Then, the compound (VII) is subjected to the reductive amination as described in Scheme A-I. The compound (VIII) may be converted into a compound of the formula (Ia) by treatment with acid catalyst such as hydrochloride (HCl) in methanol, conc.HCl in ethylacetate or CF₃CO₂H in dichloroethane.

The compounds of formula (I), and the intermediates shown in the above reaction schemes can be isolated and purified by conventional procedures, such as recrystallization or chromatographic separation.

As the compounds of formula (I) of this invention possess at least two asymmetric centers, they are capable of occurring in various stereoisomeric forms or configurations. Hence, the compounds can exist in separated (+)- and (-)-optically active forms, as well as mixtures thereof. The present invention includes all such forms within its scope. Individual isomers can be obtained by known methods, such as optical resolution, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate.

In so far as the compounds of formula (I) of this invention are basic compounds, they are all capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the base compound from the reaction mixture as a pharmaceutically

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unacceptable salt and then simply convert to the free base compound by treatment with an alkaline reagent and thereafter convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The acid which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate))salts.

The compounds of the invention which have also acidic groups are capable of forming base salts with various pharmaceutically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques.

The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic derivatives. These particular non-toxic base salts include those derived from such pharmaceutically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the aforementioned acidic compounds with an aqueous solution containing the desired pharmaceutically acceptable cation, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum production of yields of the desired final product.

United States Patent Office

3,539,584
Patented Nov. 10, 1970

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3,539,584

5-SUBSTITUTED-2,1-BENZISOTHIAZOLINES
John T. Suh and Claude L. Jodt, Mequon, and Joseph A. Skowcz, Milwaukee, Wis., assignors to Colgate-Palmolive Company, New York, N.Y., a corporation of Delaware

No Drawing. Continuation-in-part of application Ser. No. 585,765, Oct. 11, 1966. This application Nov. 14, 1967, Ser. No. 683,089

Int. Cl. C07d 91/44

U.S. Cl. 260-384

8 Claims

ABSTRACT OF THE DISCLOSURE

The compounds are 5-substituted derivatives of 2,1-benzisothiazoline-2,2-dioxides which are useful in the preparation of wood preservatives, moth proofing agents and pickling inhibitors and as pharmaceutical agents, particularly antihypertensive agents and central nervous system stimulants. Compounds disclosed include 1,3-dimethyl-5-amino-2,1-benzisothiazoline-2,2-dioxide, 1,3-dimethyl-5-methanesulfonamido-2,1-benzisothiazoline-2,2-dioxide and 1,3-dimethyl-5-acetamido-2,1-benzisothiazoline-2,2-dioxide.

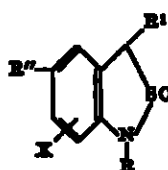
The present application is a continuation-in-part of our copending application Ser. No. 585,765, filed Oct. 11, 1966, now abandoned.

SUMMARY OF THE INVENTION

The present invention relates to novel 5-substituted derivatives of 2,1-benzisothiazoline-2,2-dioxides, methods of preparing such compounds and compositions containing them.

DETAILED DESCRIPTION

The novel compounds of the present invention may be represented by the following formula



in which X is selected from hydrogen, lower alkyl of 1 to 4 carbon atoms such as methyl, ethyl or propyl, lower alkoxy such as methoxy, ethoxy and propoxy halo and trifluoromethyl; R is selected from a lower alkyl of 1 to 4 carbon atoms, a cycloalkyl of 3 to 7 carbon atoms such as cyclopropyl, cyclopentyl or cyclohexyl, a cycloalkyl-lower alkyl in which the cycloalkyl has 3 to 7 carbon atoms such as cyclopropyl-ethyl, cyclopentyl-methyl and cyclohexyl-methyl, a nuclear substituted phenyl, particularly a lower alkoxy-substituted phenyl such as methoxyphenyl, or an aralkyl of 7 to 11 carbon atoms, particularly a phenyl-lower alkyl such as benzyl, phenethyl, phenylbutyl or phenylisopropyl; R' is selected from R or hydrogen and R'' is nitro, $-NR''$, $R''CONR'$, $R''SO_2NR'$, $R''CO$, $RCH(OH)$, $R''C(halo)CO$, $Am(CR'_2)_2CO$,

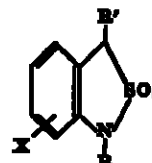
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$Am(CR'_2)_2CH(OH)$ and $Am(CR'_2)_2CH_2$, wherein n is 1 to 5, and Am is



in which R' is R or hydrogen and groups in which the R' and R' are joined together to form amino groups in which the nitrogen is part of a cyclic group such as morpholino, pyrrolidino, piperidino, 1,2,3,4-tetrahydroquinolino, 1,2,3,4-tetrahydroquinolino, a 4-lower alkyl-1-piperazino such as 4-methyl-1-piperazino, 3-hydroxypiperidino and 4-hydroxypiperidino.

A convenient starting material for the preparation of the compounds of the present invention are the corresponding sulfams which may be represented by the following formula

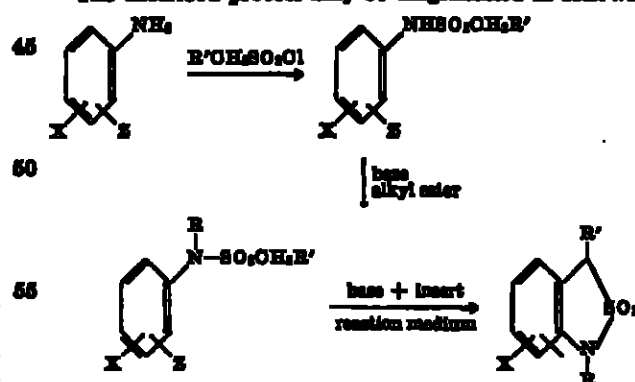


in which R and R' are as previously described and X is other than halogen.

The above sulfams may be conveniently prepared by employing a haloaniline such as o-chloroaniline or m-bromoaniline, or an N-substituted haloaniline such as N-phenyl-o-chloroaniline or N-p-methoxyphenyl-o-bromoaniline as the basic starting material.

If an unsubstituted haloaniline is employed it is first treated with methanesulfonyl chloride to form a halo-methanesulfonamide; the sulfonamide is then treated with an alkyl ester such as dimethylsulfate and a base such as potassium hydroxide, to form an N-substituted-halomethanesulfonamide. The thus obtained sulfonamide is then treated with a non-participating strong base, for example, an alkali amide such as sodium amide in an inert reaction medium such as liquid ammonia, anhydrous ether, benzene or the like, to effect ring closure.

The described process may be diagrammed as follows:



wherein X is hydrogen, lower alkyl, alkoxy or trifluoromethyl, Z is a reactive halogen and R and R' are groups which do not interfere with or partake in the reaction.

