

Señor

SUPERINTENDENTE DE INDUSTRIA Y
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03078835 00000002 Folios: 10
Fecha (AMD): 2004-10-14 16:26:25
Tramite : 011 PCT-PATENT 379 FASE NACI 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

262

Re: P1.-**ABBOTT LABORATORIES**.-Solicitud de Patente de
Invención Fase Nacional PCT para "**BENCIMIDAZOLES
UTILES EN EL TRATAMIENTO DE LA DISFUNCION
SEXUAL**".-Clase **C07D 235/06**.-Expediente número
03-078.835.-

1. Me refiero a mi memorial de 31 de Agosto de 2004 por medio del cual se presentó copia auténtica del documento que acredita mi calidad de Representante Legal de la sociedad peticionaria.
2. Anexo me permito presentar a usted documento completo del Reporte de Examen Preliminar Internacional, expedido el 3 de Septiembre de 2004 correspondiente a la solicitud internacional número PCT/US02/07791, actualmente en trámite de Fase Nacional en ese Despacho, bajo el número de la referencia.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


ALICIA LLORED A RICAURTE

T.P. 53.215

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

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(PCT Artículo 36 y Regla 70)

Registro de referencia del solicitante o agente 6789.PC.O1	PARA FUTURAS ACCIONES Ver Notificación de Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416)	
Solicitud Internacional No. PCT/US02/07791	Fecha de registro internacional (día/mes/año) 6 de Marzo de 2002 (06.03.2002)	Fecha de prioridad (día/mes/año) 9 de Marzo de 2001 (09.03.2001)
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC IPC(7): A61K 31/415 y US CL.: 514/394		
Solicitante ABBOTT LABORATORIES		
1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y es transmitido al solicitante de conformidad con el Artículo 36. 2. Este REPORTE consta de un total de <u>3</u> hojas, incluyendo esta carátula. ☐ Este reporte también está acompañado por ANEXOS, es decir, hojas de la descripción, reivindicaciones y/o dibujos los cuales han sido modificados y son la base para este reporte y/o hojas que contienen rectificaciones hechas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas de conformidad con el PCT). Estos anexos constan de un total de <u> </u> hojas.		
3. Este reporte contiene indicaciones relacionadas con los siguientes ítems: - I ☒ Bases del reporte - II ☐ Prioridad - III ☐ No establecimiento de opinión respecto a novedad, nivel inventivo y aplicabilidad Industrial - IV ☐ Falta de unidad de invención - V ☒ Afirmación razonada de conformidad con el Artículo 35(2) con respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación - VI ☐ Ciertos documentos citados - VII ☐ Ciertos defectos en la solicitud internacional - VIII ☐ Ciertas observaciones sobre la solicitud internacional		
Fecha de presentación de la demanda 20 de Septiembre de 2002 (20.09.2002)	Fecha de terminación de este reporte 3 de Septiembre de 2004 (03.09.2004)	
Nombre y dirección de correo de la IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Fax No. (703) 305-3230	Funcionario autorizado Sreeni Padmanabhan, PhD., Teléfono No. 571-272-1600	

I. Bases del reporte

1. Respecto a los elementos de la solicitud internacional:*

☒ la solicitud internacional según se presentó originalmente

☒ la descripción:

páginas 1-75 , como originalmente se presentaron

páginas NINGUNA , presentadas con la demanda

páginas NINGUNA , presentadas con la carta de

☒ las reivindicaciones:

páginas 76-110 , como originalmente se presentaron

páginas NINGUNA , según se enmendaron (junto con cualquier declaración) de conformidad con el artículo 19

páginas NINGUNA , presentadas con la demanda

páginas NINGUNA , presentadas con la carta de

☒ los dibujos:

páginas NINGUNA , como originalmente se presentaron

páginas NINGUNA , presentadas con la demanda

páginas NINGUNA , presentadas con la carta de

☐ el listado de secuencia parte de la descripción:

páginas NINGUNA , como originalmente se presentaron

páginas NINGUNA , presentadas con la demanda

páginas NINGUNA , presentadas con la carta de

2. Respecto al idioma, todos los elementos marcados anteriormente estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma en el cual la solicitud internacional fue presentada, a menos que se indique lo contrario bajo este ítem.

Estos elementos estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma el cual es:

☐ el idioma de una traducción suministrada para una búsqueda internacional (según la Regla 23.1 (b)).

☐ el idioma de una publicación de la solicitud internacional (según la Regla 48.3 (b)).

☐ el idioma de la traducción suministrada para el examen preliminar internacional (según las Reglas 55.2 y/o 55.3).

3. Respecto al nucleótido y/o secuencia amino ácida revelado en la solicitud internacional, se llevó a cabo el examen preliminar internacional según el listado de secuencia:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentada junto con la solicitud internacional en forma legible por computador.

☐ proporcionado subsiguientemente a esta Autoridad en forma escrita.

☐ proporcionado subsiguientemente a esta Autoridad en forma legible por computador.

☐ Se ha proporcionado la afirmación respecto a la cual el listado de secuencia escrito proporcionado subsiguientemente no va más allá de la revelación en la solicitud internacional según se registró.

☐ Se ha proporcionado la afirmación respecto a la cual la información registrada en forma legible por computador es idéntica al listado de secuencia escrita.

4. ☒ Las modificaciones han resultado en la cancelación de:

☒ la descripción, páginas NINGUNA

☒ las reivindicaciones, Nos. NINGUNO

☒ los dibujos, hojas/fig— NINGUNA

5. ☐ Este reporte ha sido establecido como si (algunas de) las modificaciones no se hubiesen hecho, ya que se ha considerado que van más allá de la revelación según se registró, como se indicó en Casilla Suplementaria (Regla 70.2 (c)).**

* Las hojas de remplazo que han sido proporcionadas a la Oficina que recibe en respuesta a una invitación según el Artículo 14 a las que se hace referencia en este reporte como "presentadas originalmente" y se anexan a este reporte ya que no contienen enmiendas (Reglas 70.16 y 70.17).

** Cualquier hoja de remplazo que contenga dichas modificaciones debe hacerse referencia bajo el ítem I y anexarse a este reporte.

V. Afirmación razonada bajo la Regla 66.2(a)(ii) con respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones que sustentan dicha afirmación

1. AFIRMACIÓN

Novedad (N)	Reivindicaciones	1-70 y 84-89	SI
	Reivindicaciones	71-83 y 90-112	NO
Nivel Inventivo (IS)	Reivindicaciones	1-70	SI
	Reivindicaciones	71-112	NO
Aplicabilidad Industrial (IA)	Reivindicaciones	1-112	SI
	Reivindicaciones	NINGUNA	NO

2. CITACIONES Y EXPLICACIONES

Las reivindicaciones 71-77 y 90-112 carecen de novedad bajo el Artículo 33(2) PCT previsto por WO94/22839 ('839).

El '839 muestra aquí los compuestos reivindicados (ver páginas 8-10), los compuestos de la Fórmula (IIA) y (IIB)). El '839 también muestra que los compuestos de la Fórmula (IIA) y (IIB) son útiles para tratar condiciones psicóticas tales como la esquizofrenia (Ver resumen).

Las reivindicaciones 78-83 carecen de novedad bajo el Artículo PCT 33(2) previsto por la Patente US 3,472.854 ('854).

El '854 muestra los compuestos aquí reivindicados como útiles para que actúen como agentes cardiovasculares, agentes hipotensores, y sedantes (Ver col. 1, líneas 15-20).

Las reivindicaciones 84-89 carecen de nivel inventivo bajo el Artículo 33(3) PCT por ser obvio sobre el '854. El '854 muestra los compuestos aquí reivindicados como útiles para que actúen como agentes cardiovasculares, agentes hipotensores y sedantes.

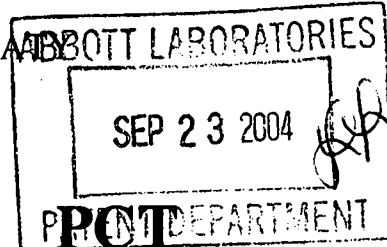
El '854 expresamente no muestra los agentes como útiles para tratar condiciones inflamatorias. Sería obvio para una persona versada en la materia en el momento que la invención fuera realizada emplear los agentes aquí reivindicados en un método de tratamiento de desórdenes inflamatorios. La inflamación tal como la artritis puede causar dolor crónico. Algunas veces los pacientes artríticos sufrirán de insomnio. El empleo de los agentes aquí reivindicados para pacientes artríticos los ayudaría a dormir dado que los agentes aquí reivindicados son sedantes.

Las reivindicaciones 1-112 cumplen el criterio especificado en el Artículo 33(4) PCT y por lo tanto provee aplicabilidad industrial porque la materia objeto reivindicada puede hacerse o usarse en la industria.

----- NUEVAS CITACIONES -----

US 3,472,854 A (ARCHER) 14 de Octubre de 1969, col. 1, líneas 14-20 y col. 8, Tabla 1.

PATENT COOPERATION TREATY



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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
MICHAEL J. WARD
ABBOTT LABORATORIES
DEPT. 377, AP6D
100 ABBOTT PARK ROAD
ABBOTT PARK, IL 60064-6050

GEJ

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

Applicant's or agent's file reference

6789.PC.O1

IMPORTANT NOTIFICATION

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US02/07791

06 March 2002 (06.03.2002)

09 March 2001 (09.03.2001)

Applicant

ABBOTT LABORATORIES

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Mail Stop PCT, Attn: IPEA/US
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P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Sreeni Padmanabhan, PhD.,

Telephone No. 571-272-1600

Form PCT/IPEA/416 (July 1992)

KW
10/1

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

267

To:
MICHAEL J. WARD
ABBOTT LABORATORIES
DEPT. 377, AP6D
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ABBOTT PARK, IL 60064-6050

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

20 SEP 2004

Applicant's or agent's file reference

6789.PC.O1

IMPORTANT NOTIFICATION

International application No.

