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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: Expediente No. 06-118.770

Solicitud de patente de invención titulada:

“DERIVADOS DE ÁCIDO CARBOXILICO DE BENCIMIDAZOLONA.”.

Solicitante: PFIZER INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 583

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, 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. Adjunto recibo por el monto de \$210.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

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

Anexo: Recibo por \$210.000 pesos

LMB/P2006/000247 080104

278
248

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

202012
Bogotá, D.C., 16 de marzo de 2010

Apoderado: Carlos Reinaldo Olarte García

ASUNTO Radicación 06-118770
 Trámite 002
 Evento 001
 Actuación 430
 Oficio 4353
 Folios

Patente de Invención ☒ Patente de Modelo de Utilidad ☒
Vía Nacional ☒
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒
No. Sol. Internacional PCT/IB2005/001825
Fecha de Presentación Internal. WO2005/123718

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:

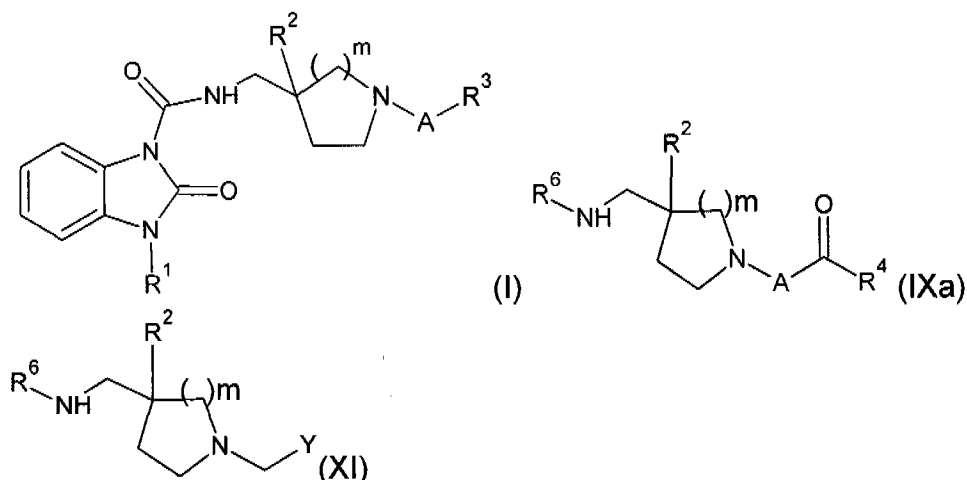
1. Documentos estudiados

- 1.1. Descripción: Folios: 83 a 222 Como se radicó inicialmente.
- 1.2. Reivindicaciones: Folios 223 a 228 Como se radicó inicialmente.
- 1.3. Prioridad: Folio 1: JP2004-177488, 15-jun-2004
 US 60/607008, 02-sep-2004
 US 60/607035, 02-sep-2004
 US 60/607048, 02-sep-2004

2. Objeto de la invención

Título de la solicitud: DERIVADOS DE ÁCIDO CARBOXILICO DE BENCIMIDAZOLONA.

El objeto de la invención son los derivados 2-oxo-N-(piperidin/pirrolidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida (I) y dos compuestos intermediarios del sustituyente sobre el carbonilo (XI) y (IXa), de las fórmulas:



- Reivindicaciones 1-6: Un compuesto de la fórmula (I).
- Reivindicación 7-8: Composiciones que los contienen
- Reivindicaciones 9-10: Procedimiento de tratamiento que consiste en administrar un compuesto a un paciente.
- Reivindicación 11: Un compuesto de fórmula (XI).
- Reivindicación 12: Un compuesto de fórmula (IXa).

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.): C07D401/12, 401/14, 405/14, A61K31/4184.

3. Unidad de invención (artículo 25 D 486 de la C.A.N.)

La presente solicitud no conserva la unidad inventiva comprende múltiples grupos inventivos:

- (i) derivados 2-oxo-N-(piperidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida (I) y derivados 2-oxo-N-(pirrolidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida (I);
- (ii) compuestos de fórmula (IXa).
- (iii) compuestos de fórmula (XI).

La porción estructural que comparten y que se conserva en todas las reivindicaciones no es nueva, por lo tanto no se puede basar sobre ella la unidad inventiva, y como debe ser sabido por el interesado, la unidad inventiva se da cuando la estructura que se conserva en las reivindicaciones es nueva, porque es la que conlleva las características técnicas especiales.

4. Excepción a la patentabilidad (artículo 20 D486 literal d) de la C.A.N.)

-Las reivindicaciones 9-10 reclaman un método de tratamiento para el cuerpo humano o animal, por lo tanto está bajo el alcance el artículo 20, literal d) D486 de la C.A.N.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 15/jun.2004.

Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos donde esta oficina tiene acceso libre, para búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

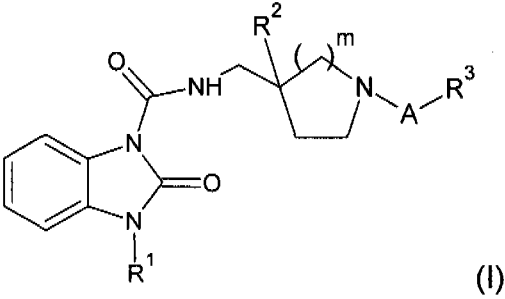
N°	Documento	Título	Fecha de Presentación*
D1	WO2005021539	Benzimidazolone compounds having 5-HT ₄ receptor agonistic activity	03-sep-2003
N°	Documento	Título	Fecha de Publicación
D2	WO9318027	Nitrogen containing heterocyclic compounds useful as pharmaceuticals	16-sep-1993
D3	EP0309425	New benzimidazoline-2-oxo-1-carbocyclic acid derivatives useful as 5-HT receptor antagonists	29-mar-1989
D4	US 5223511	Benzimidazoline-2-oxo-1-carbocyclic acid derivatives useful as 5-HT receptor antagonists	29-jun-1993
D5	US5358954	Benzimidazoline-2-oxo-1-carbocyclic acid derivatives useful as 5-HT receptor antagonists	25-oct-1994

*Se trata de una solicitud colombiana esta fecha corresponde también a la fecha de presentación de la solicitud colombiana aún sin haber sido publicada o sin habersele cumplido el plazo previsto en el art.40.

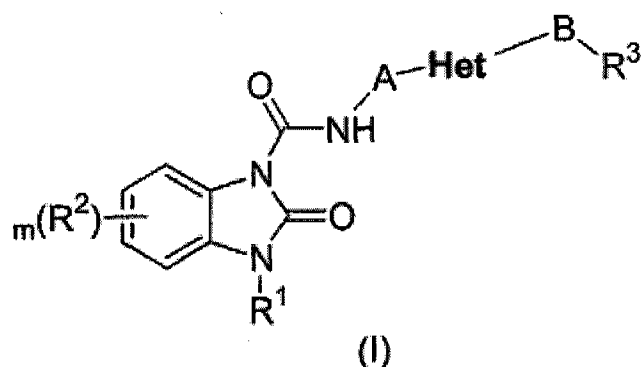
6. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

6.1. Novedad (artículo 16 D486 de la C.A.N.) Se realiza el análisis sólo para la primera invención reivindicada. (reiv 1-10)

La solicitud en estudio reclama los derivados de 2-oxo-N-(piperidin/pirrolidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida (I) que están bajo la fórmula Markush(I):



-D1 la anteriorida D1 describe compuestos 2-oxo-N-(piperidin/pirrolidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida que caen dentro de la fórmula (I):



wherein

Het represents a heterocyclic group having one nitrogen atom, to which B binds directly, and from 4 to 7 carbon atoms, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents independently selected from the group consisting of substituents α^1 ;

A represents an alkylene group having from 1 to 4 carbon atoms;

B represents a covalent bond or an alkylene group having from 1 to 5 carbon atoms, and said alkylene group being unsubstituted or substituted by an oxo group when R^3 represents a heterocyclic group;

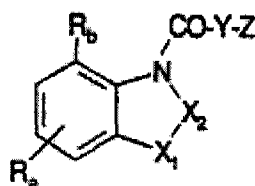
R^1 represents an isopropyl group or a cyclopentyl group;

R^2 independently represents a halogen atom or an alkyl group having from 1 to 4 carbon atoms; m is 0, 1, 2, 3 or 4; and

Véase toda la anterioridad.