If an N-substituted haloaniline is employed as the starting material, it is first treated with alkylsulfonyl chloride to form the alkylsulfonamide derivative which may be

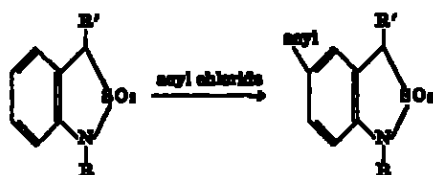
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This reaction may be diagrammed as follows:

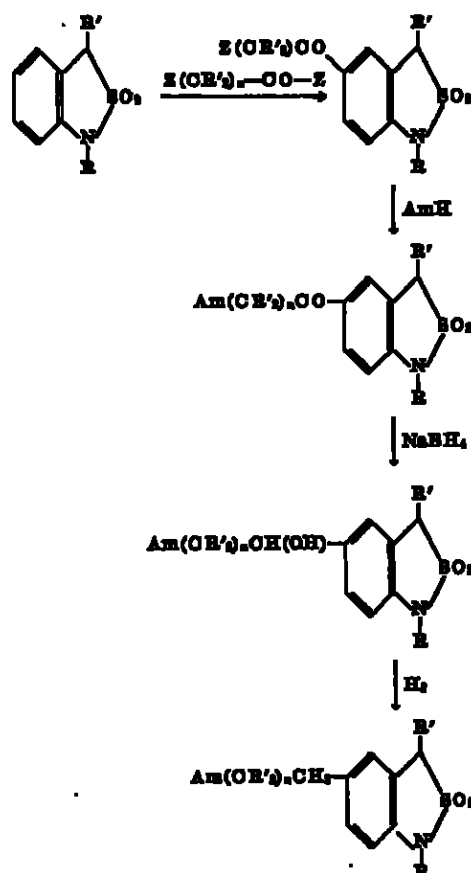


in which all symbols are as described and do not partake or interfere with the reaction.

Representative of the compounds which may be prepared by the proper choice of an acyl halide are the following:

- 1-methyl-5-acetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-benzoyl-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-acetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-propionyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-ethyl-5-acetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-propyl-5-acetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-propyl-5-phenylacetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-3-phenyl-5-acetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-phenethyl-5-acetyl-2,1-benzisothiazoline-2,2-dioxide,
- and
- 1-cyclopentylmethyl-5-acetyl-2,1-benzisothiazoline-2,2-dioxide.

The compounds of the present invention in which R'' is Am(CR')₂CO, Am(CR')₂CHOH, or Am(CR')₂CH₂ may be prepared by treating the sulfam starting material with a haloacyl halide, such as bromoacetyl bromide, to form the corresponding haloacyl derivative which can be in turn treated with a variety of amines to form acylamines which can be in turn reduced to form aminoalcohol derivatives.



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wherein Z is a halo such as chloro or bromo, and all other symbols are as described and represent groups which do not partake in or interfere with the reaction.

Representative of the haloacyl halides which can be employed in the above reaction are the following:

- Bromoacetyl bromide,
- Chloroacetyl chloride,
- Bromopropionyl bromide,
- Chloropropionyl chloride, and
- Bromobutyryl bromide.

Representative of the amines that may be employed are the following:

- 1-dimethylamino-3-propylamine,
- 1-dimethylamino-2-ethylamine,
- Dimethylamine,
- Methylamine,
- Ethylamine,
- Benzylamine,
- N-methyl-benzylamine,
- Morpholine,
- N-methyl-piperazine,
- Piperidine,
- Ammonia, and
- Isopropylamine.

Representative of the compounds that may be prepared by the above process are the following:

- 1-methyl-5-bromoacetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-bromoacetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-isopropylaminoacetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-methylbenzylaminoacetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-methylaminoacetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-isopropylaminoacetyl-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-(2'-isopropylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-(2'-isopropylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-(2'-isopropylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-(2'-isopropylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-phenyl-5-(2'-isopropylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-cyclopentylmethyl-5-(2'-isopropylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-phenethyl-5-(2'-isopropylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-(2'-methylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-(2'-methylbenzylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-(2'-methylamino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-(2'-methylaminoethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-(2'-isopropylaminoethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-(N-methylpiperazinoacetyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-(N-methylpiperazinoacetyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-(2'-N-methylpiperazino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1,3-dimethyl-5-(2'-N-methylpiperazino-1'-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide,
- 1-methyl-5-(2'-N-methylpiperazinoethyl)-2,1-benzisothiazoline-2,2-dioxide, and
- 1,3-dimethyl-5-(2'-N-methylpiperazinoethyl)-2,1-benzisothiazoline-2,2-dioxide.

ide (3 g., 0.01 mole) in 30 ml. of tetrahydrofuran is stirred at 25° for 1 hour, then evaporated to near dryness. Acetone (100 ml.) is added, and the insoluble salt filtered and dried to yield 1-methyl-5-phenethylaminoacetyl-2,1-benzisothiazoline-2,2-dioxide hydrobromide in the form of a cream-colored powder, M.P. >360° with appreciable darkening from 240°. Recrystallization from water affords stout, dull yellow needles, M.P. >360°.

Analysis.—Calcd. for $C_{18}H_{21}BrN_2O_2S$ (percent): C, 50.85; H, 4.98; N, 6.59. Found (percent): C, 50.94; H, 4.98; N, 6.67.

EXAMPLE 23

1-methyl-5-(2-phenethylamino-1-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide

The reaction of the compound of Example 22 (9.8 g., 0.023 mole) and sodium borohydride (3 g., 0.08 mole) in 125 ml. of methanol is carried out at room temperature for 40 hours, then at reflux for an additional 2 hours, in the manner described in Example 18 to yield 1-methyl-5-(2-phenethylamino-1-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide in the form of cream-colored, crystalline powder, M.P. 110–112°.

Analysis.—Calcd. for $C_{18}H_{21}N_2O_2S$ (percent): C, 62.40; H, 6.40; N, 8.09. Found (percent): C, 62.13; H, 6.27; N, 8.22.

EXAMPLE 24

1-methyl-5-(2-methylphenethylamino-1-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide hexamete

A solution of 1-methyl-5-(2-phenethylamino-1-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide (5.2 g., 0.015 mole) in formaldehyde-formic acid is allowed to react in the manner described in Example 21. The crude product then is converted to 1-methyl-5-(2-methylphenethylamino-1-hydroxy)-2,1-benzisothiazoline-2,2-dioxide hexamete, M.P. 77–79° after recrystallization from ethanol-ether.

Analysis.—Calcd. for $C_{20}H_{25}N_2O_2S$ (percent): C, 55.63; H, 6.91; N, 7.78. Found (percent): C, 55.92; H, 7.19; N, 7.57.