PCT/US02/07791

International filing date (day/month/year)

06 March 2002 (06.03.2002)

Priority date (day/month/year)

09 March 2001 (09.03.2001)

Applicant

ABBOTT LABORATORIES

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2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
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For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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Facsimile No. (703) 305-3230

Authorized officer

Sreeni Padmanabhan, PhD.,

Telephone No. 571-272-1600

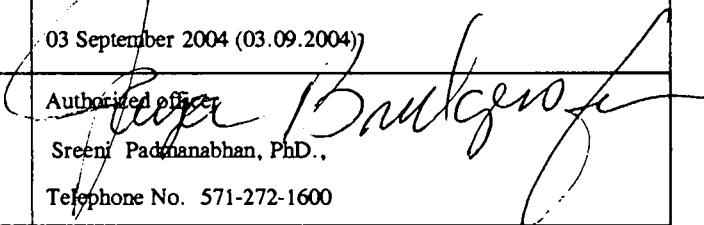
PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 6789.PC.O1	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US02/07791	International filing date (day/month/year) 06 March 2002 (06.03.2002)	Priority date (day/month/year) 09 March 2001 (09.03.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/415 and US Cl.: 514/394		
Applicant ABBOTT LABORATORIES		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u> </u> sheets. 3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 20 September 2002 (20.09.2002)	Date of completion of this report 03 September 2004 (03.09.2004)	
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer  Sreeni Padmanabhan, PhD., Telephone No. 571-272-1600	

Form PCT/IPEA/409 (cover sheet)(July 1998)

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I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-75 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☒ the claims:
pages 76-110 as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☒ the drawings:
pages None as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☐ the sequence listing part of the description:
pages NONE as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages None
- ☒ the claims, Nos. None
- ☒ the drawings, sheets/fig None

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims 1-70 and 84-89	YES
	Claims 71-83 and 90-112	NO
Inventive Step (IS)	Claims 1-70	YES
	Claims 71-112	NO
Industrial Applicability (IA)	Claims 1-112	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 71-77 and 90-112 lack novelty under PCT Article 33(2) as being anticipated by WO94/22839 ('839).

'839 teaches the herein claimed compounds (see pages 8-10, compounds of Formula (IIA) and (IIB)). '839 also teaches that the compounds of Formula (IIA) and (IIB) are useful to treat psychotic conditions such as schizophrenia (See the abstract).

Claims 78-83 lack novelty under PCT Article 33(2) as being anticipated by US Patent 3,472,854 ('854).

'854 teaches the herein claimed compounds as useful to act as cardiovascular agents, hypotensive agents, and sedatives (See col. 1, lines 15-20).

Claims 84-89 lack an inventive step under PCT Article 33(3) as being obvious over '854. '854 teaches the herein claimed compounds as useful to act as cardiovascular agents, hypotensive agents, and sedatives.

'854 does not expressly teach the agents as useful to treat inflammatory conditions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed agents in a method of treating inflammatory disorders.

One of ordinary skill in the art would have been motivated to employ the herein claimed agents in a method of treating inflammatory disorders. Inflammation such as arthritis can cause chronic pain. Sometimes arthritic patients will get insomnia. Employing the herein claimed agents to arthritic patients would help them sleep since the herein claimed compounds are sedatives.

Claims 1-112 meet the criteria set out in PCT Article 33(4), and thus provide industrial applicability because the subject matter claimed can be made or used in industry.

----- NEW CITATIONS -----

US 3,472,854 A (ARCHER) 14 October 1969, col. 1, lines 14-20, and col. 8, Table 1.

PATENT COOPERATION TREATY

PCT

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NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No. PCT/US02/07791	Applicant's or agent's file reference 6789.PC.O1	Date of informal communication (day/month/year) 03 September 2004 (03.09.2004)
Applicant ABBOTT LABORATORIES		

<u>Communication</u> ☐ by telephone ☐ personal	<u>Participants</u> ☒ Applicant: ABBOTT LABORATORIES ☒ Agent: Mr. Micheal Ward ☒ Examiner(s): Ms. Jean Vollano	☐ Identity checked	☐ authorization checked	☐ personally known
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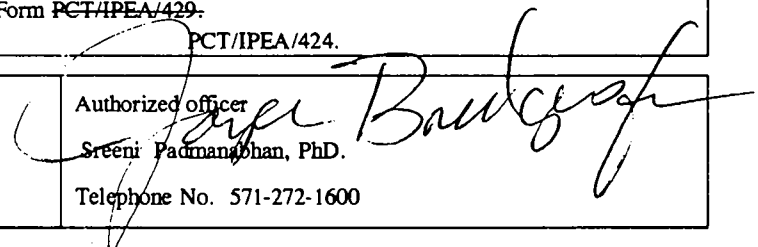
Summary of communication:

Upon request by the examiner, applicant's representative Mr. Ward agreed to proceed to the 409 IPER in order to meet the administrative deadlines for the instant application.

☐ An extension of time limit is granted (Form PCT/IPEA/427).

☐ A copy of this note is being sent to the applicant with Form PCT/IPEA/429.

PCT/IPEA/424.

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer  Sreeni Padmanabhan, PhD. Telephone No. 571-272-1600
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Form PCT/IPEA/428 (July 1992)



(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

272

(43) Date of publication:
09.12.1998 Bulletin 1998/50

(21) Application number: 96943331.7

(22) Date of filing: 27.12.1996

(51) Int. Cl.⁶: **C07D 235/08**, C07D 235/10,
C07D 235/22, C07D 235/24,
C07D 235/26, C07D 235/28,
C07D 235/30, C07D 401/06,
C07D 401/12, C07D 405/06,
C07D 417/14

(86) International application number:
PCT/JP96/03858

(87) International publication number:
WO 97/24334 (10.07.1997 Gazette 1997/30)

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

(30) Priority: 28.12.1995 JP 343425/95
08.10.1996 JP 287676/96

(71) Applicant:
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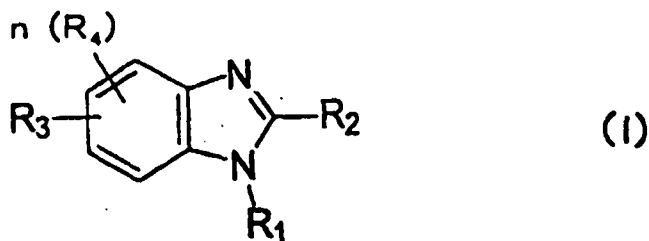
(72) Inventors:
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Hyogo 672-8071 (JP)

- **IMOTO, Takafumi**
Ibaraki 305 (JP)
- **MURAI, Yoshiyuki**
Ibaraki 305 (JP)
- **HIRAMURA, Takahiro**
Ibaraki 305 (JP)
- **OKU, Teruo**
Ibaraki 305 (JP)
- **SAWADA, Kouzou**
Ibaraki 305 (JP)

(74) Representative:
VOSSIUS & PARTNER
Siebertstrasse 4
81675 München (DE)

(54) **BENZIMIDAZOLE DERIVATIVES**

(57) Novel benzimidazole derivatives represented by the formula (I):



wherein R₃ is a carboxyl group, a esterified carboxyl group, an amidated carboxyl group, an amino group, an amido group, or a sulfonyl group, or their pharmaceutically acceptable salts. Because of their blood sugar-depressing effect or PDE5 inhibitory effect, these compounds or salts thereof are useful as medicines for treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia, or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy, tubulointerstitial disorders, renal failure, atherosclerosis, angiostenosis, distal angiopathy, cerebral apoplexy, chronic reversible obstructions, allergic rhinitis, urticaria, glaucoma, diseases characterized by entero-

Table 2

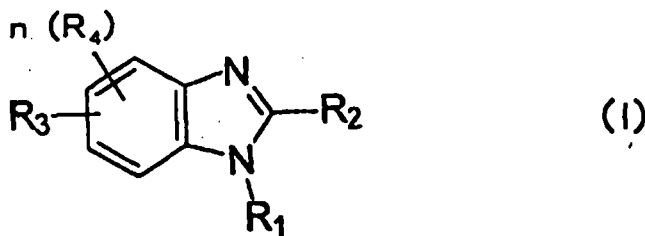
Compound No.	Dose (mg/kg)	Activity of decreasing plasma glucose (%)
(177)	30	34.5
(163)	30	72
(172)	10	70 - 80

INDUSTRIAL APPLICABILITY

Herein provided are novel benzimidazole derivatives and their pharmaceutically acceptable salts. These compounds and their salts have blood sugar level-depressing activity or PDE5-inhibiting activity, and are useful for preventing and treating impaired glucose tolerance, diabetes (type II diabetes), diabetic complications such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy, syndrome of insulin resistance (e.g., insulin receptor disorders, Rabson-Mendenhall syndrome, leprechaunism, Kobblerling-Dunnigan syndrome, Seip syndrome, Lawrence syndrome, Cushing syndrome, acromegaly, etc.), hyperlipidemia, atherosclerosis, cardiovascular disorders (e.g., stenocardia, cardiac failure, etc.), hyperglycemia (e.g., abnormal saccharometabolism such as feeding disorders, etc.), or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy (e.g., diabetic glomerulosclerosis, etc.), tubulointerstitial disorders (e.g., renopathy induced by FK506, cyclosporin, etc.), renal failure, atherosclerosis, angiostenosis (e.g., after percutaneous arterioplasty), distal angiopathy, cerebral apoplexy, chronic reversible obstructions (e.g., bronchitis, asthma (chronic asthma, allergic asthma), etc.), allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders (e.g., hypersensitive enteropathy syndrome, etc.), impotence (e.g., organic impotence, psychic impotence, etc.), and diabetic complications (e.g., diabetic gangrene, diabetic arthropathy, diabetic glomerulosclerosis, diabetic dermatopathy, diabetic neuropathy, diabetic cataract, diabetic retinopathy, etc.), nephritis, cancerous cachexia, or restenosis after PTCA.