-D2 enseña derivados de 2-oxo-N-(piperidin/pirrolidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida que están comprendidos en la fórmula:

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X_1 - X_2 is NR_2 -CO or CR_1R_2 - CR_3R_4 where

R_2 and R_1 to R_4 are independently hydrogen or C_{1-6} alkyl; and/or

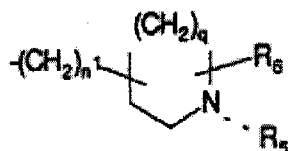
R_1/R_2 and R_3/R_4 together are a bond and/or $R_1/R_2/R_3/R_4$ are joined to form C_{3-6} polymethylene;

R_a is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkyl;

R_b is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

Y is O or NH;

Z is of sub-formula (a), (b) or (c):



(a)

wherein

n^1 is 1, 2, 3 or 4; n^2 is 0, 1, 2, 3 or 4; n^3 is 2, 3, 4 or 5;

q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2;

R_5 is hydrogen, C_{1-12} alkyl, aralkyl or R_5 is $(CH_2)_z-R_{10}$ wherein z is 2 or 3

and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy,

$C(O)C_{1-6}$ alkyl, COC_6H_5 , $-CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$

or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl;

and

R_6 , R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and

R_9 is hydrogen or C_{1-10} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

having 5-HT₄ receptor antagonist activity.

Example 1

(1-Butyl-4-piperidyl)methyl 2,3-dihydro-2-oxo-3H-benzimidazole-1-
5 carboxylate (E1)

2-Piperidylethyl 2,3-dihydro-2-oxo-3H-benzimidazole-1-carboxylate
hydrochloride (E5)

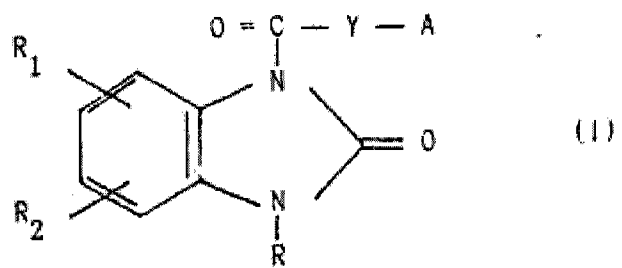
Intermedio

Preparation of N-(1-ⁿbutyl-4-piperidyl)methylamine

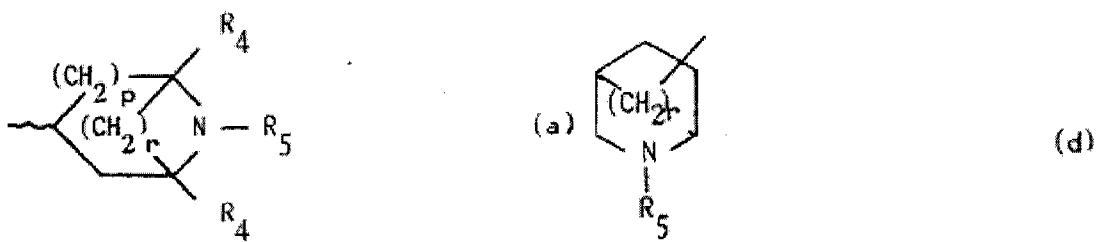
Tal como puede verse en todo D2 especialmente en los ejemplos 1, 2,5-17, se demuestra que los derivados 2-oxo-N-(piperidin/pirrolidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida, no son nuevos, como tampoco sus composiciones farmacéuticas, ni tampoco su efecto terapéutico, entonces no se observa el aporte al acervo tecnológico, ni el salto cualitativo a la regla técnica que presenta esta solicitud, por lo tanto no cumple con el requisito técnico exigido en artículo 16 D486 de la C.A.N.

-Las anterioridades D3-D5 describen derivados 2-oxo-N-(piperidin/pirrolidin-4-ilmetil)-

2,3-dihidro-1H-benzimidazol-1-carboxamida, que están comprendidos en la fórmula:



wherein R represents a hydrogen atom, C₁₋₆ alkyl, C₁₋₆ alkenyl or C₁₋₆ alkynyl; R₁ and R₂ may be at the same time or not a hydrogen atom, halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ acyl, carboxyl, C₁₋₆ alkoxycarbonyl, hydroxy, nitro, amino optionally C₁₋₄ alkyl N-mono or di-substituted, C₁₋₆ acylamino, C₁₋₆ alkoxycarbonylamino, carbamoyl optionally C₁₋₄ alkyl N-mono or di-substituted, cyano, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylsulphonyl, amino sulphonyl optionally C₁₋₄ alkyl N-mono or di-substituted, C₁₋₄ alkyl N-mono or di-substituted aminosulphonylamino, aminosulphonylamino; Y is oxygen or is N - R₃ in which R₃ is a hydrogen, a C₁₋₆ alkyl or optionally substituted by one or more C₁₋₆ alkoxy benzyl; A is a group selected from:



wherein p is 0, 1; r is 0, 1, 2, 3; R₄ is hydrogen atom or a C₁₋₄ alkyl; R₅ is a hydrogen atom, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, substituted phenyl C₁₋₄ alkyl or R₅ is a group of formula

Véase los documentos D3-D5 descripción y ejemplos, allí aparecen derivados específicos de 2-oxo-N-(piperidin/pirrolidin-4-ilmetil)-2,3-dihidro-1H-benzimidazol-1-carboxamida tal como los reclamados en la presente solicitud, con efecto antagonista de la 5-HT, entonces no son nuevos, como tampoco sus composiciones farmacéuticas, ni tampoco su efecto terapéutico, entonces no se observa el aporte al acervo tecnológico, ni el salto cualitativo a la regla técnica que presenta esta solicitud, por lo tanto no cumple con el requisito técnico exigido en artículo 16 D486 de la C.A.N.

Conclusión:

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

**La solicitud que no cumple con el requisito de novedad obviamente no posee nivel inventivo.*

Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	1-10	Novedad
D2	1-10	Novedad
D3	1-10	Novedad
D4	1-10	Novedad
D5	1-10	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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
10 March 2005 (10.03.2005)

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(51) International Patent Classification?: C07D 405/14,
413/14, 401/12, 405/06, A61K 31/4184, A61P 1/04

[JP/JP]: Pfizer Global Research and Development, 2, Aza
5-gochi, Taketoyo-cho, Chita-gun, Aichi-ken 470-2393
(JP).

(21) International Application Number:
PCT/IB2004/002741

(74) Agents: FULLER, Grover, F., Jr. et al.; Pfizer Inc., P.O.
Box 1027, St. Louis, MO 63006 (US).

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KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

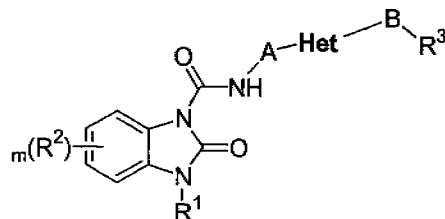
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GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
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GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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

(54) Title: BENZIMIDAZOLONE COMPOUNDS HAVING 5-HT₄ RECEPTOR AGONISTIC ACTIVITY



(I)

(57) Abstract: This invention provides
a compound of the formula (I) or a
pharmaceutically acceptable salt thereof, and
compositions containing such compounds and
the use of such compounds for the manufacture
of medicament for gastroesophageal reflux
disease, gastrointestinal disease, gastric
motility disorder, non-ulcer dyspepsia,
functional dyspepsia, irritable bowel syndrome
(IBS), constipation, dyspepsia, esophagitis,
gastroesophageal disease, nausea, central
nervous system disease, Alzheimer's disease,
cognitive disorder, emesis, migraine,

neurological disease, pain, cardiovascular disorders, cardiac failure, heart arrhythmia, diabetes and apnea syndrome. These
compounds have 5-HT₄ receptor agonistic activity, and thus are useful for the treatment of gastroesophageal reflux disease,
non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome or the like in mammalian, especially humans.

285

BENZIMIDAZOLONE COMPOUNDS

HAVING 5-HT₄ RECEPTOR AGONISTIC ACTIVITY

Technical Field

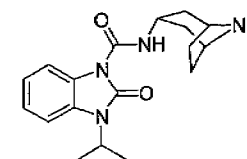
This invention relates to novel benzimidazolone compounds. These
5 compounds have selective 5-HT₄ receptor agonistic activity. The present invention
also relates to a pharmaceutical composition, a method of treatment and use
comprising the above compounds for the treatment of disease conditions mediated by
5-HT₄ receptor activity.