EXAMPLE 25

1-methyl-5-[2-N-benzyl-N-(β -hydroxyethyl)-amino-1-hydroxyethyl]-2,1-benzisothiazoline-2,2-dioxide hexamete

To a stirred solution of 13.3 g. (0.04 mole) of 1-methyl-5-(2-benzylamino-1-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide in 80 ml. of methanol containing a drop of dilute HCl is added 2.1 g. (0.048 mole) of ethylene oxide in 40 ml. of methanol. The resulting solution is stirred for 24 hours at room temperature, then treated with a small amount of 6 N NaOH, and evaporated to dryness. The remaining amber oil is eluted from 650 g. of alumina with chloroform-methanol (9:1) to afford 1-methyl-5-[2-N-benzyl-N-(β -hydroxyethyl)-amino-1-hydroxyethyl]-2,1-benzisothiazoline-2,2-dioxide as a pale yellow oil. Treatment with an equivalent amount of benzoic acid affords the salt as pale yellow crystals, M.P. 145–148°.

Analysis.—Calcd. for $C_{28}H_{33}N_2O_2S$ (percent): C, 54.03; H, 6.71; N, 7.56. Found (percent): C, 53.78; H, 6.68; N, 7.64.

EXAMPLE 26

1-methyl-5-(2-benzylaminoethyl)-2,1-benzisothiazoline-2,2-dioxide hydrochloride

To a cooled and stirred solution of 1-methyl-5-(2-benzylamino-1-hydroxyethyl)-2,1-benzisothiazoline-2,2-dioxide (4.65 g., 0.014 mole) and 3.8 g. (0.1 mole) of sodium borohydride in 75 ml. of tetrahydrofuran is added under nitrogen a solution of boron trifluoride etherate (34 ml.) in 40 ml. of tetrahydrofuran over a 30 min. period. The resulting mixture is stirred at room temperature for 1.5 hours and evaporated to dryness. Methanol (150 ml.) is added carefully to the residue, and the solution refluxed for 2 hours, stirred at room tem-

perature for an additional 12 hours and then evaporated. Water (100 ml.) is added to the residue, and the insoluble material filtered and dried. The small, pale tan flakes are heated at reflux in a solution of MeOH (200 ml.)-4 N HCl (25 ml.) for 12 hours. Cooling and dilution with ether provides 1-methyl-5-(2-benzylaminoethyl)-2,1-benzisothiazoline-2,2-dioxide hydrochloride in the form of white needles, M.P. 246–247°. Recrystallization from aqueous methanol-ether raises the M.P. to 249–250°.

Analysis.—Calcd. for $C_{17}H_{21}ClN_2O_2S$ (percent): C, 57.86; H, 6.00; N, 7.94. Found (percent): C, 57.75; H, 6.14; N, 7.88.

EXAMPLE 27

1-methyl-5-(2-methylbenzylaminoethyl)-2,1-benzisothiazoline-2,2-dioxide hydrochloride

Treatment of 4.4 g. of the hydrochloride of Example 26 with chloroform-aqueous sodium hydroxide provided the corresponding free base, which is heated with 20 ml. of 37% formaldehyde solution and 10 ml. of formic acid on a steam bath for 4 hours. The work-up procedure previously described affords a pale yellow oil with an absence of NH absorption in the infrared. Conversion of this material to a hydrochloride, followed by recrystallization from ethanol-ether, gives 1-methyl-5-(2-methylbenzylaminoethyl)-2,1-benzisothiazoline-2,2-dioxide hydrochloride as white granules, M.P. 176–178°.

Analysis.—Calcd. for $C_{19}H_{23}ClN_2O_2S$ (percent): C, 58.92; H, 6.32; N, 7.63. Found (percent): C, 59.18; H, 6.68; N, 7.60.

EXAMPLE 28

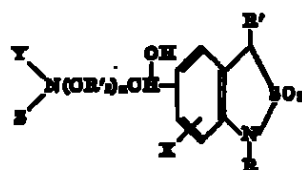
1-methyl-5-methylphenethylaminoacetyl-2,1-benzisothiazoline-2,2-dioxide hydrochloride

N-methylphenethylamine (2.7 g., 0.02 mole) and 1-methyl-5-bromoacetyl-2,1-benzisothiazoline-2,2-dioxide (3 g., 0.01 mole) are allowed to react in 30 ml. of tetrahydrofuran in the usual fashion. Chromatography of the crude product (3.4 g.) on alumina with benzene-ether (1:1) affords a yellow oil, which was treated with ethereal HCl to give 1.9 g. of a cream-colored powder, M.P. 90–100° with prior softening. Recrystallization of a 0.7 g. sample from ethanol-ether gives 1-methyl-5-methylphenethylaminoacetyl-2,1-benzisothiazoline-2,2-dioxide hydrochloride in the form of a pale yellow powder, M.P. 126–127°.

Analysis.—Calcd. for $C_{20}H_{25}ClN_2O_2S$ (percent): C, 57.78; H, 5.87; N, 7.09. Found (percent): C, 58.07; H, 5.83; N, 7.17.

We claim:

1. A compound of the formula



in which X is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 3 carbon atoms, halo and trifluoromethyl; R is alkyl of 1 to 4 carbon atoms; R' is hydrogen or alkyl of 1 to 4 carbon atoms, n is 1 to 5 and Y and Z are selected from hydrogen, alkyl of 1 to 4 carbon atoms and phenyl-alkyl in which the alkyl group is 1 to 4 carbon atoms, and pharmaceutically acceptable salts thereof.

2. A compound of claim 1 in which X is hydrogen, R is methyl, R' is hydrogen and Y and Z are hydrogen, methyl, ethyl, isopropyl, benzyl or phenethyl.

3. A compound of claim 1 in which X is hydrogen, R is methyl, R' is hydrogen, n is 1 and Y and Z are lower alkyl.

4. A compound of claim 1 in which X is hydrogen, R is methyl, R' is hydrogen, n is 1, Y is methyl and Z is benzyl.

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5. A compound of claim 1 in which X is hydrogen, R is methyl, R' is hydrogen, n is 1, Y is methyl and Z is hydrogen.

is methyl, R' is hydrogen, n is 1, Y is hydrogen and Z is isopropyl.

6. A compound of claim 1 in which X is hydrogen, R is methyl, R' is hydrogen, n is 1, Y is hydrogen and Z is benzyl.

No references cited.

7. A compound of claim 1 in which X is hydrogen, R is methyl, R' is hydrogen, n is 1, Y is hydrogen and Z is phenethyl.

8 JAMES H. TURNIPSEED, Assistant Examiner

U.S. Cl. X.R.

8. A compound of claim 1 in which X is hydrogen, R

260—247.1, 268, 288, 293.4; 252—380; 424—248, 250, 258, 263, 267, 273

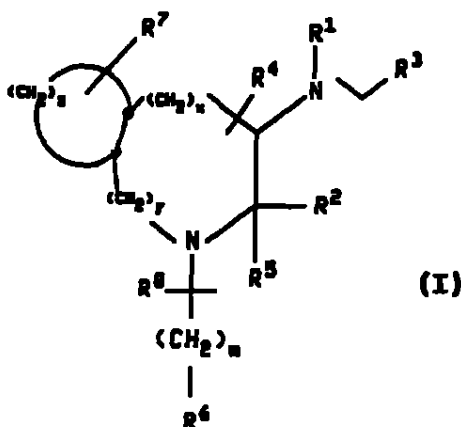
PCT

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(54) Title: FUSED RING ANALOGS OF NITROGEN CONTAINING NONAROMATIC HETEROCYCLES



(57) Abstract

The present invention relates to novel fused ring analogs of nitrogen containing heterocycles, and specifically, to compounds of formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , x , y , and z and m are defined as below. These novel compounds are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders.