Claims

1. A pharmaceutical composition for preventing and treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy, tubulointerstitial disorders, renal failure, atherosclerosis, angiostenosis, distal angiopathy, cerebral apoplexy, chronic reversible obstructions, allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders, impotence, diabetic complications, nephritis, cancerous cachexia, or restenosis after PTCA, which comprises, as an active ingredient, a compound of the following formula or its pharmaceutically acceptable salt:



wherein R_1 represents a hydrogen atom, an arylsulfonyl group, or a lower alkyl group; said lower alkyl group may be substituted by an aryl group or an aryl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, an aryl-lower alkyl group, an aryl-lower alkoxy group, a haloaryl-lower alkoxy group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, a cyanoaryl group,

and a heterocyclic group, or by a heterocyclic group;

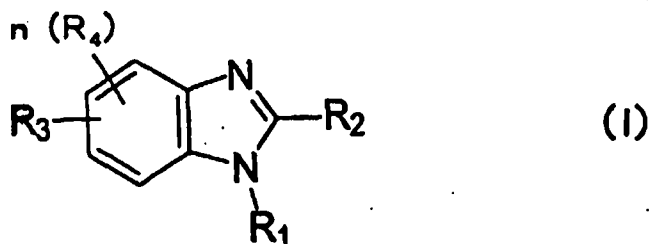
R_2 represents a hydrogen atom, a lower cycloalkyl group, a hydroxyl group, a lower alkoxy group, a mercapto group, a lower alkylthio group, an amino group, a lower alkylamino group, a carboxyl group, an aryl group, or a lower alkyl group; said lower alkyl group may be substituted by a halogen atom, a lower alkoxy group, a cyano group, a chlorocarbonyl group, an aryl group, or a heterocyclic group;

R_3 represents a carboxyl group, an esterified carboxyl group, an amidated carboxyl group, an amino group, an amido group, or a sulfonyl group; said amino group and said amido group may be substituted by an acyl group or a sulfonyl group; and a halogen atom, an amino group, or an acylamino group is bonded to said sulfonyl group; or R_3 may be bonded to the skeleton via a lower alkylene or alkenylene group;

R_4 represents a neutral substituent; and

n means an integer from 0 to 3.

2. Use of a compound of the following formula or its pharmaceutically acceptable salt for preparing a pharmaceutical composition for preventing and treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy, tubulointerstitial disorders, renal failure, atherosclerosis, angiostenosis, distal angiopathy, cerebral apoplexy, chronic reversible obstructions, allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders, impotence, diabetic complications, nephritis, cancerous cachexia, or restenosis after PTCA:



wherein R_1 represents a hydrogen atom, an arylsulfonyl group, or a lower alkyl group; said lower alkyl group may be substituted by an aryl group or an aryl group substituted by one or two substituents selected from a halogen atom, a haloaryl group, a lower alkyl group, a halo-lower alkyl group, a lower alkoxy group, a nitro group, an amino group, a cyano group, an aryl group, an aryl-lower alkyl group, an aryl-lower alkyloxy group, a haloaryl-lower alkyloxy group, an arylsulfonyl-lower alkyl group, an arylsulfonylamino group, a cyanoaryl group, and a heterocyclic group, or by a heterocyclic group;

R_2 represents a hydrogen atom, a lower cycloalkyl group, a hydroxyl group, a lower alkoxy group, a mercapto group, a lower alkylthio group, an amino group, a lower alkylamino group, a carboxyl group, an aryl group, or a lower alkyl group; said lower alkyl group may be substituted by a halogen atom, a lower alkoxy group, a cyano group, a chlorocarbonyl group, an aryl group, or a heterocyclic group;

R_3 represents a carboxyl group, an esterified carboxyl group, an amidated carboxyl group, an amino group, an amido group, or a sulfonyl group; said amino group and said amido group may be substituted by an acyl group or a sulfonyl group; and a halogen atom, an amino group, or an acylamino group is bonded to said sulfonyl group; or R_3 may be bonded to the skeleton via a lower alkylene or alkenylene group;

R_4 represents a neutral substituent; and

n means an integer from 0 to 3.

3. A method for preventing or treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia or hypertension; or stenocardia, hypertension, pulmonary hypertension, congestive heart failure, glomerulopathy, tubulointerstitial disorders, renal failure, atherosclerosis, angiostenosis, distal angiopathy, cerebral apoplexy, chronic reversible obstructions, allergic rhinitis, urticaria, glaucoma, diseases characterized by enteromotility disorders, impotence, diabetic complications, nephritis, cancerous cachexia, or restenosis after PTCA, which comprises administering a compound of the following formula or its pharmaceutically acceptable salt:

1

3,472,854

1-[(BENZIMIDAZOLYL)-LOWER-ALKYL]-4-SUBSTITUTED-PIPERAZINES

Sydney Archer, Bethlehem, N.Y., assignor to Sterling Drug Inc., New York, N.Y., a corporation of Delaware
No Drawing. Continuation-in-part of application Ser. No. 481,075, Aug. 19, 1965, which is a continuation-in-part of application Ser. No. 254,475, Jan. 28, 1963. This application May 29, 1967, Ser. No. 642,171
Int. Cl. C07d 57/00; A61k 27/00
U.S. Cl. 260—268

6 Claims

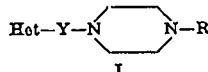
ABSTRACT OF THE DISCLOSURE

New 1-[(benzimidazolyl)-lower-alkyl]-4-substituted-piperazines indicated to be useful as tranquilizers, sedatives, skeletal muscle relaxants, adrenolytics, hypothermic agents, anti-convulsants, hypotensives, and cardiovascular agents.

This application is a continuation-in-part of my copending application Ser. No. 481,075, filed Aug. 19, 1965, now U.S. Patent 3,362,956, patented Jan. 9, 1968, which in turn is a continuation-in-part of my prior application Ser. No. 254,475, filed Jan. 28, 1963, and now abandoned.

This invention relates to certain 1-[(benzimidazolyl)-lower-alkyl]-4-substituted-piperazines, their acid-addition and quaternary ammonium salts, and to intermediates and processes therefor.

The compounds of the invention are represented by the general formula:



wherein R is hydrogen or a lower-alkyl, hydroxy-lower-alkyl, phenyl, phenyl-lower-alkyl, benzhydryl, phenyl-lower-alkenyl, cycloalkyl-lower-alkyl, or pyridyl radical; Y is lower-alkylene of from one to six carbon atoms; and Het is a 1- or 2-benzimidazolyl radical.

In the above general Formula I, when R represents a lower-alkyl radical, it can be straight or branched and can contain from one to about six carbon atoms and thus stands, inter alia, for methyl, ethyl, isobutyl, n-hexyl, and the like.

When R represents a hydroxy-lower-alkyl radical, it can be straight or branched, can contain from two to six carbon atoms and is such that the oxygen atom of the hydroxy-lower-alkyl group and the nitrogen atom of the piperazine ring are separated by at least two carbon atoms. R thus also stands, inter alia, for 2-hydroxyethyl, 3-hydroxy-1-methylpropyl, 6-hydroxyhexyl, and the like.

When R represents cycloalkyl-lower-alkyl, the cycloalkyl moiety contains from three to seven ring carbon atoms, while the lower-alkyl moiety contains from one to four carbon atoms. R thus also stands for cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cycloheptylmethyl, 2-cyclohexylethyl, and the like.

When R represents phenyl, phenyl-lower-alkyl, benzhydryl, or phenyl-lower-alkenyl, the benzene ring of said radicals can be unsubstituted or can bear one or more substituents of low molecular weight and of such nature that they do not interfere with or take part in the reactions, to be described hereinafter, used in the preparation of the compounds. Moreover, the nucleus of the group, Het, can also be further substituted by one or more of such substituents. Examples of such substituents include halogen (including fluorine, chlorine, bromine, and iodine), lower-alkyl, hydroxy, lower-alkoxy, methylenedioxy, ethylenedioxy, lower-alkylmercapto, lower-alkylsul-

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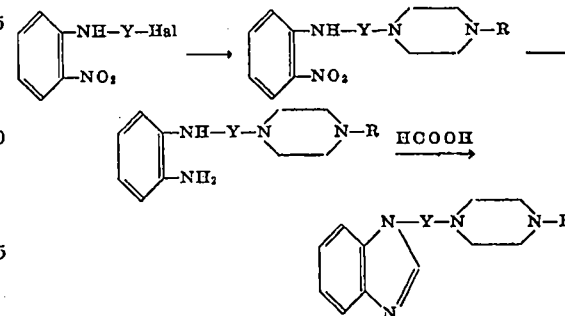
finyl, lower-alkylsulfonyl, nitro, lower-alkanoyl, sulfamyl, trifluoromethyl, and the like.

When R represents a phenyl-lower-alkyl radical, the lower-alkyl moiety of said radical can contain from one to four carbon atoms, and when R represents a phenyl-lower-alkenyl radical, the lower-alkenyl moiety of said radical can contain from three to four carbon atoms. Thus R represents, inter alia, phenyl, benzyl, phenethyl, 4-phenylbutyl, benzhydryl, or cinnamyl, or such radicals substituted in the benzene ring by one or more substituents of the nature described above.

In the above general Formula I, the group Y represents lower-alkylene of from one to six carbon atoms, can be straight or branched, and when the group Y is attached to a nitrogen atom of the heterocyclic group, Het, is such that at least two carbon atoms separate the nitrogen atoms of the heterocyclic group and the piperazine ring. The lower-alkylene group, Y, thus stands, inter alia, for methylene, 1,2-ethylene, 1,3-propylene, 2-methyl-1,4-butylene, 1,6-hexylene, and the like.

The compounds of Formula I can also be substituted on the carbon atoms of the piperazine ring by one or more lower-alkyl radicals each containing from one to four carbon atoms.

The compounds of Formula I where Het is a 1-benzimidazolyl radical are prepared by reacting a 2-nitro-N-(halo-lower-alkyl)aniline with a 1-substituted-piperazine. The reaction is preferably carried out at a temperature in the range from about 50° C. to about 175° C. in the presence of an acid-acceptor, the purpose of which is to take up the hydrogen halide split out during the course of the reaction. The acid-acceptor is a basic substance which forms preferably water-soluble by-products easily separable from the main product of the reaction and includes such substances as alkali metal salts of weak acids, e.g. sodium carbonate, sodium acetate, sodium alkoxides, and the like. The acid-acceptor can also be in the form of an excess quantity of the 1-substituted-piperazine. The nitro group of the resulting 1-[(2-nitrophenylamino)-lower-alkyl]-4-substituted-piperazine derivative is reduced with hydrogen over a suitable catalyst, for example palladium-on-charcoal or Raney nickel, in an organic solvent inert under the conditions of the reaction, for example a lower-alkanol, to give the corresponding 1-[(2-amino-phenylamino)-lower-alkyl]-4-substituted-piperazine derivative. Reaction of the latter with formic acid affords the compounds of Formula I where Het is a 1-benzimidazolyl radical. The latter reaction is preferably carried out using excess formic acid as the solvent at the reflux temperature of the medium. The procedure is illustrated by the following reaction sequence where R and Y have the meanings given above, and Hal represents halogen.