Background Art

10 In general, 5-HT₄ receptor agonists are found to be useful for the treatment of
a variety of diseases such as gastroesophageal reflux disease, gastrointestinal disease,
gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel
syndrome (IBS), constipation, dyspepsia, esophagitis, gastroesophageal disease,
nausea, central nervous system disease, Alzheimer's disease, cognitive disorder,
15 emesis, migraine, neurological disease, pain, cardiovascular disorders, cardiac failure,
heart arrhythmia, diabetes and apnea syndrome (See *TiPs*, 1992, 13, 141; Ford A. P.
D. W. et al., *Med. Res. Rev.*, 1993, 13, 633; Gullikson G. W. et al., *Drug Dev.*
Res., 1992, 26, 405; Richard M. Eglen et al, *TiPS*, 1995, 16, 391; Bockaert J. Et al.,
CNS Drugs, 1, 6; Romanelli M. N. et al., *Arzheim Forsch./Drug Res.*, 1993, 43,
20 913; Kaumann A. et al., *Naunyn-Schmiedeberg's*. 1991, 344, 150; and Romanelli M.
N. et al., *Arzheim Forsch. /Drug Res.*, 1993, 43, 913). Also, Mosapride is known to be
useful for the treatment of diabetes.

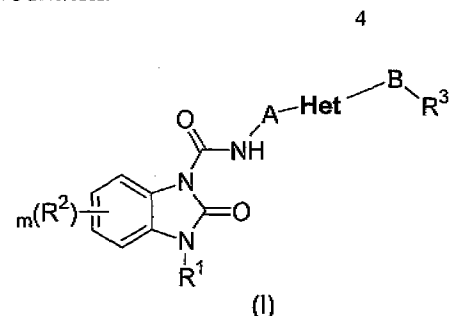
It would be desirable if there were provided 5-HT₄ receptor agonists which
have more 5HT₄ receptor agonistic activities.

25 US5223511 discloses benzimidazole compounds as 5-HT₄ receptor
antagonists. Especially, compounds represented by the following formula is
disclosed:



Compound A

285



wherein

Het represents a heterocyclic group having one nitrogen atom, to which B binds directly, and from 4 to 7 carbon atoms, and said heterocyclic group being

5 unsubstituted or substituted by 1 to 4 substituents independently selected from the group consisting of substituents α^1 ;

A represents an alkylene group having from 1 to 4 carbon atoms;

B represents a covalent bond or an alkylene group having from 1 to 5 carbon atoms, and said alkylene group being unsubstituted or substituted by an oxo group when R^3

10 represents a heterocyclic group;

R^1 represents an isopropyl group or a cyclopentyl group;

R^2 independently represents a halogen atom or an alkyl group having from 1 to 4 carbon atoms; m is 0, 1, 2, 3 or 4; and

R^3 represents

15 (i) a cycloalkyl group having from 3 to 8 carbon atoms, and said cycloalkyl group being substituted by 1 to 5 substituents independently selected from the group consisting of substituents α^2 , or

(ii) a heterocyclic group having from 3 to 8 atoms, and said heterocyclic group being unsubstituted or substituted by 1 to 5 substituents independently

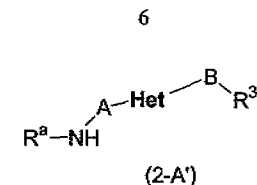
20 selected from the group consisting of substituents β ,

said substituents α^1 are independently selected from a hydroxy group and an amino group;

said substituents α^2 are independently selected from a hydroxy group, an amino group, a hydroxy-substituted alkyl group having from 1 to 4 carbon atoms, a carboxyl

25 group and an alkoxy group having from 1 to 4 carbon atoms; and

said substituents β are independently selected from a hydroxy group, a hydroxy-



wherein

R^4 represents a hydrogen atom or a N-protecting group;

Het represents a heterocyclic group having one nitrogen atom, to which B binds

5 directly, and from 4 to 7 carbon atoms, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents independently selected from the group consisting of substituents α^1 ;

A represents an alkylene group having from 1 to 4 carbon atoms;

B represents a covalent bond or an alkylene group having from 1 to 5 carbon atoms, and said alkylene group being unsubstituted or substituted by an oxo group when R^3 represents a heterocyclic group;

R^3 represents

(i) a cycloalkyl group having from 3 to 8 carbon atoms, and said cycloalkyl group being substituted by 1 to 5 substituents independently selected from the group consisting of substituents α^2 , or

15 (ii) a heterocyclic group having from 3 to 8 atoms, and said heterocyclic group being unsubstituted or substituted by 1 to 5 substituents independently selected from the group consisting of substituents β ,

said substituents α^1 are independently selected from a hydroxy group and an amino group;

20 said substituents α^2 are independently selected from a hydroxy group, an amino group, a hydroxy-substituted alkyl group having from 1 to 4 carbon atoms, a carboxyl group and an alkoxy group having from 1 to 4 carbon atoms; and

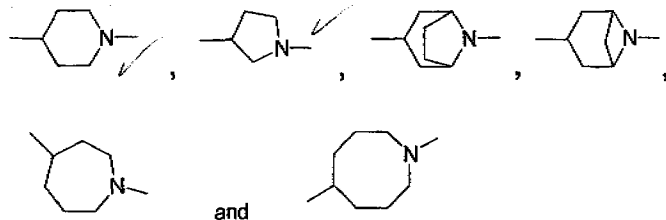
said substituents β are independently selected from a hydroxy group, a hydroxy-substituted alkyl group having from 1 to 4 carbon atoms, a carboxyl group, an amino group, an alkyl group having from 1 to 4 carbon atoms, an amino-substituted alkyl group having from 1 to 4 carbon atoms and a carbamoyl group,

Detailed Description of the Invention

287

287

As used herein, the term "heterocyclic" of "Het" means a heterocyclic group having one nitrogen atom and from 4 to 7 carbon atoms such as



As used herein, the term "alkylene" in "A" means straight or branched chain saturated radicals having 1 to 4 carbon atoms, including, but not limited to methylene, ethylene, *n*-propylene, isopropylene, *n*-butylene, isobutylene, *sec*-butylene, *tert*-butylene. The "alkylene" in "A" represents preferably a methylene group, an ethylene group or a propylene group; more preferably a methylene group or an ethylene group; most preferably a methylene group.

As used herein, the term "alkylene" in "B" means straight or branched chain saturated radicals having 1 to 5 carbon atoms, including, but not limited to methylene, ethylene, *n*-propylene, isopropylene, *n*-butylene, isobutylene, *sec*-butylene, *tert*-butylene, *n*-pentylene, isopentylene, *sec*-pentylene, *tert*-pentylene. The "alkylene" in "B" represents preferably an alkylene group having from 1 to 4 carbon atoms; more preferably an alkylene group having from 1 to 3 carbon atoms; much more preferably a methylene group or an ethylene group; further more preferably a methylene group.

As used herein, the term "halogen" in "R²" means fluoro, chloro, bromo and iodo, preferably fluoro or chloro.

As used herein, the term "alkyl" in "R²"; "alkyl" of "a hydroxy-substituted alkyl group" and "an alkoxy group having from 1 to 4 carbon atoms" in "substituents α^2 "; "alkyl" in "substituents β "; and "alkyl" of "a hydroxy-substituted alkyl group" and "an amino-substituted alkyl group" in "substituents β " mean straight or branched chain saturated radicals having 1 to 4 carbon atoms, including, but not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl.

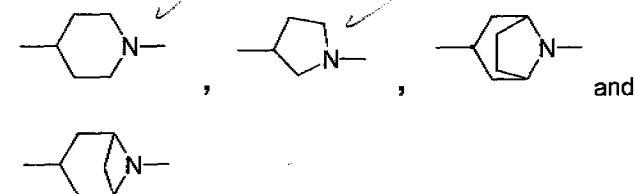
As used herein, the term "cycloalkyl" in "R³" means cyclic alkyl group having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

cycloheptyl, cyclooctyl, and etc.

As used herein, the term "heterocyclic" of "R³" means a heterocyclic ring which has one or more hetero atoms in the ring, preferably has 2 to 6 carbon atoms and 1 to 3 heteroatoms, including aziridinyl, azetidiny, piperidinyl, morpholinyl (including morpholino), pyrrolidinyl, pyrazolidinyl, piperazinyl, tetrahydropyrazolyl, pyrazolinyl, tetrahydropyranyl and etc.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment" as used herein refers to the act of treating, as "treating" is defined immediately above.