* See back of page

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acetic acid, 80 mg of PtO₂ and 48 mL of ethanol, and the mixture was shaken under an atmosphere (40 psi) of hydrogen (Parr apparatus) for 6 hours at room temperature. The mixture was filtered through diatomaceous earth (Celite(trademark)), and the filter pad was rinsed with ethanol. The filtrate was concentrated in vacuo. The residue was partitioned between CH₂Cl₂ and saturated aqueous sodium bicarbonate, the layers were separated, the aqueous phase was extracted with CH₂Cl₂, and the combined organic fractions were dried (Na₂SO₄) and concentrated. The crude material was purified by flash column chromatography to obtain 260 mg of 3-carboethoxy-2-phenyl-1,2,3,4-tetrahydroquinoline.

¹H NMR (CDCl₃) δ 1.20 (t, 3H, J=6), 2.85-2.95 (m, 2H), 3.22-3.30 (m, 1H), 4.08-4.18 (m, 2H), 4.42 (bs, 1H), 4.95 (d, 1H, J=4), 6.60 (d, 1H, J=10), 6.70 (t, 1H, J=8), 7.02-7.34 (m, 7H).

This material was converted to the title compound using procedures analogous to those of Examples 2B-2G.

¹H NMR (CDCl₃) δ 2.62-2.74 (m, 1H), 2.84-2.94 (m, 1H), 3.12-3.21 (m, 1H), 3.59 (s, 3H), 3.74 (d, 1H, J=9), 3.82 (d, 1H, J=9), 4.61 (d, 1H, J=3), 6.50-6.82 (m, 4H), 6.92-7.36 (m, 9H).

EXAMPLE 4

Trans-4-(2-methoxybenzylamino)-2-methyl-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone

A solution of trans-4-amino-2-methyl-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone (2.36 g, 9.36 mmol), prepared according to the method of I. Attanassova *et al.*, Commun. Dept. Chem., Bulg. Acad. Sci., 17(2), 172-9 (1984), in 40 mL acetic acid was treated with 1.5 g of 3Å molecular sieves (Aldrich Chemical Co.) followed by the addition of 1.59 g (11.7 mol) of ortho-anisaldehyde. Sodium triacetoxymethylborohydride (Aldrich) was added in three 1.32 g portions (total of 3.97 g, 18.7 mmol), and then stirred at 25 °C overnight. The sieves were removed by filtration through a pad of diatomaceous earth (Celite (trademark)),

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the pad being washed with additional acetic acid, and the combined filtrates were concentrated in vacuo. The residue was treated with 30 mL H₂O, acidified with 1 N HCl and extracted with diethyl ether. The aqueous layer was made
5 alkaline with 2 N NaOH and was reextracted with diethyl ether. After drying over MgSO₄, the ether was removed in vacuo to give the crude title compound as an oil (1.65 g). Chromatography on silica gel (230-400 mesh) eluting with methylene chloride:methanol:concentrated ammonium hydroxide
10 (97:2:1) gave the pure trans isomer of the title compound as a clear oil (0.80g, 23%).

MS, m/e 372 (M⁺), 253, 132, 121.

¹H NMR (300 MHz, CDCl₃, δ) 3.14 (s, 3H), 3.78 (s, 3H), 3.72-3.92 (m, 3H), 4.88 (bs, 1H), 6.82-6.98 (m, 4H), 7.10-
15 7.42 (m, 9H), 8.18 (d, 1H).

EXAMPLE 5

Trans-4-(2-methoxybenzylamino)-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone

Using the procedure described in Example 4, trans-4-amino-3-phenyl-3,4-dihydro-1(2H)-isoquinolinone (which
20 was prepared by the method of I. Attanassova et al., Commun. Dept. Chem., Bulg. Acad. Sci., 17 (2), 179-9 (1984) except that N-(trimethylsilyl)benzylidenamine was substituted for N-benzylidenamethylamine in the first step
25 of the synthesis), was immediately reacted with ortho-anisaldehyde to produce the title compound as a pale yellow viscous oil (0.100 g).

MS, m/e 358 (M⁺), 253, 132, 121.

¹H NMR (CDCl₃, 300 MHz, δ) 3.74 (s, 3H), 3.78-4.00 (m, 3H), 4.94 (t, 1H), 6.16 (bs, 1H), 6.82 (d, 1H), 6.92 (t, 1H), 7.12-7.50 (m, 10H), 8.15 (d, 1H).

EXAMPLE 6

Trans-4-(2-methoxybenzylamino)-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline

35 The title compound from Example 4 (0.8 g, 2.15 mmol) was dissolved in 10 mL dry THF under nitrogen and treated with lithium aluminum hydride (LAH, 0.4 g, 10.5 mmol).

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US005604252A

United States Patent [19]
O'Neill

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[45] **Date of Patent:** **Feb. 18, 1997**

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[73] **Assignee:** Pfizer Inc., New York, N.Y.

[21] **Appl. No.:** 167,851

[22] **PCT Filed:** Jun. 11, 1992

[86] **PCT No.:** PCT/US92/04697

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§ 102(e) Date: Dec. 14, 1993

[87] **PCT Pub. No.:** WO93/00330

PCT Pub. Date: Jan. 7, 1993

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[51] **Int. Cl.⁶** C07D 487/04; C07D 207/14;
A61K 31/40

[52] **U.S. Cl.** 514/413; 514/426; 548/453;
548/557

[58] **Field of Search** 548/453, 557;
514/413, 426

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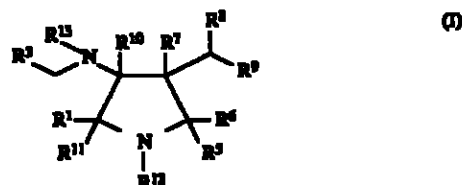
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Primary Examiner—David B. Springer

Attorney, Agent, or Firm—Peter C. Richardson; Paul H. Ginsburg; Karen DeBenedictis

[57] **ABSTRACT**

The present invention relates to novel azanorbornane derivatives having the formula



wherein R¹ through R¹² are defined as below, and to novel intermediates used in their synthesis. The compounds having formula I are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders.

12 Claims, No Drawings

basic with 2N NaOH and extracted with ethyl acetate (2x15 mL). The organic phase was dried and evaporated. The residue was chromatographed on silica gel using CH₂Cl₂/CH₃OH, NH₄OH (97:2:1) to afford 17 mg (61%) of the desired material.