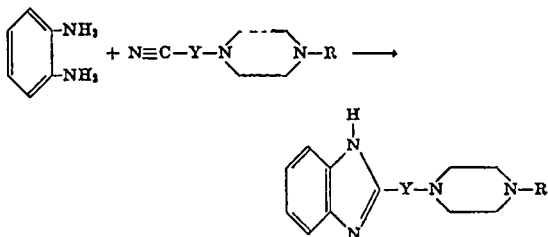


The 2-nitro-N-(halo-lower-alkyl)anilines required as starting materials are prepared by reacting a 2-halo-nitrobenzene with an amino-lower-alkanol to give a 2-nitro-N-

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(hydroxy-lower-alkyl)aniline which is then reacted with a halogenating agent, for example a thionyl halide, to give the desired 2-nitro-N-(halo-lower-alkyl)aniline.

The compounds of Formula I where Hct is a 2-benzimidazolyl radical are prepared by reacting a 1-(cyano-lower-alkyl)-4-substituted-piperazine with an o-phenylenediamine in the presence of a lower-alkanol and anhydrous hydrogen chloride. The reaction is preferably carried out in an organic solvent inert under the conditions of the reaction, for example chloroform, ethylene dichloride, benzene, and the like. The procedure is illustrated by the following reaction sequence where R and Y have the meanings given above:



The 1-(cyano-lower-alkyl)-4-substituted-piperazines required as starting materials are prepared by reacting a 1-substituted-piperazine with a halo-lower-alkyl-nitrile preferably in the presence of an acid-acceptor. The nitriles where Y is 1,2-ethylene are conveniently prepared by reacting a 1-substituted-piperazine with acrylonitrile.

The novel compounds of the instant invention are the bases of Formula I and the acid-addition and quaternary ammonium salts of said bases, and said acid-addition and quaternary ammonium salts are considered to be the full equivalents of the free bases. The compounds of the invention in free base form are converted to the acid-addition salt form by interaction of the base with an acid. In like manner, the free bases can be regenerated from the acid-addition salt form in the conventional manner, that is, by treating the salts with strong aqueous bases, for example alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates. The bases thus regenerated can then be interacted with the same or a different acid to give back the same or a different acid-addition salt. Thus the novel bases and all of their acid-addition salts are readily interconvertible.

The quaternary ammonium salts are obtained by the addition of esters of strong acids to the free base form of the compounds, said esters having a molecular weight less than about 200. A preferred class of esters comprises alkyl, alkenyl, and monocarbocyclic aryl-lower-alkyl esters of strong inorganic acids or organic sulfonic acids, including such compounds as methyl chloride, methyl bromide, methyl iodide, ethyl bromide, propyl chloride, allyl chloride, allyl bromide, methyl sulfate, methyl benzenesulfonate, methyl p-toluenesulfonate, benzyl chloride, benzyl bromide, and substituted benzyl halides, such as p-chlorobenzyl chloride, p-nitrobenzyl chloride, p-methoxybenzyl chloride, o-chlorobenzyl chloride, and the like.

The quaternary ammonium salts are prepared by mixing the free base and ester of a strong acid in an inert solvent. Heating may be used to facilitate the reaction, although salt formation usually takes place readily at room temperature. The quaternary ammonium salt separates directly or can be obtained by concentration of the solution.

It is also possible to convert one quaternary ammonium salt to another in which the anion is different. If the anion of the original quaternary salt forms a water-insoluble silver salt the quaternary salt will react with silver oxide in aqueous medium to form the corresponding quaternary ammonium hydroxide, the original anion being removed as a precipitate. The quaternary ammonium hydroxide solution can then be neutralized with any desired acid,

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weak or strong, to produce a new quaternary ammonium salt in which the anion is different from that of the original salt. In this way quaternary ammonium salts in which the anion is derived from a weak acid can be prepared.

It will thus be appreciated that Formula I not only represents the structural configuration of the bases of my invention but is also representative of the respective structural entity which is common to all of my respective compounds, whether in the form of the free bases or in the form of the acid-addition salts of the bases. I have found that by virtue of this common structural entity, the bases and their acid-addition salts have inherent pharmacodynamic activity of a type to be more fully described hereinbelow. This inherent pharmacodynamic activity can be enjoyed in useful form for pharmaceutical purposes by employing the free bases themselves or the acid-addition salts formed from pharmaceutically-acceptable acids, that is, acids whose anions are innocuous to the animal organism in effective doses of the salts so that beneficial properties inherent in the common structural entity represented by the free bases are not vitiated by side-effects ascribable to the anions.

In utilizing this pharmacodynamic activity of the salts of the invention, I prefer of course to use pharmaceutically-acceptable salts. Although water-insolubility, high toxicity, or lack of crystalline character may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water-insoluble or toxic salts can be converted to the corresponding pharmaceutically-acceptable bases by decomposition of the salt with aqueous base as described above, or alternatively they can be converted to any desired pharmaceutically-acceptable acid-addition salt by double decomposition reactions involving the anion, for example by ion-exchange procedures.

Moreover, apart from their usefulness in pharmaceutical applications, my salts are useful as characterizing or identifying derivatives of the free bases or in isolation or purification procedures. Like all of the acid-addition salts, such characterizing or purification salt derivatives can, if desired, be used to regenerate the pharmaceutically-acceptable free bases by reaction of the salts with aqueous base, or alternatively can be converted to a pharmaceutically-acceptable acid-addition salt by, for example, ion-exchange procedures.

It will be appreciated from the foregoing that all of the acid-addition and quaternary ammonium salts of my new bases are useful and valuable compounds, regardless of considerations of solubility, toxicity, physical form, and the like, and are accordingly within the purview of the instant invention.

The novel feature of the compounds of the invention, then, resides in the concept of the bases and cationic forms of the new 1-[(benzimidazolyl)-lower-alkyl]-4-substituted-piperazines and not in any particular acid or quaternary moiety or acid anion associated with the salt forms of my compounds; rather, the acid or quaternary moieties or anions which can be associated in the salt forms are in themselves neither novel nor critical and therefore can be any acid anion or acid-like substance capable of salt formation with bases. In fact in aqueous solutions, the base form or water-soluble acid-addition salt form of the compounds of the invention both possess a common protonated cation or ammonium ion.

Thus the acid-addition salts discussed above and claimed herein are prepared from any organic acid, inorganic acid (including organic acids having an inorganic group therein), or organo-metallic acid, organic mono- and polysulfonic and sulfinic acids, organic phosphonic and phosphinic acids, organic acids of arsenic and antimony, organic heterocyclic carboxylic, sulfonic, and sulfinic acids, acidic ion-exchange resins, and inorganic acids of any acid forming element or combination of elements. In addition, other salt-forming compounds which are acidic in their chemical properties but which

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are not generally considered as acids in the same sense as carboxylic or sulfonic acids are also considered to be among the numerous acids which can be used to prepare acid-addition salts of the compounds of the invention. Thus there is also comprehended acidic phenolic compounds and acidic compounds having "activated" or acidic hydrogen atoms, as for example, picronic acid, or barbituric acid derivatives having an acidic proton. Also comprehended as salt forming agents are so-called Lewis acids which lack a pair of electrons in the outer "electron shell" and react with basic compounds having an unshared pair of electrons to form salts, for example boron trifluoride.

Thus appropriate acid-addition salts are those derived from such diverse acids as formic acid, acetic acid, isobutyric acid, alpha-mercaptopropionic acid, malic acid, fumaric acid, succinic acid, succinamic acid, tartaric acid, citric acid, lactic acid, benzoic acid, 4-methoxybenzoic acid, phthalic acid, anthranilic acid, 1-naphthalenecarboxylic acid, cinnamic acid, cyclohexanecarboxylic acid, mandelic acid, tropic acid, crotonic acid, acetylene dicarboxylic acid, sorbic acid, 2-furancarboxylic acid, cholic acid, pyrenecarboxylic acid, 2-pyridinecarboxylic acid, 3-indoleacetic acid, quinic acid, sulfamic acid, methanesulfonic acid, isethionic acid, benzenesulfonic acid, p-toluenesulfonic acid, p-aminophenylarsinic acid, phenylstibnic acid, phenylphosphinous acid, methylphosphonic acid, phenylphosphinic acid, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid, perchloric acid, nitric acid, sulfuric acid, phosphoric acid, hydrocyanic acid, phosphotungstic acid, molybdic acid, phosphomolybdic acid, pyrophosphoric acid, arsenic acid, picric acid, picronic acid, barbituric acid, boron trifluoride, and the like.

The acid-addition salts are prepared either by dissolving the free base in an aqueous solution containing the acid, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

Pharmacological evaluation of the compounds of Formula I has demonstrated that they possess a variety of depressant actions on the autonomic nervous system, the cardiovascular system, and the skeletal muscular system. They depress psychomotor activity as evidenced by studies in mice in standard activity cages; they possess sedative activity as shown by the potentiation of sleeping time in mice induced by ether, thiopental sodium or hexobarbital sodium. They show skeletal muscle relaxant activity in mice in the inclined screen test. When administered to rats, they show adrenolytic activity as evidenced by antagonism of the pressor effects of epinephrine; they lower the rectal temperature in mice; they possess anti-convulsant activity in mice as evidenced by their ability to protect mice from pentylenetetrazol-induced convulsions; they lower the blood pressure in rats; and they show cardiovascular activity in dogs as evidenced by the increase in heart force. These activities indicate their usefulness as tranquilizers, sedatives, skeletal muscle relaxants, adrenolytic agents, hypothermic agents, anti-convulsants, hypotensive agents and cardiovascular agents.

Thus in psychomotor depressant activity studies in mice using the method described by Dews, Brit. J. Pharmacol. 8, 46-48 (1953), 1-[2-(1-benzimidazolyl)ethyl]-4-(2-methoxyphenyl)-piperazine, described below in Example 1, was found to have an ED_{50} of 44.8 ± 12.0 mg./kg. on oral administration, and 1-[2-(1-benzimidazolyl)ethyl]-4-phenylpiperazine, described below in Example 2, was found to be active at 300 mg./kg. on oral administration.

In adrenolytic activity studies in rats using the procedure described by Luduena et al., Arch. int. Pharmacodyn. 122, 111-122 (1959), 1-[2-(1-benzimidazolyl)ethyl]-4-phenylpiperazine, described below in Example 2, was found to have an ED_{50} of 186 mcg./kg. on intravenous administration.