A preferred compound of formula (I) of this invention is that wherein Het represents a heterocyclic group selected from



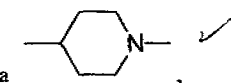
said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents

independently selected from the group consisting of substituents α^1 ; and

A represents an alkylene group having from 1 to 3 carbon atoms.

A more preferred compound of formula (I) of this invention is that wherein

Het represents a group of formula



and this group being unsubstituted or substituted by one substituent selected from the group consisting of substituents α^1 ;

A represents an alkylene group having from 1 to 2 carbon atoms;

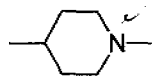
B represents an alkylene group having from 1 to 4 carbon atoms, and said alkylene group being unsubstituted or substituted by an oxo group when R³ represents a heterocyclic group;

R² independently represents a halogen atom or an alkyl group having from 1 to 2 carbon atoms; m is 0, 1 or 2; and

R³ represents

- (i) a cycloalkyl group having from 4 to 7 carbon atoms, and said cycloalkyl group being substituted by 1 to 3 substituents independently selected from the group consisting of substituents α^2 , or
- 5 (ii) a heterocyclic group having from 4 to 7 atoms, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of substituents β .

Also, a further preferred compound of formula (I) of this invention is the compound or its pharmaceutically acceptable salt wherein



- 10 **Het** represents a group of formula and this group being unsubstituted or substituted by one substituent selected from the group consisting of substituents α^1 ;

A represents a methylene group;

B represents an alkylene group having from 1 to 2 carbon atoms;

- 15 **R¹** represents an isopropyl group;

R² independently represents a fluorine atom, a chlorine atom or a methyl; and

R³ represents

- (i) a cycloalkyl group having from 5 to 7 carbon atoms, and said cycloalkyl group being substituted by 1 to 2 substituents independently selected from the group consisting of substituents α^2 , or
- 20 (ii) a heterocyclic group having from 5 to 7 atoms, and said heterocyclic group being unsubstituted or substituted by 1 to 2 substituents independently selected from the group consisting of substituents β ,

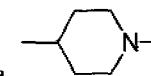
said substituents α^2 are independently selected from a hydroxy group, an amino

- 25 group and an alkoxy group having from 1 to 2 carbon atoms; and

said substituents β are independently selected from a hydroxy group, a hydroxy-substituted alkyl group having from 1 to 2 carbon atoms, a carboxyl group, an amino group, an amino-substituted alkyl group having from 1 to 2 carbon atoms and a carbamoyl group.

- 30 A further preferred compound of formula (I) of this invention is the compound

Most preferred compounds of formula (I) of this invention is the compound or its pharmaceutically acceptable salt, wherein



Het represents a group of formula

A represents a methylene group;

- 5 **B** represents a methylene group;

R¹ represents an isopropyl group;

R² represents a fluorine atom; **m** is 0; and

R³ represents

- (i) a cyclohexyl group substituted by 1 or 2 hydroxy group (especially dihydroxycyclohexyl), or
- 10 (ii) a tetrahydropyran group substituted by 1 or 2 hydroxy group (especially hydroxytetrahydropyranyl).

In the compounds of formula (I) or the pharmaceutically acceptable salt, **R²** preferably represents a fluorine atom, a chlorine atom, a methyl group or an ethylene group; more preferably a fluorine atom, a chlorine atom, a methyl group; most preferably a fluorine atom.

In the compounds of formula (I) or the pharmaceutically acceptable salt, **m** is preferably 0, 1 or 2; more preferably 0 or 1; much more preferably 0.

Preferred individual compound of this invention is:

- 20 *N*-({1-[(4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl]piperidin-4-yl)methyl}-3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;
- N*-({1-[(*trans*-1,4-dihydroxyhexyl)methyl]piperidin-4-yl)methyl}-3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide;
- N*-({1-[(*cis*-1,4-dihydroxyhexyl)methyl]piperidin-4-yl)methyl}-3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide; and
- 25 6-fluoro-*N*-({1-[(4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl]piperidin-4-yl)methyl}-3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carboxamide,
- or a pharmaceutically acceptable salt thereof.

A preferred compound of formula (2-A') of this invention is that wherein

- 30 **R^a** represents a hydrogen atom or a *t*-butoxycarbonyl group;



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(54) Title: NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS USEFUL AS PHARMACEUTICALS			
(I)			
(57) Abstract			
Compounds of formula (I) and pharmaceutically acceptable salts thereof and their use as pharmaceuticals in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.			

NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS USEFUL AS PHARMACEUTICALS

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

5

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT₄ receptor, and that ICS 205-930, which is also a 5-HT₃ receptor antagonist, acts as an antagonist at this receptor.

10

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT₄ receptor antagonists in the treatment of atrial arrhythmias and stroke.

15

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT₄ antagonist activity.

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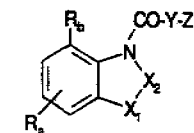
EP-A-309423 (Istituto de Angeli S.p.A) and EP-A-247266 (Beecham Group p.l.c.) describe 5-HT₃ receptor antagonists derived from a benzimidazolone or indoline nucleus.

25

A class of novel, structurally distinct compounds has now been discovered, which compounds include benzimidazolone derivatives. These compounds have 5-HT₄ receptor antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:

30



(I)

wherein:

X₁-X₂ is NR₂-CO or CR₁R₂-CR₃R₄ where

R₂ and R₁ to R₄ are independently hydrogen or C₁-6 alkyl; and/or

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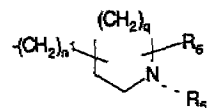
R_1/R_2 and R_3/R_4 together are a bond and/or $R_1/R_2/R_3/R_4$ are joined to form C_{3-6} polymethylene;

R_a is hydrogen, halo, C_{1-6} alkyl, amino, nitro or C_{1-6} alkyl;

R_b is hydrogen, halo, C_{1-6} alkyl or C_{1-6} alkoxy;

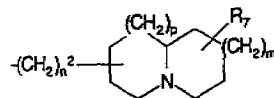
5 Y is O or NH;

Z is of sub-formula (a), (b) or (c):



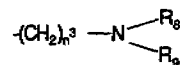
(a)

10



(b)

15



(c)

wherein

n^1 is 1, 2, 3 or 4; n^2 is 0, 1, 2, 3 or 4; n^3 is 2, 3, 4 or 5;

20 q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2;

R_5 is hydrogen, C_{1-12} alkyl, aralkyl or R_5 is $(CH_2)_z-R_{10}$ wherein z is 2 or 3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5 , $-CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and

25

R_6 , R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and

R_9 is hydrogen or C_{1-10} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

30 having 5-HT₄ receptor antagonist activity.

Examples of alkyl or alkyl containing groups include C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , C_{10} , C_{11} or C_{12} branched, straight chained or cyclic alkyl, as

appropriate. C_{1-4} alkyl groups include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

5 Aryl includes phenyl and naphthyl optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy.

Halo includes fluoro, chloro, bromo and iodo.

10 A suitable bioisostere for the amide or ester linkage containing Y in formula (I), is of formula (d):



15

(d)

wherein

the dotted circle represents one or two double bonds in any position in the 5-membered ring; H, J and I independently represent oxygen, sulphur, nitrogen or carbon, provided that at least one of H, J and I is other than carbon; U represents nitrogen or carbon.

20

Suitable examples of (d) are as described for X, Y and Z in EP-A-328200 (Merck Sharp & Dohme Ltd.), such as an oxadiazole moiety.

25

Suitable examples of X_1-X_2 when $CR_1R_2-CR_3R_4$ include CH_2-CH_2 and $CH=CH$. X_1-X_2 is preferably NR_2-CO , however, such as $NH-CO$ or $NEt-CO$.

R_a is preferably hydrogen.

30

R_b is preferably hydrogen or halo, such as iodo.

Y is preferably O or NH.

291

When Z is of sub-formula (a), n^1 is preferably 2, 3 or 4 when the azacycle is attached at the nitrogen atom and n^1 is preferably 1 when the azacycle is attached at a carbon atom, such as the 4-position when q is 2.

- 5 When Z is of sub-formula (b), n^2 is preferably such that the number of carbon atoms between the ester or amide linkage is from 2 to 4 carbon atoms.

Suitable values for p and m include $p = m = 1$; $p = 0$, $m = 1$, $p = 1$, $m = 2$, $p = 2$, $m = 1$.

10

- When Z is of sub-formula (c), n^3 is preferably 2, 3 or 4.