¹H NMR (CDCl₃, 250 MHz) δ 7.31–7.05 (m, 12H), 6.83–6.70 (m, 2H), 4.21–4.17 (d, 1H, J=12.1 Hz), 3.71–3.67 (d, 1H, J=13.7 Hz), 3.55 (s, 3H), 3.54–3.45 (m, obs, 1H), 3.45–3.39 (d, 1H, J=13.7 Hz), 3.09–3.05 (d, 1H, J=9.8 Hz), 2.74–2.64 (m, 3H), 2.47–2.43 (m, 1H), 2.18–2.15 (d, 1H, J=9.9 Hz), 1.68–1.50 (m, 1H), 1.09–1.04 (m, 1H) ppm.

¹³C NMR (CDCl₃, 62.9 MHz) δ 157.3, 129.3, 128.9, 128.4, 127.8, 127.7, 127.3, 126.2, 125.8, 119.9, 109.8, 72.0, 63.6, 56.1, 55.1, 54.8, 50.8, 47.2, 41.4, 26.9 ppm.

Mass spectrum m/e 399 (p+), 231, 121.

The dihydrochloride salt was prepared by treatment of the free base with saturated HCl (g) in ether. The solid was allowed to granulate overnight to afford 10 mg white solid. M.P. -211° C. (decomp).

EXAMPLE 2

(1SR, 2SR, 3SR, 4RS)-1-aza-2-phenyl-3-(2-methoxyphenyl)methylaminobicyclo[2.2.1]heptane

A. (2SR, 3RS, 4RS)-1N-phenylmethyl-2-phenyl-3-nitro-4-carbomethoxymethyl pyrrolidine

A solution of nitrostyrene (3.09 g, 20.73 mmol) (25 trans-B-nitrostyrene from Aldrich) and 5.00 g (22.8 mmol) of previously prepared methyl-4-phenylmethylamino-2-butenate (the product of Example 1A) in 250 mL methanol was stirred at room temperature for 16 hours. The reaction mixture was evaporated in vacuo and the residue was chromatographed on silica gel with 9/1 hexane/ethyl acetate. There was obtained 7.4 g (100%) of the desired material as a single isomer.

¹H NMR (CDCl₃, 250 MHz) δ 7.5–7.23 (m, 10 H), 5.02–4.97 (dd, 1H, J=8.4 Hz, J=4.5 Hz), 4.32–4.31 (d, 1H, J=4.5 Hz), 3.93–3.88 (d, 1H, J=13.1 Hz), 3.65 (s, 3H), 3.43–3.37 (d, 1H, J=13.1 Hz), 3.29–3.23 (t, 1H, J=6.8 Hz), 3.17–3.07 (m, 1H), 2.57–2.50 (t, 1H, J=9.5 Hz), 2.43–2.41 (d, 2H, J=7.4 Hz) ppm.

¹³C NMR (CDCl₃, 62.9 MHz) δ 171.4, 139.8, 128.9, 128.6, 128.4, 128.3, 127.3, 127.2, 95.2, 73.0, 57.4, 56.5, 51.9, 37.6, 32.1 ppm.

IR (CHCl₃) 1737, 1546, 1376 cm⁻¹.

Mass spectrum m/e 353 (p-), 308, 234, 91.

B. (2SR, 3SR, 4RS)-1N-phenylmethyl-2-phenyl-3-nitro-4-carbomethoxymethyl pyrrolidine

A solution of 780 mg (2.2 mmol) of the previous product (the product of Example 2A) in 10 mL of ether was treated with 100 mg (0.66 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The reaction mixture was seeded or scratched to induce crystallization and after 2 hours a white solid was filtered and dried to afford 482 mg of the desired product. The mother liquor was allowed to stir for 16 hours whereupon an additional 46 mg was obtained (total yield 68%).

¹H NMR (CDCl₃, 250 MHz) δ 7.47–7.25 (m, 10 H), 5.09–5.03 (dd, 1H, J=8.5 Hz, J=5.2 Hz), 4.02–3.98 (d, 1H, J=8.5 Hz), 3.93–3.88 (d, 1H, J=13.3 Hz), 3.65 (s, 3H), 3.52–3.41 (m, 2H), 3.09–3.03 (d, 1H, J=13.3 Hz), 2.55–2.50 (m, 2H), 2.09–2.02 (m, 1H) ppm.

IR (CHCl₃) 1737, 1553, 1377 cm⁻¹.

Mass spectrum m/e 354 (p+) 308 (p-46), 234, 91.

C. (2SR, 3SR, 4RS)-1N-phenylmethyl-2-phenyl-3-amino-4-(2-hydroxyethyl) pyrrolidine

A solution of 464 mg (1.31 mmol) of the compound prepared above was dissolved in 50 mL of methanol and was treated with 1.2 g of (water washed) R₄NI (pH 7) stored under ethanol. The mixture was placed in a Parr pressure bottle and placed under 50 psi hydrogen for a period of approximately 4 hours. The reaction mixture was purged with nitrogen and then filtered. The filtrate was evaporated in vacuo and the residue (426 mg) was used directly in the next step.

¹H NMR (CDCl₃, 300 MHz) δ 7.40–7.21 (m, 10 H), 3.92–3.87 (d, 1H, J=13.3 Hz), 3.63 (s, 3H), 3.61–3.59 (d, 1H, J=7.1 Hz), 3.32–3.27 (dd, 1H, J=9.3 Hz, J=7.1 Hz), 3.11–3.06 (m, obs, 1H), 3.06–3.02 (d, 1H, J=13.3 Hz), 2.68–2.60 (dd, 1H, J=15.6 Hz, J=6.0 Hz), 2.43–2.35 (dd, 1H, J=15.6 Hz, J=8.6 Hz), 2.32–2.11 (m, 1H), 1.93–1.87 (t, 1H, J=9.3 Hz).

¹³C NMR (CDCl₃, 75.5 MHz) δ 173.5, 139.4, 139.5, 128.8, 128.6, 128.5, 128.2, 127.4, 126.9, 73.3, 60.7, 58.4, 57.8, 51.6, 43.1, 37.6 ppm.

Mass spectrum m/e 324 (p+), 307, 233, 118, 91.

IR (CHCl₃) 1733 cm⁻¹.

A solution of lithium aluminum hydride was prepared by dilution of 3.57 mL of 1M reagent THF with 45 mL of anhydrous THF. The solution was cooled to 0° C. and was treated with 579 mg (1.79 mmol) of material derived from several runs of previous step (the penultimate product of Example 2C) in 8 mL THF. The reaction mixture was stirred for 60 min at 0° C. The reaction was quenched by the sequential addition of 135 μL water, 135 μL 15% aqueous sodium hydroxide and 405 μL water. The resultant precipitate was granulated for 15 min and the slurry was filtered through Celite®. The residue after evaporation was chromatographed on silica gel eluting with CH₂Cl₂/CH₃OH, NH₄OH (97:2:1) to afford 380 mg of the desired product (72%).