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The compounds can be prepared for use by dissolving under sterile conditions a salt form of the compounds in water (or an equivalent amount of a non-toxic acid if the free base is used), or in a physiologically compatible aqueous medium such as saline, and stored in ampoules for intramuscular injection. Alternatively, they can be incorporated in unit dosage form as tablets or capsules for oral administration or in combination with suitable adjuvants such as calcium carbonate, starch, lactose, talc, magnesium stearate, gum acacia, and the like. Still further the compounds can be formulated for oral administration in aqueous alcohol, glycol, or oil solution or oil-water emulsions in the same manner as conventional medicinal substances are prepared.

The chemical structures of the compounds of the invention are established by their mode of synthesis and are corroborated by the correspondence between calculated values for the elements and values found by chemical analysis.

The following examples will further illustrate specific embodiments of the invention without the latter being limited thereto.

EXAMPLE 1

1-[2-(1-benzimidazolyl)ethyl] - 4 - (2-methoxyphenyl) piperazine [I: Het is 1-benzimidazolyl; Y is CH_2CH_2 ; R is $2-CH_3OC_6H_4$]

A mixture of 5 g. (0.318 mole) of 2-chloronitrobenzene and 61 g. (1.0 mole) of ethanolamine was heated under reflux for five minutes in a 500 ml. flask equipped with a thermometer, reflux condenser, and a stirrer. The reaction mixture was then cooled to room temperature and poured into an ice-water mixture, and the precipitated solid was collected, dried and recrystallized from aqueous ethanol to give 37 g. of 2-nitro-N-(2-hydroxyethyl) aniline, M.P. $74-78^\circ C.$ (uncorr.).

Thirty-one grams of the above 2-nitro-N-(2-hydroxyethyl)aniline (0.17 mole) were suspended in 100 ml. of benzene, and the mixture was heated to the boiling point. To the warm solution was added dropwise over a period of about one hour 47 g. (0.4 mole) of thionyl chloride. When addition was complete, the solvent was removed under reduced pressure and the residual oil taken into ethanol and diluted with water. The solid which separated was collected, dried, and recrystallized from ethanol giving 26 g. of 2-nitro-N-(2-chloroethyl)aniline, M.P. $57-59^\circ C.$ (uncorr.).

The above 2-nitro-N-(2-chloroethyl)aniline (10.0 g., 0.05 mole) and 19.2 g. (0.1 mole) of 1-(2-methoxyphenyl)piperazine were warmed briefly to $145^\circ C.$ and the mixture allowed to cool. The partially solid reaction mixture was stirred with ice water, and the solid collected and recrystallized from ethanol giving 11.5 g. of 1-[2-(2-nitrophenylamino)ethyl]-4-(2-methoxyphenyl)piperazine, M.P. $116.5-119.5^\circ C.$ (uncorr.).

Eleven grams (0.031 mole) of the above 1-[2-(2-nitrophenylamino)ethyl]-4-(2-methoxyphenyl)piperazine were dissolved in 250 ml. of ethanol, and reduced over 10% palladium-on-charcoal under a hydrogen pressure of about 45 pounds p.s.i. When reduction was complete, the catalyst was removed by filtration and the solvent evaporated under reduced pressure. The residue was crystallized from boiling hexane giving 8.3 g. of 1-[2-(2-aminophenylamino)ethyl]-4 - (2 - methoxyphenyl)piperazine, M.P. $110-114^\circ C.$

Seven grams (0.02 mole) of the above 1-[2-(2-aminophenylamino)ethyl]-4-(2-methoxyphenyl)piperazine were refluxed for four and a half hours with 70 ml. of formic acid. The solvent was then removed in vacuo and the residual gum triturated with dilute sodium hydroxide. The supernatant was decanted and the gum taken into ethanol and diluted with a large volume of water. The gum which separated gradually solidified and was collected and recrystallized from ethyl acetate giving 2.2 g. of 1-[2-(1-

benzimidazolyl)ethyl]-4-(2-methoxyphenyl)piperazine, M.P. 121.5-122.6° C. (corr.).

1-[2-(1-benzimidazolyl)ethyl]-4-(2-methoxyphenyl)piperazine can be reacted with hydriodic acid to form 1-[2-(1-benzimidazolyl)ethyl]-4-(2-methoxyphenyl)piperazine hydriodide, useful as a characterizing intermediate.

1-[2-(1-benzimidazolyl)ethyl]-4-(2-methoxyphenyl)piperazine in the form of its hydriodide salt, can be converted to the hydrochloride salt by passing an aqueous solution of the former over an ion-exchange resin saturated with chloride ions.

1-[2-(1-benzimidazolyl)ethyl]-4-(2-methoxyphenyl)piperazine can be converted to its hydriodide salt and the latter recrystallized for purification purposes from an appropriate organic solvent. On suspension of the hydriodide in dilute aqueous sodium hydroxide, extraction of the suspension with chloroform, and removal of the chloroform from the extracts, 1-[2-(1-benzimidazolyl)ethyl]-4-(2-methoxyphenyl)piperazine can be recovered in purified free base form.

EXAMPLE 2

1-[2-(1-benzimidazolyl)ethyl]-4-phenylpiperazine
[I: Het is 1-benzimidazolyl; Y is CH₂CH₂; R is C₆H₅]

Twelve grams (0.06 mole) of 2-nitro-N-(2-chloroethyl)aniline and 19.5 g. (0.12 mole) of 1-phenylpiperazine were heated on a hot plate to 150° C. for five minutes, and the mixture allowed to cool to room temperature. The solid mass was broken up in cold water, filtered and recrystallized from ethanol giving 15.8 g. of 1-[2-(2-nitrophenylamino)ethyl]-4-phenylpiperazine, M.P. 114-116° C. (uncorr.).

The latter (3.3 g., 0.01 mole), dissolved in ethanol, was reduced with hydrogen over palladium oxide under a hydrogen pressure of about 36 pounds p.s.i. using the manipulative procedure described above in Example 1. The product was recrystallized from hexane giving 2.1 g. of 1-[2-(2-aminophenylamino)ethyl]-4-phenylpiperazine, M.P. 77.6-78.0° C. (corr.).

Eight grams (0.03 mole) of the above 1-[2-(2-aminophenylamino)ethyl]-4-phenylpiperazine were refluxed with 80 ml. of 98% formic acid using the manipulative procedure described above in Example 1. The crude product was recrystallized from ethyl acetate giving 5.5 g. of 1-[2-(1-benzimidazolyl)ethyl]-4-phenylpiperazine, M.P. 121-122.6° C.

EXAMPLE 3

1-[2-(2-benzimidazolyl)ethyl]-4-phenylpiperazine
[I: Het is 2-benzimidazolyl; Y is CH₂CH₂; R is C₆H₅]

Acrylonitrile (17.5 g., 0.33 mole) was added over a period of ninety minutes to 48.6 g. (0.3 mole) of 1-phenylpiperazine while maintaining the temperature below 35° C. The reaction mixture was stirred for one hour at 35° C., heated to boiling for one hour, and the excess acrylonitrile removed under reduced pressure. The residue, on cooling, solidified and was collected giving 63 g. of 1-(2-cyanoethyl)-4-phenylpiperazine, M.P. 66-69° C. (corr.).

The above 1-(2-cyanoethyl)-4-phenylpiperazine (21.5 g., 0.1 mole) was dissolved in 500 ml. of chloroform containing 5.9 ml. of absolute ethanol, and the solution saturated with anhydrous hydrogen chloride. The reaction mixture was taken to dryness under reduced pressure while maintaining the temperature below 20° C. The residual solid was dissolved in 500 ml. of tetrahydrofuran, and the mixture treated with 10.8 g. (0.08 mole) of *o*-phenylenediamine. The mixture was allowed to stand at room temperature for two hours, refluxed for one and a half hours, poured into water, and the mixture rendered alkaline with solid potassium hydroxide. On addition of ether, a solid separated which was collected and dried giving 35 g. of crude product. The latter was recrystallized

from ethanol giving 2 g. of 1-[2-(2-benzimidazolyl)ethyl]-4-phenylpiperazine, M.P. 200.5-202.9° C. (corr.).

EXAMPLES 4-26

By reacting 2-nitro-N-(2-chloroethyl)aniline with an appropriate 1-substituted-piperazine following the manipulative procedure described above in Example 1, there can be obtained the compounds of Formula I in Table 1 below where, in each instance, Het is 1-benzimidazolyl and Y is CH₂CH₂.

TABLE 1

Example	R	Piperazine substituent
4	CH ₃	
5	HOC ₂ H ₄ CH ₂	
6	4-ClC ₆ H ₄	2-CH ₃
7	3-CH ₃ C ₆ H ₄	
8	4-HOC ₆ H ₄	6-CH ₃
9	2-CH ₃ OC ₆ H ₄	
10	3,4-OC ₆ H ₃ OC ₆ H ₃	3-CH ₃
11	3,4-OC ₆ H ₃ CH ₂ OC ₆ H ₃	6-CH ₃
12	4-CH ₃ SC ₆ H ₄	2-n-C ₄ H ₉
13	4-CH ₃ SO ₂ C ₆ H ₄	3-CH(CH ₃) ₂
14	4-CH ₃ SO ₂ C ₆ H ₄	2,2-di-CH ₃
15	4-CF ₃ C ₆ H ₄	2,6-di-CH ₃
16	4-NO ₂ C ₆ H ₄	2-CH ₃
17	3-CH ₃ CO ₂ C ₆ H ₄	
18	4-NH ₂ SO ₂ C ₆ H ₄	
19	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	
20	2-Cl-4-CH ₃ C ₆ H ₃	2,6-di-CH ₃
21	C ₆ H ₅ CH ₂	3,6-di-CH ₃
22	C ₆ H ₅ CH=CHCH ₃	2,6-di-n-C ₄ H ₉
23	(C ₆ H ₅) ₂ CH	
24	C ₆ H ₅ N	
25	C ₆ H ₅ CH ₂	
26	C ₆ H ₅ CH ₂	

EXAMPLE 27

1-[2-(1-benzimidazolyl)ethyl]-2,6-dimethylpiperazine
[I: Het is 1-benzimidazolyl; Y is CH₂CH₂; R is H]

By reducing the 1-[2-(1-benzimidazolyl)ethyl]-4-benzyl-2,6-dimethylpiperazine described above in Example 21 with hydrogen over a palladium-on-charcoal catalyst in an ethanol solvent, there is obtained 1-[2-(1-benzimidazolyl)ethyl]-2,6-dimethylpiperazine.