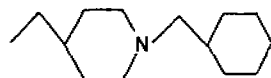
R_8 and R_9 are preferably both alkyl, especially one of R_8 and R_9 is C_4 or larger alkyl.

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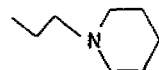
Specific values of Z of particular interest are as follows:



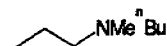
(i)



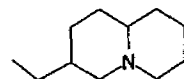
(ii)



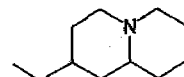
(iii)



(iv)



(v)



(vi)

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It is believed that platelet-derived 5-HT induces atrial arrhythmias which encourage atrial fibrillation and atrial disorders are associated with symptomatic cerebral and systemic embolism. Cerebral embolism is the most common cause of ischaemic stroke and the heart the most common source of embolic material. Of particular concern is the frequency of embolism associated with atrial fibrillation.

- 10 Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, *Mol Pharmacol.*, 34, 880-887). Activity may be demonstrated in standard animal models, the social interaction test and the X-maze test.

- 15 Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, *Migraine*, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, *Headache* 16, 160-167). It is believed that a migraine, including the prodromal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT₄ receptors, and hence
20 that administration of a 5-HT₄ antagonist is of potential benefit in relieving a migraine attack.

- The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a
25 pharmaceutically acceptable carrier.

- Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders,
30 granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusible solutions or suspensions. Sublingual or transdermal administration is also envisaged. Orally administrable compositions are preferred, since they are more convenient for general use.

- 35 Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings,

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Example 1

(1-Butyl-4-piperidyl)methyl 2,3-dihydro-2-oxo-3H-benzimidazole-1-carboxylate (E1)

A solution of (1-butyl-4-piperidyl)methyl 2-aminophenylcarbamate (D1b), (2.90g, 0.0095 mole) in dichloromethane (50ml) with triethylamine (1.5ml) was added to a stirred solution of trichloromethyl chloroformate (1.88g, 1.15ml, 0.0095 mole) in dichloromethane (50ml) at 50°C under nitrogen. After 1h the solution was allowed to warm to room temperature and left for a further 1h. The solution was treated with dilute HCl acid (50ml) and the white solid produced was filtered off. The solid was suspended in 10% Na₂CO₃ (aqueous) solution (50ml) and extracted with dichloromethane (3x100ml). The organic extracts were combined, dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound (E1) as an off white solid (2.20g, 70%) mp 130-132°C.

¹H NMR 250MHz (CDCl₃) δ: 9.85 (br s, 1H), 7.92 (dd, 1H), 7.13-7.34 (m, 3H), 4.45 (d, 2H), 3.05-3.20 (m, 2H), 2.40-2.55 (m, 2H), 1.90-2.20 (m, 5H), 1.35-1.70 (m, 6H), 1.02 (t, 3H).

MS (EI) MH⁺ 332.

Example 2

(1-Butyl-4-piperidyl)methyl 2,3-dihydro-2-oxo-3-ethylbenzimidazole-1-carboxylate hydrochloride (E2)

To a stirred solution of (1-butyl-4-piperidyl)methyl 2,3-dihydro-2-oxo-3H-benzimidazole-1-carboxylate (E1, 0.5g, 0.0015 mole) in dry DMF (15ml) under nitrogen at room temperature was added, portionwise, sodium hydride as an 80% dispersion in mineral oil (45mg, 0.0015 mole). After hydrogen evolution had subsided (90min), the solution was treated with ethyl iodide (0.235g, 0.12ml, 0.0015 mole) and left to stir overnight. The resulting solution was basified via addition of 10% aqueous Na₂CO₃ solution (30 ml) and extracted into ethyl acetate (3x50ml). The organic extracts were combined

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D3

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EUROPEAN PATENT APPLICATION

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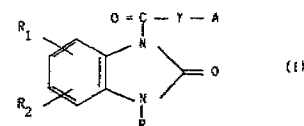
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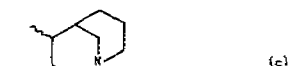
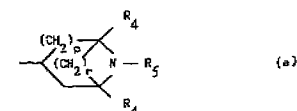
New benzimidazole-2-oxo-1-carboxylic acid derivatives useful as 5-HT receptor antagonists.

New pharmacologically active benzimidazole-2-oxo-1-carboxylic acid derivatives which are 5-HT receptor antagonists useful as antiemetic agents and as gastric prokinetic agents of the following formula:



wherein R represents a hydrogen atom, C₁₋₆ alkyl, C₁₋₆ alkenyl or C₁₋₆ alkynyl; R₁ and R₂ may be at the same time or not a hydrogen atom, halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ acyl, carboxyl, C₁₋₆ alkoxy-carbonyl, hydroxy, nitro, amino optionally C₁₋₄ alkyl N-mono or di-substituted, C₁₋₆ acylamino, C₁₋₆ alkoxy-carbonylamino, carbamoyl optionally C₁₋₄ alkyl N-mono or di-substituted, cyano, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylsulphonyl, amino sulphonyl optionally C₁₋₄ alkyl N-mono or di-substituted, C₁₋₄ alkyl N-mono or di-substituted aminosulphonylamino, aminosulphonylamino; Y is oxygen or is N-R₃ in which R₃ is a hydrogen, a C₁₋₆ alkyl or optionally

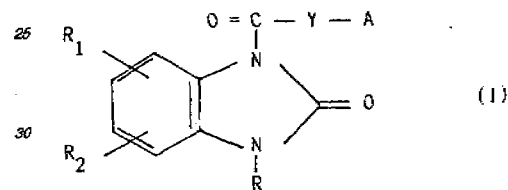
substituted by one or more C₁₋₆ alkoxy benzyl; A is a group selected from:



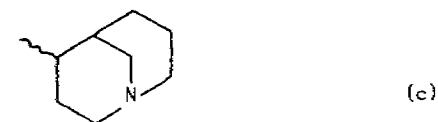
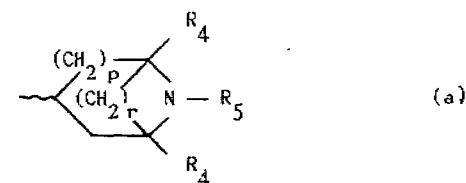
Description

NEW BENZIMIDAZOLINE-2-OXO-1-CARBOXYLIC ACID DERIVATIVES USEFUL AS 5-HT RECEPTOR ANTAGONISTS

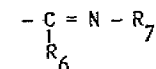
The present invention relates to novel pharmacologically active benzimidazoline-2-oxo-1-carboxylic acid derivatives, to the process for their preparation and to the pharmaceutical compositions containing them. The new compounds are 5-HT receptor antagonists useful as anti-emetic agents and as gastric prokinetic agents. Serotonin (5-HT) is known to play a major role both in Central Nervous System (CNS) and in Peripheral Nervous System (PNS). Compounds acting as 5-HT receptor antagonists may be effectively used in the prevention or treatment of migraine, cluster headaches and trigeminal neuralgia. They may also be used in the treatment of certain CNS disorders such as anxiety and psychosis. Since 5-HT antagonists may have a beneficial role on gastrointestinal motility a further use of these compounds is in delayed gastric emptying, dyspepsia, flatulence, oesophageal reflux, peptic ulcer, constipation and irritable bowel syndrome. Very recently it has been also discovered that a number of 5-HT antagonists may be particularly useful in the treatment of chemotherapy induced nausea and emesis (J.R. Fozard-Trends in Pharmacological Sciences 8 44, 1987, and references cited therein). We have now synthesized, and this is the object of the present invention, a novel class of structurally distinct compounds showing specific 5-HT receptor blocking activity which may be useful in the treatment of chemotherapy and radiation induced nausea and emesis and/or of delayed gastric emptying. They may be also of value in the treatment of motion sickness, arrhythmia, migraine, cluster headaches, trigeminal neuralgia, anxiety and psychosis. Moreover they may be used in gastrointestinal motility disorders such as dyspepsia, flatulence, oesophageal reflux, peptic ulcer, constipation, irritable bowel syndrome and ipokinesia. The compounds, object of the present invention, have the general formula (I)



wherein R represents a hydrogen atom, C₁₋₆ alkyl, C₁₋₆ alkenyl or C₁₋₆ alkynyl; R₁ and R₂ may be at the same time or not a hydrogen atom, halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ acyl, carboxyl, C₁₋₆ alkoxycarbonyl, hydroxy, nitro, amino optionally C₁₋₄ alkyl N-mono or di-substituted, C₁₋₆ acylamino, C₁₋₆ alkoxycarbonylamino, carbamoyl optionally C₁₋₄ alkyl N-mono or di-substituted, cyano, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylsulphonyl, amino sulphonyl optionally C₁₋₄ alkyl N-mono or di-substituted, C₁₋₄ alkyl N-mono or di-substituted aminosulphonylamino, aminosulphonylamino; Y is oxygen or is N - R₅ in which R₅ is a hydrogen, a C₁₋₆ alkyl or optionally substituted by one or more C₁₋₆ alkoxy benzyl; A is a group selected from:

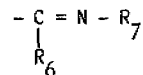


wherein p is 0, 1; r is 0, 1, 2, 3; R₄ is hydrogen atom or a C₁₋₄ alkyl; R₅ is a hydrogen atom, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₂₋₈ cycloalkyl, C₁₋₄ alkyl, substituted phenyl, C₁₋₄ alkyl or R₅ is a group of formula



wherein R₆ is hydrogen atom, C₁₋₄ alkyl or an amino group and R₇ is hydrogen atom or C₁₋₆ alkyl.