¹H NMR (CDCl₃, 300 MHz) δ 7.43–7.24 (m, 10H), 3.89–3.84 (d, 1H, J=13.1 Hz), 3.76–3.56 (m, 3H), 3.25–3.22 (d, 1H, J=8.3 Hz), 3.18–3.13 (d, 1H, J=13.2 Hz), 3.08–3.02 (dd, 1H, J=8.8 Hz, J=6.0 Hz), 2.28 (s, 1H), 2.06–1.98 (dd, 1H, J=10.7 Hz, J=8.9 Hz), 1.83–1.56 (m, 1H) ppm.

Mass spectrum m/e 296 (p+), 279, 209, 188, 118, 91.

D. (2SR, 3SR, 4RS)-1N-phenylmethyl-2-phenyl-3-(2-methoxyphenyl)methylamino-4-(2-hydroxyethyl)-pyrrolidine

A solution of 320 mg (1.08 mmol) of material from the previous step (the final product of Example 2C) in 30 mL of acetic acid was treated with 3 Å molecular sieves, 126 mg (0.928 mmol) anisaldehyde (Aldrich) and 328 mg (1.55 mmol) sodium triacetoxyborohydride. The reaction mixture was stirred for 16 hours and was then evaporated in vacuo. The residue was partitioned between 1N HCl and ether (50 mL). The aqueous layer was made basic to pH 12 and then was extracted with ethyl acetate. After drying and evaporation there was obtained 265 mg (59%) of the desired diamine.

¹H NMR (CDCl₃, 300 MHz) δ 7.53–7.10 (m, 11H), 6.75–6.68 (m, 2H), 6.54–6.52 (d, 1H, J=7.3 Hz), 3.93–3.92 (d, 1H, J=8.8 Hz), 3.78–3.74 (d, 1H, J=13.1 Hz), 3.63 (s, 3H), 3.54–3.47 (t, 1H, J=9.9 Hz), 3.35–3.11 (m, 3H), 3.05–2.95 (m, 1H), 2.11 (m, 2H), 1.79–1.70 (m, 1H), 1.60–1.49 (m, 1H) ppm.

¹³C NMR (CDCl₃, 75.5 MHz) δ 157.5, 140, 138.5, 130.1, 129.8, 128.7, 128.5, 128.4, 128.1, 127.6, 126.8, 120.3,

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PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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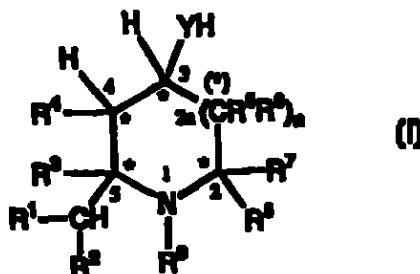
(51) Internationale Patentsklassifikation ⁶ : C07D 207/12, 209/52, 291/04, C07C 381/10, C07F 7/10		A1	(11) Internationale Veröffentlichungsnummer: WO 99/58500 (43) Internationales Veröffentlichungsdatum: 18. November 1999 (18.11.99)
(21) Internationales Aktenzeichen: PCT/DE99/01417 (22) Internationales Anmeldedatum: 10. Mai 1999 (10.05.99) (30) Prioritätsdaten: 198 21 418.9 13. Mai 1998 (13.05.98) DE (71) Anmelder (für alle Bestimmungstaaten ausser US): SOLVAY PHARMACEUTICALS GMBH [DE/DE]; Hans-Böckler-Allee 20, D-30173 Hannover (DE). (72) Erfinder, und (75) Erfinder/Anmelder (nur für US): REGGELIN, Michael [DE/DE]; Steinbacherweg 7, D-65589 Hadamar (DE). HEINRICH, Timo [DE/DE]; Albert-Schweitzer-Strasse 4, D-63517 Rodenbach (DE). JUNKER, Bernd [DE/DE]; Joseph-Haydn-Strasse 32, D-65812 Bad Soden (DE). ANTEIL, Jochen [DE/DE]; Lauenauerstrasse 63, D-31848 Bad Münder (DE). PRUSCHOFF, Ulf [DE/DE]; Meyer- holzweg 5, D-29125 Uelzen (DE). (74) Anwalt: LAUER, Dieter; Solvay Pharmaceuticals GmbH, Hans-Böckler-Allee 20, D-30173 Hannover (DE).		(81) Bestimmungstaaten: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), europäisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Veröffentlicht <i>Mit internationalem Recherchenbericht.</i> <i>Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>	

(54) Title: **METHOD FOR STEREOCHEMICALLY CONTROLLED PRODUCTION OF ISOMERICALLY PURE HIGHLY SUBSTITUTED AZACYCLIC COMPOUNDS**

(54) Bezeichnung: **VERFAHREN ZUR STEREOCHEMISCH KONTROLLIERTEN HERSTELLUNG ISOMERENREINER HOCHSUBSTITUIERTER AZACYCLISCHER VERBINDUNGEN**

(57) Abstract

The invention relates to a method for stereochemically controlled production of azacyclic compounds of general formula (I), whereby the substituents have the meaning cited in the description. The invention also relates to intermediate products of this method and to novel azacyclones.



(57) Zusammenfassung

Es werden ein Verfahren zur stereochemisch kontrollierten Herstellung von azacyclischen Verbindungen der allgemeinen Formel (I), worin die Substituenten die in der Beschreibung angegebene Bedeutung besitzen sowie Zwischenprodukte dieses Verfahrens und neue Azacyclen beschrieben.

hielt 113 mg kristalline Titelverbindung, Fp. = 84,5 °C, optischer Drehwert $[\alpha]_D^{20} = -46,4^\circ$ ($c = 1,04$ in Dichlormethan).

Beispiel 5

(+)-(2S,3S,4R,5S)-3-Amino-5-methyl-2-phenyl-1-aza-(N-tert.-butoxycarbonyl)-bicyclo[3.3.0]octan

- A) Zu einer Lösung von 200 mg (-)-(2S,3R,4R,5S)-3-Hydroxy-5-methyl-2-phenyl-1-azabicyclo[3.3.0]octan in 1,5 ml THF wurden bei Raumtemperatur unter Argonatmosphäre und Feuchtigkeitsausschluß 241 mg Triphenylphosphin und 135 mg Phthalimid gegeben. Anschließend gab man innerhalb von 2 min. 0,14 ml DEAD zu. Nach 10 Stunden Reaktionszeit dampfte man das Lösungsmittel unter vermindertem Druck ein und nahm den Rückstand in 5 ml Ether auf. Nach Abfiltrieren von ungelöstem Rückstand und Eindampfen des Lösungsmittels unter vermindertem Druck erhielt man das (2S,3S,4R,5S)-5-Methyl-2-phenyl-3-phthalimido-1-azabicyclo[3.3.0]octan als Rohprodukt, welches ohne weitere Reinigung für die nachfolgende Reaktion verwendet wurde.
- B) 174 mg des vorstehend erhaltenen Rohproduktes wurden in 3 ml Dioxan gelöst. Zu dieser Vorlage gab man 220 mg Di-tert.-butyldicarbonat und 63 mg Natriumhydrogencarbonat sowie 0,5 ml Wasser zu und rührte das entstandene Gemisch 16 Stunden lang bei Raumtemperatur. Das Lösungsmittel wurde unter vermindertem Druck eingedampft und der verbliebene Rückstand wurde in Wasser und Ether aufgenommen. Man trennte die Phasen und extrahierte die wäßrige Phase 2 mal mit jeweils 5 ml Ether. Die vereinigten organischen Phasen wurden über Magnesiumsulfat getrocknet, bevor das Lösungsmittel unter vermindertem Druck eingedampft wurde. Chromatographie des verbliebenen Rückstandes an Kieselgel (Laufmittel: Ether/n-Hexan

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843

1:3 v/v) lieferte 115 mg öliges (2S,3S,4R,5S)-5-Methyl-2-phenyl-3-phthalimido-1-aza-(N-tert.-butoxycarbonyl)-bicyclo[3.3.0]octan.