EXAMPLES 28-33

By following the manipulative procedure described above in Example 1, replacing the 2-chloronitrobenzene used therein with a molar equivalent amount of an appropriate substituted-2-chloronitrobenzene, there can be obtained the compounds of Formula I in Table 2 below where, in each instance, Het is 1-benzimidazolyl, R is 2-CH₃OC₆H₄, and Y is CH₂CH₂.

TABLE 2

Example	Het substituent
28	5-HO.
29	6-CH ₃ .
30	4-CH ₃ O.
31	5-CH ₃ CO.
32	5-Cl.
33	6-CH ₃ -7-HO.

EXAMPLES 34-38

By following the manipulative procedure described above in Example 3, substituting for the 1-(2-cyanoethyl)-4-phenylpiperazine used therein a molar equivalent amount of an appropriate 1-(cyano-lower-alkyl)-4-phenylpiperazine (prepared by reacting in the presence of sodium carbonate, 1-phenylpiperazine with, respectively, α -chloroacetonitrile, γ -bromobutyronitrile, γ -bromo- β -methylbutyronitrile, δ -bromovaleronitrile, and ω -oceanthyl nitrile), there can be obtained the compounds of Formula I in Table 3 below where, in each instance, Het is 2-benzimidazolyl, and R is unsubstituted phenyl.

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3,472,854

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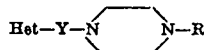
TABLE 3

Example:

	Y
34	CH ₂
35	(CH ₂) ₃
36	CH ₂ CHCH ₂ CH ₂
37	(CH ₂) ₄
38	(CH ₂) ₆

I claim:

1. A compound of the formula



wherein Het is 1- or 2-benzimidazolyl; R is hydrogen or lower-alkyl, hydroxy-lower-alkyl, phenyl, phenyl-lower-alkyl, benzhydryl, phenyl-lower-alkenyl, cycloalkyl-lower-alkyl, or pyridyl; and Y is lower alkylene of from one to six carbon atoms.

2. A compound according to claim 1 wherein Het is 1-benzimidazolyl, and R is phenyl.

3. A compound according to claim 1 wherein Het is 2-benzimidazolyl, and R is phenyl.

10

4. 1 - [2-(1-benzimidazolyl)ethyl]-4-(2-methoxyphenyl)-piperazine according to claim 2 wherein Y is 1,2-ethylene, and R is 2-methoxyphenyl.

5. 1 - [2-(1-benzimidazolyl)ethyl]-4-phenyl-piperazine according to claim 2 wherein Y is 1,2-ethylene.

6. 1 - [2-(2-benzimidazolyl)ethyl]-4-phenyl-piperazine according to claim 3 wherein Y is 1,2-ethylene.

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10	2,927,924	3/1960	Mills	260—268
	2,935,514	5/1960	Hoffmann et al.	260—268 X
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15	3,133,069	5/1964	Ash et al.	260—268
	3,293,260	12/1966	Sunagawa et al.	260—268 X
	3,318,880	5/1967	Almirante et al.	260—268 X

DONALD G. DAUS, Primary Examiner

U.S. Cl. X.R.

260—240, 258, 573, 578, 646, 689; 424—250

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



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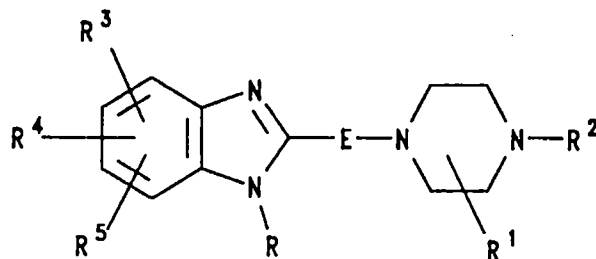
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 235/14, A61K 31/415, 31/495, C07D 409/12	A1	(11) International Publication Number: WO 94/22839 (43) International Publication Date: 13 October 1994 (13.10.94)
(21) International Application Number: PCT/GB94/00607 (22) International Filing Date: 23 March 1994 (23.03.94) (30) Priority Data: 9306578.7 30 March 1993 (30.03.93) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): KULAGOWSKI, Janusz, Jozef [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). LEESON, Paul, David [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).	(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: ANTIPSYCHOTIC BENZIMIDAZOLE DERIVATIVES (57) Abstract A class of benzimidazole derivatives, substituted at the 2-position by a substituted piperazinylmethyl or piperazinylethyl moiety, are antagonists of dopamine receptor subtypes within the brain, having a selective affinity for the dopamine D ₄ receptor subtype over other dopamine receptor subtypes, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia whilst manifesting fewer side-effects than those associated with classical neuroleptic drugs.		

- 24 -

CLAIMS:

1. The use of a compound of formula I, or a
 pharmaceutically acceptable salt thereof or a prodrug
 5 thereof:



(I)

wherein

E represents $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$;R represents hydrogen or C_{1-6} alkyl;

- R^1 represents hydrogen, or an optionally
 20 substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6}
 alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy,
 aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, heteroaryl,
 heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or
 heteroaryl(C_{2-6})alkynyl group;

- 25 R^2 represents an optionally substituted C_{1-6}
 alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl,
 aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl,
 aryl(C_{2-6})alkynyl, heteroaryl, heteroaryl(C_{1-6})alkyl,
 heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

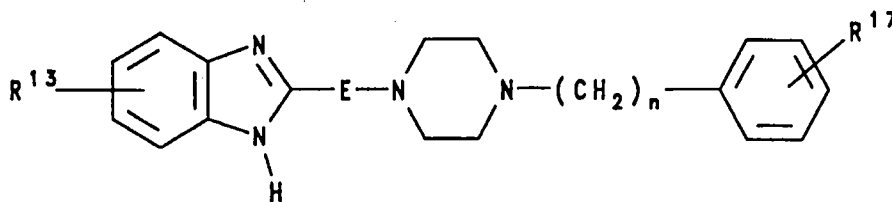
- 30 R^3 , R^4 and R^5 independently represent hydrogen,
 hydrocarbon, a heterocyclic group, halogen, cyano,
 trifluoromethyl, nitro, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{SOR}^a$, $-\text{SO}_2\text{R}^a$,
 $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{COR}^b$, $-\text{NR}^a\text{CO}_2\text{R}^b$, $-\text{COR}^a$, $-\text{CO}_2\text{R}^a$ or
 $-\text{CONR}^a\text{R}^b$; and

- 35 R^a and R^b independently represent hydrogen,
 hydrocarbon or a heterocyclic group;

- 25 -

for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

2. The use as claimed in claim 1 of a
5 compound represented by formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIA)

wherein

- E is as defined in claim 1;
n is zero, 1, 2 or 3; and
20 R¹³ and R¹⁷ independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₁₋₆ alkyl, C₁₋₆ alkoxy, aryl(C₁₋₆)alkoxy or C₂₋₆ alkylcarbonyl.

- 25 3. The use as claimed in claim 1 of a compound selected from:
2-(4-phenylpiperazin-1-ylmethyl)benzimidazole;
2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]benzimidazole;
2-(4-benzylpiperazin-1-ylmethyl)benzimidazole;
30 2-[2-(4-phenylpiperazin-1-yl)ethyl]benzimidazole;
and pharmaceutically acceptable salts thereof and prodrugs thereof.

- 35 4. A method for the treatment and/or prevention of psychotic disorders, which comprises administering to a patient in need of such treatment an

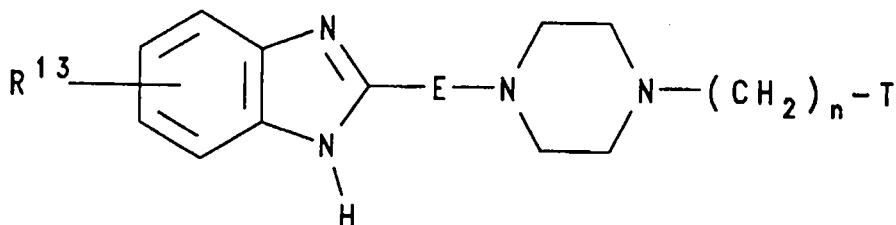
- 26 -

effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

5 5. The method as claimed in claim 4 wherein the compound administered is represented by formula IIA as defined in claim 2, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

10 6. The method as claimed in claim 4 wherein the compound administered is selected from:
 2-(4-phenylpiperazin-1-ylmethyl)benzimidazole;
 2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]benzimidazole;
 2-(4-benzylpiperazin-1-ylmethyl)benzimidazole;
 15 2-[2-(4-phenylpiperazin-1-yl)ethyl]benzimidazole;
 and pharmaceutically acceptable salts thereof and prodrugs thereof.

20 7. A compound of formula IIB, or a salt or prodrug thereof:



(I I B)

wherein

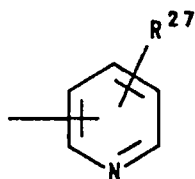
E is as defined in claim 1;

n and R¹³ are as defined in claim 2; and

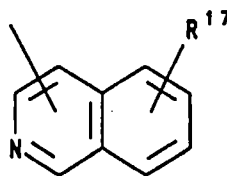
35 T represents a group of formula (i), (ii), (iii) or (iv):

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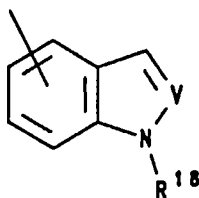
- 27 -



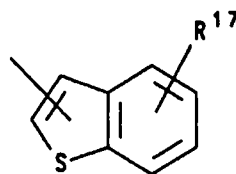
(I)



(II)



(III)



(IV)

in which

V represents nitrogen or CH;

R¹⁷ is as defined in claim 2;

R¹⁸ represents hydrogen or methyl; and

20 R²⁷ represents C₁₋₆ alkyl, halogen, trifluoromethyl, C₁₋₆ alkoxy, cyano, nitro, amino, C₁₋₆ alkylamino or di(C₁₋₆)alkylamino.

8. A compound selected from:

25 2-[4-(4-methoxyphenyl)piperazin-1-ylmethyl]benzimidazole;
2-[4-(2-phenylethyl)piperazin-1-ylmethyl]benzimidazole;
6-chloro-2-(4-phenylpiperazin-1-ylmethyl)benzimidazole;
6-methoxy-2-(4-phenylpiperazin-1-ylmethyl)benzimidazole;
2-[4-(benzothiophen-2-yl)piperazin-1-ylmethyl]-
30 benzimidazole;
and salts and prodrugs thereof.