For the pharmaceutical use the compounds of general formula (I) are used as such or under the form of tautomers or of physiologically compatible acid addition salts. The term "acid addition salts" includes salts with inorganic or organic acids. Physiologically compatible acids used for the salification include, for example, maleic, citric, tartaric, fumaric, methanesulphonic, hydrochloric, hydrobromic, iodoiodic, nitric, sulphuric, phosphoric, acetic, benzoic, ascorbic acid. Physiologically acceptable salts include also quaternary derivatives of compounds of formula (I) obtained by reaction of the above compounds with compounds of formula R₈ - Q wherein R₈ is C₁₋₆ alkyl, phenyl, C₁₋₆ alkyl or C₃₋₇ cycloalkyl, C₁₋₄ alkyl and Q is a leaving group such as halogen, p-toluenesulphonate, mesylate. Preferred R₈ groups are methyl, ethyl, n-propyl, i-propyl, cyclopropylmethyl. Physiologically acceptable salts include also internal salts of compounds of formula (I) such as N-oxides. The compounds of formula (I) and their physiologically acceptable salts may also exist as physiologically acceptable solvates, such as hydrates, which constitute a further feature of the present invention. It has to be understood that the carbonyl group in position two of the general formula (I) might exist in its enol form when R is hydrogen and that there are also the tautomers of the amidino derivatives of formula (I) wherein R₅ is a group of formula



and R_6 and R_7 are as hereinbefore defined. The present invention therefore includes in its scope these tautomeric forms both in term of the compounds and of the manufacturing process.

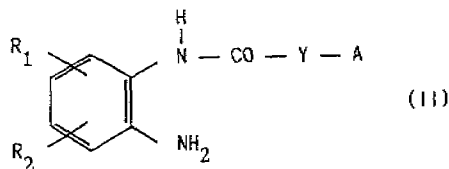
Some of the compounds of formula (I) according to the present invention contain chiral or prochiral centres and thus may exist in different stereoisomeric forms including enantiomers of (+) and (-) type or mixtures of them. The present invention includes in its scope both the individual isomers and the mixtures thereof.

It has to be understood that, when mixtures of optical isomers are present, they may be separated according to the classic resolution methods based on their different physico-chemical properties, e.g. by fractional crystallization of their acid addition salts with a suitable optically active acid or by the chromatographic separation with a suitable mixture of solvents.

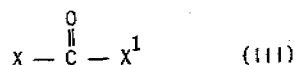
In the present invention the term A of formula (a) means 3-linked 8-azabicyclo [3.2.1] octane or 3-linked 9-azabicyclo [3.3.1] nonane or 2-linked-7-azabicyclo [2.2.1] heptane, 4-linked piperidine, the one of formula (b) means 3 or 4-linked 1-azabicyclo [2.2.2] octane, the one of formula (c) means 4-linked 1-azabicyclo [3.3.1] nonane and the one of formula (d) means 5-linked 2-azabicyclo [2.2.2] octane.

The term halogen means fluorine, chlorine, bromine or iodine. It has also to be understood that in compounds of formula (I) the azabicyclic moieties of group A may be endo or exo substituted. Compounds of formula (I) containing the pure endo or exo moieties may be prepared starting from the appropriate precursors or by separating mixtures of the endo or exo isomers not stereospecifically synthesized by conventional methods such as e.g.: chromatography.

The compounds of general formula (I) when R is H may be prepared by reacting a compound of general formula (II)

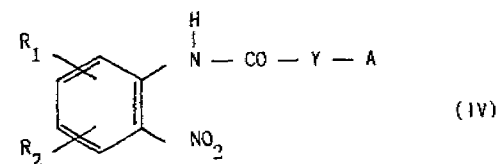


wherein R_1 , R_2 , Y and A are as hereinbefore defined, with a reactive carbonyl derivative of formula (III)



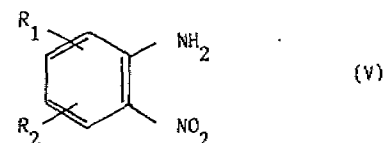
wherein X and X^1 are leaving groups identical or different from each other such as halogen, alogenated alkoxy, alkoxy, heterocycle. Preferred groups are chlorine, trichloromethoxy, methoxy, ethoxy or imidazolyl. The reaction may be conventionally carried out in aprotic solvents such as benzene, toluene, ethylacetate, acetonitrile, tetrahydrofurane, methylene chloride, chloroform, carbontetrachloride or dimethylformamide at a temperature ranging from 0° to 100°C, preferably at 5°C or at the boiling point of the solvent of choice. The presence of an acid acceptor such as triethylamine may be beneficial in some instances.

Compounds of general formula (II), used as starting materials in the above mentioned process, may be prepared by reducing a compound of formula (IV)



wherein R_1 , R_2 , Y and A are as hereinbefore defined, with hydrogen or a hydrogen donor such as ammonium formate, cyclohexene, cyclohexadiene, hydrazine. The reduction is preferably carried out with hydrogen in the presence of a suitable catalyst, preferably 5% or 10% Pd/C or Raney nickel in the presence of a suitable solvent such as methanol, ethanol, toluene, water or a mixture of them. The same reduction may be conveniently carried out with iron in acidic medium or in the presence of $FeCl_3$, with Zn in acetic or hydrochloric acid, with $SnCl_2$ in hydrochloric acid or with other reducing agents such as titanium trichloride, ferrous sulphate, hydrogen sulphide or its salts, sodium hydrosulphite.

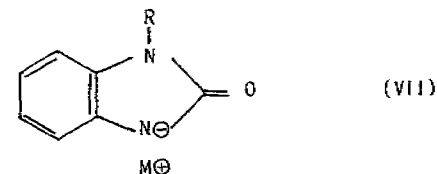
Compounds of general formula (IV) may be prepared by reacting a compound of general formula (V)



wherein R_1 and R_2 are as hereinbefore defined, with a reactive intermediate of general formula (VI)

$X-I-Y-A$ (VI) wherein X, Y and A are as hereinbefore defined. The reaction is carried out in an aprotic solvent such as tetrahydrofurane, acetonitrile, chloroform, toluene, chlorobenzene or without solvents, and optionally in the presence of an acid acceptor, preferably in pyridine at a temperature ranging from 20° to 100°C preferably at 20° or at 80°C.

The compounds of general formula (I), wherein R_1 and R_2 are both hydrogen atoms and R, Y and A are as hereinbefore defined, may conveniently be obtained by reacting a compound of formula (VII)



wherein M is a metal atom, such as sodium, potassium or lithium, preferably sodium with a compound of formula (VI). The reaction is preferably carried out in a polar aprotic solvent, such as dimethyl formamide or tetrahydrofurane at a temperature ranging from 0° to 100°C, preferably at room temperature.

Compound (VII) is generated "in situ" from the corresponding hydrogen compounds by means of sodium, potassium, sodium hydride, potassium hydride, potassium tert-butyrate, butyllithium, lithium diisopropylamide, preferably sodium hydride.

The compounds of general formula (I), wherein R_1 and R_2 are both hydrogen atoms R, Y and A are as hereinbefore defined, may be also prepared by reacting a reactive compound of general formula (VIII)

[54] BENZIMIDAZOLINE-2-OXO-1-CARBOXYLIC ACID COMPOUNDS USEFUL AS 5-HT RECEPTOR ANTAGONISTS

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[73] Assignee: Boehringer Ingelheim Italia S.p.A., Florence, Italy

[21] Appl. No.: 845,891

[22] Filed: Mar. 4, 1992

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 768,497, Sep. 30, 1991, abandoned, which is a continuation of Ser. No. 552,353, Jul. 12, 1990, abandoned, which is a continuation of Ser. No. 243,949, Sep. 13, 1988, abandoned.