- C) Eine Lösung von 115 mg des vorstehend erhaltenen Phthalimido-bicyclo[3.3.0]octans in 2 ml Ethanol wurde mit 400 mg Hydrazinhydrat (24%ig) versetzt und das entstandene Gemisch wurde 8 Stunden lang zum Rückfluß erhitzt. Man dampfte das Lösungsmittel unter vermindertem Druck ein, nahm den verbliebenen Rückstand in 10 ml Ether auf und extrahierte die organische Phase mit 10 ml einer 10%igen wäßrigen Natronlauge. Die wäßrige Phase wurde 2 mal mit jeweils 10 ml Ether extrahiert und die vereinigten organischen Phasen wurden über Magnesiumsulfat getrocknet. Man dampfte das Lösungsmittel unter vermindertem Druck ab und erhielt 74 mg kristalline Titelverbindung, Fp. = 92,1 °C, $[\alpha]_D^{20} = +24,1^\circ$ (c = 1,0 in Dichlormethan).

Nach den vorstehend angegebenen Methoden können auch die in der nachfolgenden Tabelle angegebenen Verbindungen der Formel I hergestellt werden.

In der Tabelle werden folgende Abkürzungen verwendet:

i-Bu = Isobutyl
Bn = Benzyl
BOC = tert.-Butyloxycarbonyl
TBOM = tert.-Butyloxymethyl
Ph = Phenyl
Z. = Zersetzung beim Erhitzen
N.N. = Eintrag nicht besetzt

(12)

EUROPEAN PATENT APPLICATION

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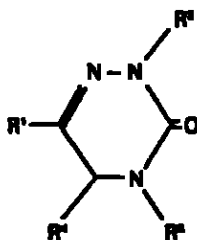
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(54) Triazine derivatives, processes for preparation thereof and pharmaceutical compositions comprising the same.

(57) New triazine derivatives represented by the formula:



wherein

R¹ is a 1, 2, 3, 4-tetrahydroquinolyl,
2-oxo-1, 2, 3, 4-tetrahydroquinolyl,
2-oxo-1, 2-dihydroquinolyl,
indolyl,
2-oxoindolyl,
benzothiazolyl,
2-oxobenzothiazolyl,
3,4-dihydro-1H-2, 1-benzothiazinyl in which the S atom
optionally oxidized, or
3-oxo-2, 3-dihydro-4H-1, 4-benzoxazinyl, each of which
may have one or more substituent(s) selected from lower
alkyl, hydroxy (lower) alkyl, lower alkylamino, lower alkanoyl,

cyclic lower alkanoyl, lower alkoxy (lower) alkyl, lower
alkylamino (lower) alkanoyl, benzyl, benzoyloxy (lower) alkyl,
lower alkoxy carbonyl (lower) alkyl and

4-(2-hydroxyethyl) piperazin-1-yl-carbonylmethyl;

R² is a hydrogen, lower alkanyl, benzyl, carboxy (lower)-
alkyl or lower alkoxy carbonyl (lower) alkyl;

R³ and R⁴, which may be the same or different, are each
hydrogen or lower alkyl or together represent a bond;
provided that when R¹ is 2-oxo-1, 2, 3, 4-tetrahydroquinolyl
which is unsubstituted or substituted by a lower alkyl, then, R²
is a hydrogen or R³ is a lower alkanyl, benzyl, carboxy (lower)
alkyl or lower alkoxy carbonyl (lower) alkyl; and pharmaceuti-
cally acceptable salt thereof, which are useful in the treatment
of hypertension, thrombosis and ulcer in human beings and
animals.

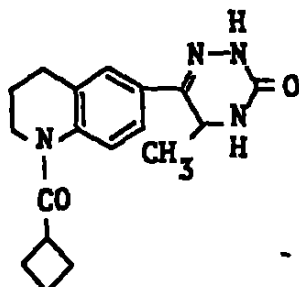
methyl-4,5-dihydro-1,2,4-triazin-3(2H)-one (0.26 g).

mp: 215 to 219°C (dec.)

IR (Nujol) : 3210, 3090, 1700, 1655 cm^{-1}

NMR (DMSO- d_6 , δ) : Ca: 0.6-1.2 (4H, m), 1.23 (3H, d, $J=7\text{Hz}$), 1.7-2.2 (3H, m), 2.78 (2H, t, $J=6.4\text{Hz}$), 3.76 (2H, t, $J=6.4\text{Hz}$), 4.63 (1H; d, q; $J=3, 7\text{Hz}$), 7.40 (1H, b.s.), 7.50 (3H, b.s.), 9.91 (1H, d, $J=1.8\text{Hz}$)

Example 14 : Synthesis of the compound of the formula :



6-(1-Cyclobutanecarbonyl-1,2,3,4-tetrahydroquinolin-6-yl)-5-methyl-4,5-dihydro-1,2,4-triazin-3(2H)-one (0.45 g) was obtained from 6-(1,2,3,4-tetrahydroquinolin-6-yl)-5-methyl-4,5-dihydro-1,2,4-triazin-3(2H)-one (0.6 g) in a similar manner to that of Example 13..

mp: 247 to 251°C (from 70% aqueous ethanol)

IR (Nujol) : 3210, 3080, 1693, 1655 cm^{-1}

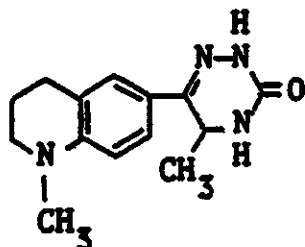
NMR (DMSO- d_6 , δ) : 1.21 (3H, d, $J=6.6\text{Hz}$), 1.5-2.5 (6H, m), 2.5-3.0 (4H, m), 3.40 (1H, m), 3.66 (2H, m), 4.65 (1H, m), 7.3-7.7 (3H, m), 7.42 (1H, b.s.), 9.95 (1H, b.s.)