9. A pharmaceutical composition comprising a
compound as claimed in claim 7 or claim 8 in association
35 with a pharmaceutically acceptable carrier.

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10. A compound as claimed in claim 7 or claim 8 for use in therapy.

5 11. The use of a compound as claimed in claim 7 or claim 8 for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

10 12. A method for the treatment and/or prevention of psychotic disorders, which comprises administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 7 or claim 8.

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

2020
Bogotá, D.C., 27/08/2007

Abogado(a)
Alicia Lloreda Ricaurte
Apoderado(a)

ASUNTO	Radicación	03 78835
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	16791
	Folios	008

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒

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

1. Documentos estudiados

- 1.1. Descripción: Folios: 26 a 36
- 1.2. Reivindicaciones: Folios: 137 a 179
- 1.3. Datos PCT:
- | | |
|-----------------------------|----------------|
| Solicitud Internacional: | PCT/US02/07791 |
| Capítulo II | |
| Fecha Sol. Internacional: | 06/03/2002 |
| Publicación. Internacional: | WO02/088093 |
| Fecha Pub. Internacional: | 07/11/2002 |
| Fecha Inicio Fase Nacional: | 09/10/2003 |
| Solicitud Nacional: | CO 03 78835 |
| Fecha Sol. Nacional: | 09/09/2003 |
- 1.3. Prioridad:
- | |
|----------------------------|
| US09/803.537 de 09/03/2001 |
| US09/874.484 de 05/06/2001 |
| US10/017.939 de 14/12/2001 |

2. Modificaciones no aceptadas (artículo 34 D.486 y art. 22 Tratado PCT)

El capítulo originalmente presentado ante la oficina receptora y la publicación internacional WO02/088093, realizada en virtud del Tratado PCT, dan noticia de un objeto diametralmente diferente al radicado ante la Superintendencia de Industria y

Comercio en la fecha 09/09/2003 con motivo del cumplimiento del término para ingresar a la fase nacional del trámite de patentes en Colombia.

Como puede entenderse de la lectura del capítulo publicado en fase internacional la materia reclamada trata de un método para el tratamiento de la disfunción sexual que consiste en la administración de cantidades efectivas de compuestos que responden a la fórmula (I) y son las cláusulas 1 a 89 las que solicitan protección para materia que se encuentra exceptuada de patentabilidad por el ordenamiento comunitario andino. Se entiende por esta Dependencia que en un intento fallido de modificar el alcance de la invención se transforman las reivindicaciones de método a compuesto repitiendo de manera innecesario el objeto reclamado en las cláusulas 90 a 112 en las cláusulas 1 a 89.

Al presentarse un pliego reivindicatorio en fase nacional el cual no responde a ninguna de las modificaciones previstas por el Tratado de Cooperación en materia de patentes en fase internacional, es decir, a las modificaciones previstas por el artículo 19 y 34 del texto normativo del PCT, se exceden las facultades que confiere el tratado al solicitante para modificar el pliego reclamado. De esta manera, el nuevo clausulado no podrá tenerse en cuenta dado que producto de las modificaciones realizadas *mutuo proprio*, las cláusulas 1 a 89 anteriormente definidas como método de tratamiento y ahora encabezadas en términos de compuesto, modifican diametralmente el alcance de la invención y exceden las facultades que confiere el texto del tratado en cuanto a modificaciones se refiere en torno al alcance y ámbito de la invención.

Así las cosas, esta Dependencia procederá a realizar el examen correspondiente al clausulado originalmente presentado en fase internacional y en virtud de la normativa andina, esto es, al texto originalmente publicado por la oficina internacional, por cuanto las modificaciones realizadas no responden a las previstas por el tratado y amplían de manera inaceptable el objeto inicialmente reclamado por la solicitud.

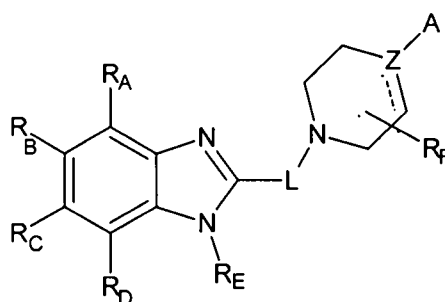
3. Objeto de la invención

Título de la solicitud

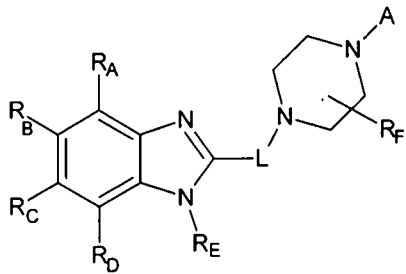
Bencimidazoles útiles en el tratamiento de la disfunción sexual

Reivindicaciones

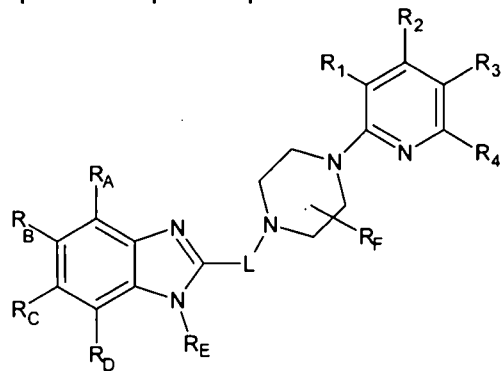
Reivindicaciones 1 a 89: Se reivindica un método para el tratamiento de la disfunción sexual en mamíferos que comprende administrar a un mamífero que lo necesite cantidades terapéuticamente efectivas de un compuesto de fórmula (I):



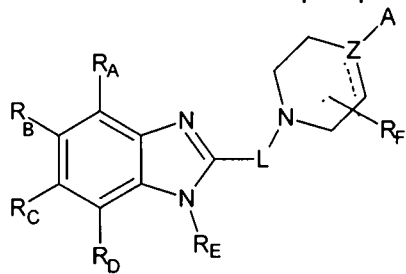
Reivindicaciones 90: Se reivindica un compuesto de fórmula (II) o una sal aceptable para uso farmacéutico.



Se reivindican compuestos que responden a la fórmula (III):



Se reivindican compuestos caracterizados porque responden a la fórmula (IV):



En particular se reclama protección para los compuestos:

- 2-[(4-pirimidin-2-ilpiperazin-1-il)metil]-1H-bencimidazol
- 6-[4-(1H-bencimidazol-2-ilmetil)piperazin-1-il]piridin-3-ol
- 2-[(2-metil-4-piridin-2-ilpiperazin-1-il)metil]-1H-bencimidazol
- 2-[(2S)-2-metil-4-piridin-2-ilpiperazin-1-il]metil}-1H-bencimidazol
- 2-[(2R)-2-metil-4-piridin-2-ilpiperazin-1-il]metil}-1H-bencimidazol
- N-{2-[4-(1H-bencimidazol-2-ilmetil)piperazin-1-il]piridin-3-il}metansulfonamida

Sustento Descriptivo

La invención se relaciona con el uso de bencimidazoles y las composiciones que los contienen para el tratamiento de disfunciones sexuales, en particular la disfunción eréctil masculina.

La invención identifica un uso terapéutico para los bencimidazoles de fórmula (I) en el tratamiento de las disfunciones sexuales en mamíferos. Más específicamente, estos compuestos son de utilidad en el tratamiento de las disfunciones sexuales incluyendo, pero sin limitaciones, la disfunción eréctil masculina.

Además se relaciona la invención con un método de tratamiento de la disfunción sexual en un mamífero, en particular en seres humanos, que comprende

administrar a dicho mamífero una cantidad eficaz en términos terapéuticos de un compuesto de la fórmula (I).

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K ³¹/4188** de la **Clasificación Internacional de Patentes**.

4. De la solicitud de Patente

4.1. Reivindicaciones (artículo 30 D. 486)

Una vez realizado el estudio del objeto reclamado esta dependencia se permite señalar:

- En las connotaciones que toman cada uno de los radicales R₁, R₂, R₃, R₄, R₅, Z₁ Z₂, R_A, R_B, R_C y R_D no se determina el número de átomos que conforman la cadena carbonada en los sustituyentes: alcoxi, alquilo, alquilsulfino, alquilsulfonilo, alquiltio, alquinilo, alcoxicarbonilo, alquilcarbonilo, alquilcarboniloxi, carboxi, haloalcoxi, haloalquilo, hidroxialquilo; por esta razón se recomienda al solicitante precisar el alcance de las definiciones presentadas para los radicales en comento incluyendo el número de átomos de la cadena.

5. Excepción a la patentabilidad (artículo 20 D. 486 literal a)-d))

- Las cláusulas 1 a 89 que reivindican un método de tratamiento farmacoterapéutico basado en la actividad de los compuestos de fórmula (I) se relacionan directamente con la excepción que contempla el artículo 20 literal d) de la norma andina, en el que se excluye de patentabilidad los métodos para el tratamiento humano o animal indiscriminadamente de su fundamento. En consecuencia, las cláusulas en comento no pueden ser objeto de estudio y por consiguiente deben eliminarse del alcance de la invención.

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 09/03/2001, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

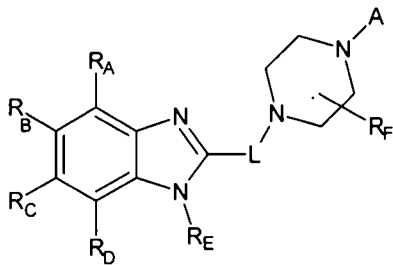
Nº	Documento	Título	Fecha de Publicación*
D1	EP0882718	"Benzimidazole Derivatives"	09/12/1998
D2	US3472854	"1-[(benzimidazolyl)-lower-alkyl]-4-substituted-piperazines"	14/12/1969
D3	WO9422839	"Antipsychotic benzimidazole derivatives"	13/12/1994

Anterioridades D1, D2 y D3 en los folios 272 a 285

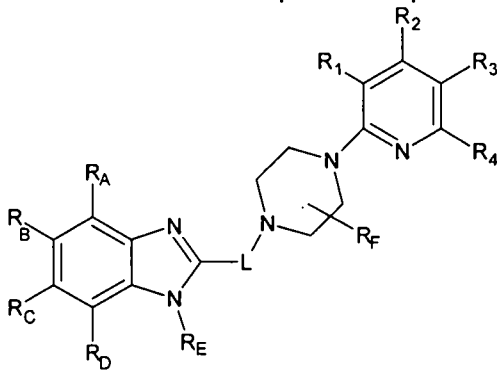
7. Análisis de patentabilidad (artículo 14 D. 486)

7.1. Novedad (artículo 16 D. 486)

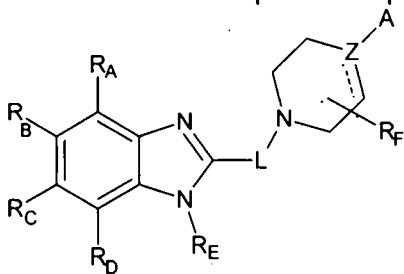
Se reivindica un compuesto de fórmula (II) o una sal aceptable para uso farmacéutico.