[30] Foreign Application Priority Data

Sep. 23, 1987 [IT] Italy 21997 A/87

[51] Int. Cl.⁵ C07D 451/12; A61K 31/46

[52] U.S. Cl. 514/304; 546/126

[58] Field of Search 546/126; 514/304

References Cited

U.S. PATENT DOCUMENTS

4,871,744 10/1989 King et al. 546/126

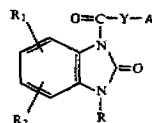
FOREIGN PATENT DOCUMENTS

0223385 5/1987 European Pat. Off. 546/126

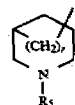
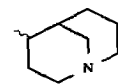
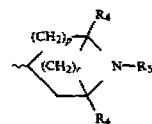
Primary Examiner—C. Warren Ivy
Assistant Examiner—Zinna N. Davis
Attorney, Agent, or Firm—David E. Frankhouser, Alan R. Stempel; Mary-Ellen M. Timbers

ABSTRACT

New pharmacologically active benzimidazoline-2-oxo-1-carboxylic acid derivatives which are 5-HT receptor antagonists useful as antiemetic agents and as gastric prokinetic agents of the following formula:



wherein R is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl; R₁ is hydrogen; R₂ is hydrogen, halogen or C₁₋₆ alkoxy; Y is oxygen or N—R₃ in which R₃ is hydrogen; A is a group selected from:



wherein p is 1; r is 0, 2 or 3; R₄ is hydrogen; R₅ is hydrogen, C₁₋₆ alkyl, or R₅ is a group of the formula —CR₆—N—R₇ wherein R₆ is hydrogen, C₁₋₄ alkyl or amino and R₇ is hydrogen or C₁₋₆ alkyl; or a pharmaceutically acceptable acid addition salt thereof.

The processes for the preparation of the compounds of formula (I) as well as pharmaceutical compositions containing them are also described.

9 Claims, No Drawings

BENZIMIDAZOLINE-2-OXO-1-CARBOXYLIC ACID COMPOUNDS USEFUL AS 5-HT RECEPTOR ANTAGONISTS

RELATED APPLICATIONS

This is a continuation-in-part of application Ser. No. 768,497, filed Sep. 30, 1991, now abandoned, which is a continuation of application Ser. No. 552,353, filed Jul. 12, 1990, now abandoned, which is a continuation of application Ser. No. 243,949, filed Sep. 13, 1988, now abandoned.

FIELD OF THE INVENTION

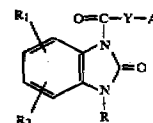
The present invention relates to novel pharmacologically active benzimidazoline-2-oxo-1-carboxylic acid derivatives, to the process for their preparation and to the pharmaceutical compositions containing them. The new compounds are 5-HT receptor antagonists useful as antiemetic agents and as gastric prokinetic agents.

BACKGROUND OF THE INVENTION

Serotonin (5-HT) is known to play a major role both in Central Nervous System (CNS) and in Peripheral Nervous System (PNS). Compounds acting as 5-HT receptor antagonists may be effectively used in the prevention or treatment of migraine, cluster headaches and trigeminal neuralgia. They may also be used in the treatment of certain CNS disorders such as anxiety and psychosis. Since 5-HT antagonists may have a beneficial role on gastrointestinal motility a further use of these compounds is in the treatment of delayed gastric emptying, and related disorders such as dyspepsia, flatulence, oesophageal reflux, peptic ulcer, constipation and irritable bowel syndrome. Very recently it has been also discovered that a number of 5-HT antagonists may be particularly useful in the treatment of chemotherapy induced nausea and emesis (J. R. Fozard-Trends in Pharmacological Sciences 8 44, 1987, and references cited therein).

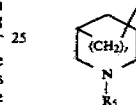
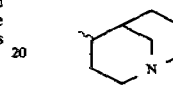
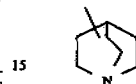
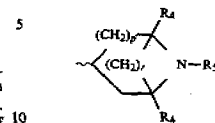
DESCRIPTION OF THE INVENTION

We have now synthesized, and this is the object of the present invention, a novel class of structurally distinct compounds which exhibit a specific 5-HT receptor blocking activity which are useful in the treatment of chemotherapy and radiation induced nausea and emesis and/or of delayed gastric emptying. They are also of value in the treatment of motion sickness, arrhythmia, migraine, cluster headaches, trigeminal neuralgia, anxiety and psychosis. Moreover they are useful in the treatment of gastrointestinal motility disorders such as gastrointestinal hypomotility and related disorders such as dyspepsia, flatulence, oesophageal reflux, peptic ulcer, constipation, irritable bowel syndrome. The compounds, object of the present invention, have the general formula (I)



wherein R is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl; R₁ is hydrogen; R₂ is hydrogen, halogen, or

C₁₋₆ alkoxy; Y is oxygen or N—R₃, in which R₃ is hydrogen; A is a group selected from:



wherein p is 1; r is 0, 2 or 3; R₄ is hydrogen; R₅ is hydrogen, C₁₋₆ alkyl, or R₅ is a group of the formula —CR₆—N—R₇ wherein R₆ is hydrogen, C₁₋₄ alkyl or amino and R₇ is hydrogen or C₁₋₆ alkyl.

For pharmaceutical use the compounds of general formula (I) can be used in the form shown, or in the form of tautomers or as physiologically acceptable acid addition salts. The term "acid addition salts" includes salts with inorganic or organic acids. Physiologically acceptable acids used for the salification include, for example, maleic, citric, tartaric, fumaric, methanesulphonic, hydrochloric, hydrobromic, iodoacetic, nitric, sulphuric, phosphoric, acetic, benzoic, ascorbic acid. Physiologically acceptable salts include also quaternary derivatives of compounds of formula (I) obtained by reaction of the above compounds with compounds of formula R₈—Q wherein R₈ is C₁₋₆ alkyl, phenyl, C₁₋₆ alkyl or C₃₋₇ cycloalkyl, C₁₋₄ alkyl and Q is a leaving group such as halogen, p-toluenesulphonate, mesylate. Preferred R₈ groups are methyl, ethyl, n-propyl, isopropyl and cyclopropylmethyl. Physiologically acceptable salts also include internal salts of compounds of formula (I) such as N-oxides. The compounds of formula (I) and their physiologically acceptable salts may also exist as physiologically acceptable solvates, such as hydrates, which constitute a further aspect of the present invention. It has to be understood that the carbonyl group in position two of the general formula (I) might exist in its enol form when R is hydrogen and that there are also the tautomers of the amidino derivatives of formula (I) wherein R₃ is a group of formula —CR₆—N—R₇ and R₆ and R₇ are as hereinbefore defined. The present invention therefore includes in its scope these tautomeric forms.

Some of the compounds of formula (I) according to the present invention contain chiral or prochiral centres and thus may exist in different stereoisomeric forms including enantiomers of (+) and (−) type or mixtures

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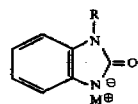
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preferably halogen and halogenated alkoxy. The reaction is carried out in aprotic solvents such as tetrahydrofuran, acetonitrile, methylene chloride or chloroform at a temperature between 10° C. and the boiling point of the solvent of choice, preferably at room temperature. Compounds of general formula (VI) are preferably isolated as hydrochloride salts.

Compounds of general formula (VII) are either commercially available or may be prepared according to known procedures, for example, endo-9-methyl-9-azabicyclo[3.3.1]nonan-3-ol is prepared according to C. L. Zirkle et al. *J. Org. Chem.* 26, 395 (1961), endo-8-phenyl-methyl-8-azabicyclo[3.2.1]octan-3-ol is prepared according to Nador et al. *Arzneim. Forsch.* 12, 305 (1962).

The compounds of general formula (I), wherein R₁ and R₂ are both hydrogen atoms and R, Y and A are as hereinbefore defined, may conveniently be obtained by reacting a compound of formula (VIII)

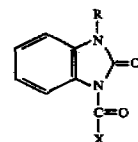


wherein M is a metal atom, such as sodium, potassium or lithium, preferably sodium with a compound of formula (VI). The reaction is preferably carried out in a polar aprotic solvent, such as dimethyl formamide or tetrahydrofuran at a temperature ranging from 0° to 100° C., preferably at room temperature.