Anal Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_2$: C, 66.24; H, 6.79; N, 17.17
Found :: C, 66.16; H, 6.85; N, 17.01

Example 15: Synthesis of the compound of the formula :

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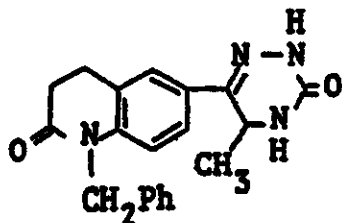


Sodium cyanoborohydride (0.19 g) was added portionwise to a suspension of 6-(1,2,3,4-tetrahydroquinolin-6-yl)-5-methyl-4,5-dihydro-1,2,4-triazin-3(2H)-one (0.74 g), 36% aqueous formaldehyde (0.34 ml), acetic acid (1 ml) and methanol (3 ml) at room temperature. After stirring for 0.5 hours at the same temperature, the resultant precipitates were collected by filtration, washed with methanol, dried, and recrystallized from 70% aqueous ethanol to give 0.66 g of 6-(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)-5-methyl-4,5-dihydro-1,2,4-triazin-3(2H)-one.

mp : >255°C (dec.)
IR (Nujol) : 3200, 3080, 1690 cm^{-1}
NMR (DMSO- d_6 , δ) : 1.17 (3H, d, $J=6.4\text{Hz}$), 1.6-2.2 (2H, m), Ca. 2.5-2.9 (2H, m), 2.85 (3H, s), 3.1-3.4 (2H, m), 4.3-4.8 (1H, m), 6.53 (1H, d, $J=9.8\text{Hz}$), 7.1-7.5 (3H, m), 9.63 (1H, b.s.)

Example 16 : Synthesis the compound of the formula :

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(1) 1-Benzyl-6-(2-hydroxyiminopropionyl)-2-oxo-1,2,3,4-tetrahydroquinoline (5.45 g) was obtained from

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6-(1-Dimethylaminoacetamido-1,2,3,4-tetrahydroquinolin-6-yl)-5-methyl-4,5-dihydro-1,2,4-triazin-3(2H)-one (0.42 g) was obtained by reacting the object compound (0.7 g) of Example 10-(6) with 2-dimethylaminoacetyl chloride hydrochloride (0.771 g) according to a similar manner to that of Example 13.

mp : 239 to 246°C

IR (Nujol) : 3200, 3100, 1690, 1655 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.20 (3H, d, $J=6.8\text{Hz}$),

Ca. 1.5-2.3 (2H, m), 2.21 (6H, s), 2.76 (2H,

b.t., $J=7\text{Hz}$), 3.29 (2H, s), 3.75 (2H, b.t.,

$J=6.6\text{Hz}$), 4.62 (1H; d, q; $J=3.6, 6.8\text{Hz}$),

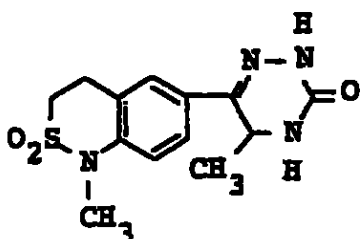
7.40 (1H, br s), Ca. 7.4-7.8 (3H, m), 9.91

(1H, d, $J=2\text{Hz}$)

Anal. Calcd. for $\text{C}_{17}\text{H}_{23}\text{N}_5\text{O}_2$: C, 61.99; H, 7.04; N, 21.26

Found : C, 61.73; H, 6.94; N, 21.30

Example 19.



(1) 6-(2-Hydroxyiminopropionyl)-1-methyl-3,4-dihydro-1H-2,1-benzothiazine 2,2-dioxide (2.6 g) was obtained from 1-methyl-6-propionyl-3,4-dihydro-1H-2,1-benzothiazine 2,2-dioxide (5.1 g) according to a similar manner to that of Example 4-(1).

mp : 178 to 180°C

IR (Nujol) : 3440, 1650, 1330, 1155, 1145 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.04 (3H, s), 3.00-3.68 (4H, m),

3.27 (3H, s), 7.16 (1H, d, $J=8.5\text{Hz}$),

7.79 (1H, br s), 7.83 (1H, dd, $J=8.5\text{Hz}, 2\text{Hz}$),

12.34 (1H, s)

848

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(2) 6-(2-Hydroxyimino-1-thiosemicarbazonopropyl)-1-methyl-3,4-dihydro-1H-2,1-benzothiazine 2,2-dioxide (2.70 g) was obtained from the reaction product of Example 19-(1) (2.50 g) according to a similar manner to that of Example 1-(1).

mp : 227°C (dec.)

IR (Nujol) : 3460, 3340; 3125, 1610, 1340, 1155 cm⁻¹

NMR (DMSO-d₆, δ) : 3.23 (3H, s), 3.32-3.80 (4H, m),
7.00-10.67 (6H, m), 1.95 (s) } 3H, 11.72 (s) } 1H
2.12 (s) }

(3) 6-(5-Methyl-3-methylthio-1,2,4-triazin-6-yl)-1-methyl-3,4-dihydro-1H-2,1-benzothiazine 2,2-dioxide (1.20 g) was obtained from the reaction product of Example 19-(2) (2.10 g) according to a similar manner to that of Example 4-(3).

mp : 162 to 164°C (recrystallized from ethyl acetate)

IR (Nujol) : 1345, 1160 cm⁻¹

NMR (DMSO-d₆, δ) : 2.50 (3H, s), 2.62 (3H, s),
3.27 (3H, s), 3.45-3.70 (4H, m), 7.20 (1H,
d, J=8Hz), 7.57 (1H, d, J=2Hz), 7.62 (1H,
dd, J=2Hz, 8Hz)

(4) 6-(5-Methyl-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-1-methyl-3,4-dihydro-1H-2,1-benzothiazine 2,2-dioxide (1.40 g) was obtained from the reaction product of Example 19-(3) (1.60 g) according to a similar manner to that of Example 4-(4).

mp : 291 to 293°C (recrystallized from a mixture of ethanol and N,N-dimethylformamide)

IR (Nujol) : 3225, 3075, 1700, 1350, 1165, 1130 cm⁻¹

NMR (DMSO-d₆, δ) : 1.23 (3H, d, J=7Hz), 3.24 (3H, s),
3.27-3.64 (4H, m), 4.54-4.77 (1H, m), 7.12 (1H,
d, J=9Hz), 7.43 (1H, br s), 7.61 (1H, br s),
7.64 (1H, d, J=9Hz), 9.96 (1H, d, J=2Hz)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 2-84184

EDICTO No. 6188

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

839

Que esta Superintendencia profirió Resolución No. 7874 de 23-MAR-2007. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud

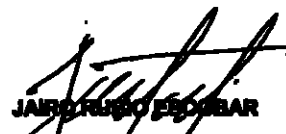
correspondiente a "COMPUESTOS QUE CONTIENEN BENZAMIDO-PIPERIDINÁ Y COMPUESTOS RELACIONADOS ", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos Reinaldo Ojarte García, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 23 MAR 2007

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIME RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaría General Ad-Hoc 10-ABR-2007
Secretaría General Ad-Hoc
EDICTO No. 6188

Este edicto se desfija hoy 23-ABR-2007 a las 4:30 p.m.