Se reivindican compuestos que responden a la fórmula (III):



Y se reivindican compuestos que responden a la fórmula (IV):



Para los cuales:

RA, RB, RC, RD se seleccionan independientemente de hidrógeno, alcoxi, alquenilo, alquilo, alquilsulfinilo, alquilsulfonilo, alquiltio, alquinilo, formilo, alquilcarbonilo.

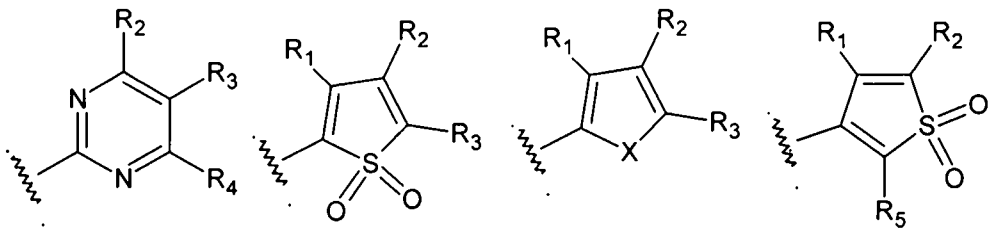
RE se selecciona entre hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, arilcarbonilo, cicloalquilcarbonilo

RF se selecciona entre hidrógeno y alquilo

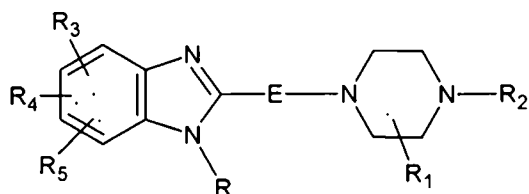
L es -CH₂-

Z es -C- o -CH-

A es un grupo que se selecciona entre



- El estado del arte más próximo a la invención relaciona el documento **D3** que contempla el uso de compuestos que responden a la fórmula estructural (I):



Para los cuales: **E** es $-\text{CH}_2-$

R es hidrógeno o alquilo $\text{C}_1\text{-C}_6$

R₁ es hidrógeno o alquilo $\text{C}_1\text{-C}_6$ opcionalmente sustituido, alcoxilo $\text{C}_1\text{-C}_6$, alquenilo $\text{C}_2\text{-C}_6$

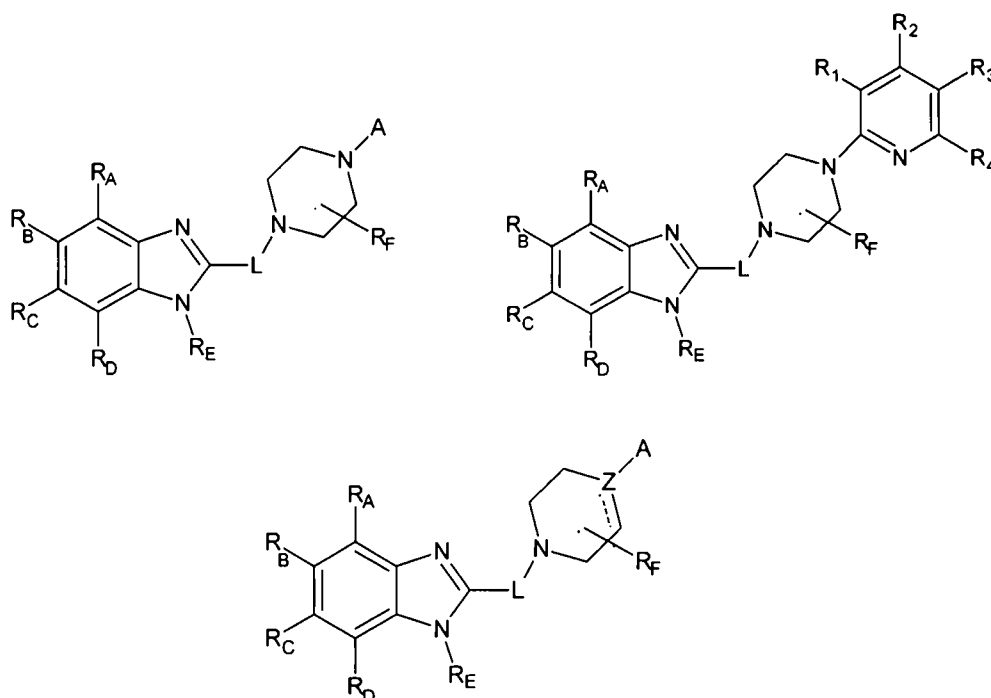
R₂ representa un grupo alquilo $\text{C}_1\text{-C}_6$, alcoxilo $\text{C}_1\text{-C}_6$, alquenilo $\text{C}_2\text{-C}_6$, alquinilo, arilo, heteroarilo

R₃, R₄ y R₅ son independientemente hidrógeno, hidrocarbilo o un grupo heterocíclico

De esta manera, al realizar la comparación elemento por elemento entre el objeto reclamado junto a las connotaciones que toman sus radicales y el objeto revelado por el estado del arte más próximo a la invención es posible señalar que los elementos característicos de las fórmulas (II), (III) y (IV) ya eran conocidos y se presentan identidad, química, estructural y funcional con el objeto definido en la anterioridad **D3**, en consecuencia, por la anticipación del documento se afecta la novedad de la materia reclamada a lo largo de las cláusulas 90 a 112.

7.2 Nivel Inventivo (Artículo 18 D. 486)

Como se señaló en el aparte anterior el objeto reclamado versa sobre compuestos de fórmula estructural (II), (III) y (IV):



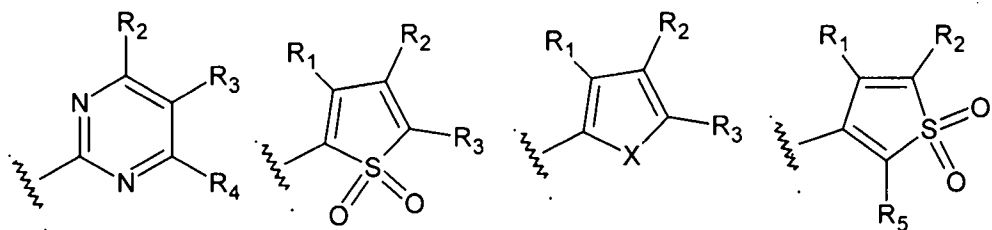
Para las cuales:

RA, RB, RC, RD se seleccionan independientemente de hidrógeno, alcoxi, alquenilo, alquilo, alquilsulfinilo, alquilsulfonilo, alquiltio, alquinilo, formilo, alquilcarbonilo.

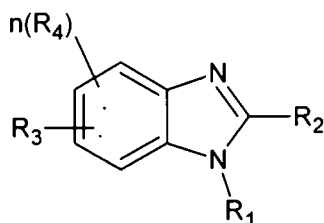
RE se selecciona entre hidrógeno, alcóxicarbonilo, alquilo, alquilcarbonilo, arilcarbonilo, cicloalquilcarbonilo

RF se selecciona entre hidrógeno y alquilo

L es -CH₂-
Z es -C- o -CH-
A es un grupo que se selecciona entre

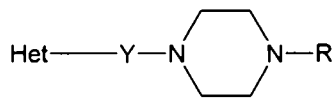


- El estado del arte más cercano a la invención contempla en el documento **D1** compuestos de la fórmula estructural (I):



Para los cuales, **R₂** representa un grupo alquilo sustituido por un grupo heterociclo
R₁ es un grupo hidrógeno, alquilo
R₃ representa un grupo carboxilo, un grupo carboxilo amidado
n es un número de 0 a 3 y
R₄ representa un sustituyente neutro

Además, el estado del arte reporta el documento **D2** en el cual se revelan compuestos de fórmula estructural (I):



Para los cuales, **Het** representa al grupo 2-Bencimidazolil
R es hidrógeno o alquilo o fenil o piridil
Y es alquileno de uno a seis átomos de carbono

Al realizar la comparación entre los elementos característicos de la materia reclamada y los objetos definidos en los anterioridades **D1** y **D2** es posible determinar que la única diferencia estructural estriba en la incorporación de sustituyentes heterocíclicos adicionales sobre el anillo de piperazina y enlazados por un grupo alquilo. No obstante, si se combinan las enseñanzas reveladas por el documento **D3** (que afecta la novedad de la materia reclamada) y las contempladas en uno cualquiera de los documentos anteriormente señalados, esto es **D1** o **D2**, resulta indiscutible que la materia reclamada se deriva evidentemente de las anticipaciones del estado del arte y por consiguiente se encuentra afectado su nivel inventivo para acceder al privilegio de patente de invención.

Ahora bien, si se tiene en cuenta el alcance del sustento descriptivo de la solicitud es posible determinar que se trata de un método de tratamiento farmacoterapéutico orientado hacia el control de la disfunción sexual masculina y femenina, hecho este que incuestionablemente señala la falta de una solución técnica orientado hacia el diseño y desarrollo de un producto farmacéutico que resuelva un problema particular,

por el contrario, la solicitud se orienta hacia objetos exceptuados legalmente de patentabilidad por la norma andina sobre propiedad industrial en su artículo 20.

8. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	EP0882718	90 a 112	Nivel Inventivo
D2	US3472854	90 a 112	Nivel Inventivo
D3	WO9422839	90 a 112	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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
28 DIC. 2007

CONCEPTO TÉCNICO No. 2660	EXAMINADOR TÉCNICO Código No. 202044
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