Compound (VIII) is generated "in situ" from the corresponding hydrogen compounds by means of sodium, potassium, sodium hydride, potassium hydride, potassium tert-butyrate, butyllithium, lithium diisopropylamide, preferably sodium hydride.

Compounds which can be used to prepare the hydrogen compounds of formula (VIII) are either commercially available or may be prepared according to Z. Eckstein et al. *J. Chem. Engineering Data* 28, 279 (1983), or the references cited therein.

The compounds of general formula (I), wherein R₁ and R₂ are both hydrogen atoms R, Y and A are as hereinbefore defined, may be also prepared by reacting a reactive compound of general formula (IX)

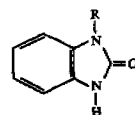


wherein R and X are as hereinbefore defined, with a compound of formula (X)



wherein Z is a hydrogen atom, a metal preferably Li, Na or K, Y and A are as hereinbefore defined. The reaction is carried out in an aprotic solvent such as tetrahydrofuran, chloroform, acetonitrile, o-dichlorobenzene and optionally in the presence of an acid acceptor such as pyridine or triethylamine, preferably pyridine, at a temperature ranging from 0° to 200° C., preferably

erably between 20° and 160° C. Compounds of general formula (IX), used as starting materials in the above mentioned process, wherein R is hereinbefore defined and X is chlorine, may be prepared according to the method described by W. H. W. Lunn U.S. Pat. No. 4,061,861. Alternatively the same compounds may be prepared by reacting a compound of general formula (XI)



wherein R is an hereinbefore defined, with a compound of general formula (III), wherein X and X' are as hereinbefore defined, preferably they are halogen and halogenated alkoxy. The reaction is preferably carried out in an inert solvent, such as tetrahydrofuran, dioxane or dichlorobenzene optionally in the presence of charcoal at temperature between 50° C. and 150° C., preferably at the boiling point of the solvent. Compounds of general formula (XI) are either commercially available or they may be prepared according to Z. Eckstein et al. *J. Chem. Engineering Data* 28, 279 (1983).

Compounds of general formula (X), used as starting materials in the above mentioned process, wherein Z is a metal atom as hereinbefore defined, may be conveniently prepared by reacting a compound of general formula (VII)



wherein Y and A are as hereinbefore defined, with a metal, a metal hydride or a strong base such as, for example, sodium hydride, potassium hydride, metallic sodium or potassium, potassium t-butyrate, butyl lithium, lithium diisopropylamide, preferably sodium hydride or butyl lithium in an aprotic solvent such as tetrahydrofuran, diethyl ether or dimethylformamide. The reaction is preferably carried out at a temperature between -78° C. to room temperature. Compounds of formula (VII) are either commercially available or may be prepared according to known procedures (c.f., for example, C. L. Zirkle et al. *J. Org. Chem.* 26, 395 (1961); *J. Med. Chem.* 16, 853 (1973); S. Archer *J. Am. Chem. Soc.* 79, 41 (1957); *Chemical Abstract* 94, 65477 (1981); *European Patent Application* 94,742 (1983); E. F. Elslager *J. Med. Chem.* 17, 75 (1974); G. Kraiss et al. *Tetrahedron Lett.* 12, 57 (1971); P. Dorstert et al. *Eur. J. Med. Chem.* 19, 105 (1984). It has to be understood that compounds of general formula (I) containing an R, R₁, R₂, R₃ and R₅ group which may give rise to another R, R₁, R₂, R₃ and R₅ group, are useful novel intermediates. Some of these transformations may also occur in the intermediates for compounds of general formula (I). Some examples of such conversions, which obviously are not exhaustive of all possibilities, are:

- 1) a nitro group may be transformed into an amino group by reduction;
- 2) an amino group may be transformed into a C₁₋₆ acyl-amino group by acylation with a suitable carboxylic acid derivative;
- 3) an amino group may be transformed into a C₁₋₄ alkyl N-mono or di-substituted group by alkylation;

- 4) an amino group may be transformed into a C₁₋₆ alkoxy carbonyl amino group by reaction with a suitable reactive C₁₋₆ alkyl carbonic acid monoester derivative;
- 5) a carboxyl group may be transformed into a C₁₋₆ alkoxy carbonyl group, or into a carbamoyl group optionally C₁₋₄ alkyl N-mono or di-substituted by reaction of a suitable reactive carboxylic acid derivative with appropriate alcohols and amines;
- 6) a carbamoyl group may be transformed into a cyano group by dehydration;
- 7) a C₁₋₆ alkyl thio or a C₁₋₆ alkyl sulphanyl group may be transformed into a C₁₋₆ alkyl sulphanyl or a C₁₋₆ alkyl-sulphonyl group by oxidation;
- 8) an aromatic hydrogen group may be transformed into a nitro group by nitration;
- 9) a hydrogen group may be transformed into a halogen group by halogenation;
- 10) a secondary amide group, optionally conjugated with other carboxamidic moieties, may be transformed into a C₁₋₆ N-alkyl tertiary amide group by alkylation;
- 11) a secondary amino group may be transformed into an amidino derivative by reaction with appropriate reactive compounds such as e.g. ethyl formimide, ethyl acetimidate or cyanamide;
- 12) a tertiary amino group may be transformed into a quaternary ammonium derivative by reaction with a suitable alkylating agent such as methyl bromide or methyl iodide;
- 13) a tertiary amidic group optionally conjugated with other carboxamidic moieties may be transformed into a secondary amidic group by removing an optionally C₁₋₆ alkoxy substituted benzyl.

These transformations are well known to any expert of the branch.

The compounds of general formula (I) prepared according to the process as above described may optionally be converted with inorganic or organic acids into the corresponding physiologically compatible acid addition salts, for example, by conventional methods such as by reacting the compound, as base, with a solution of the corresponding acid in a suitable solvent. Particularly preferred acids include for example hydrochloric, hydrobromic, sulphuric, acetic, citric, tartaric acids.

Particularly preferred compounds, according to the present invention are the following:

- N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 28).
- N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-3-methyl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 31).
- N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 26).
- N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 27).
- N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-methyl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 32).
- 2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid (endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl) ester (Compound 19).
- N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide (Compound 45).

- 3-Ethyl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl) ester (Compound 60).
- 2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid (endo-8-amidino-8-azabicyclo[3.2.1]oct-3-yl) ester (Compound 44).

As already mentioned hereinbefore the new compounds of formula (I), according to the present invention, have useful pharmacological properties owing to their ability to antagonize the physiological 5-HT effects in warm-blooded animals. Therefore the new compounds are commercially viable in the prevention and in the treatment of disorders wherein 5-HT receptors are involved such as chemotherapy or radiation induced nausea and emesis, delayed gastric emptying, psychosis, and anxiety.

The following tests show that the compounds according to the present invention have favorable characteristics in these respects.

PHARMACOLOGY

Bezold-Jarisch reflex in anaesthetized rats
Rats (250-275 g) were anaesthetized with urethane (1.25 g/kg ip.). Blood pressure was recorded from the left femoral artery by means of a pressure transducer (Statham) and heart rate was recorded by feeding a cardiometer with the blood pressure signal.

The Bezold-Jarisch effect was elicited by rapid bolus intravenous injection of 5-HT (20 µg/kg).

Increasing doses of antagonists were injected 5 min before 5-HT to evaluate their effect on the initial abrupt cardiac slowing and associated fall in blood pressure resulting from the reflex vagal stimulation. ED₅₀ values were calculated by linear regression analysis of the data expressed as percentage inhibition.

The obtained potency of the compounds, object of the present invention, is reported in the table I.

TABLE I

Compound	ED ₅₀ (µg/kg. i.v.)	
	Bradycardia	Hypotension
1	5.4	5.9
19	3.4	6.8
24	5.7	7.8
25	12.0	8.5
26	0.3	0.4
27	0.35	6.5
28	1.0	1.5
31	0.49	1.97
32	1.7	3.9
37	3.7	3.9
44	0.0003	0.0004
45	1.7	1.0
47	1.7	2.2
48	4.7	6.4
50	6.1	5.8
51	0.4	1.3
52	0.3	1.1
54	0.6	2.0
56	1.3	1.4
57	4.0	3.1
60	3.2	5.2

Guinea pig ileum longitudinal muscle-myenteric plexus

Male guinea pigs (Dunkin Hartley, 450-550 g) were killed by cervical dislocation. A 2 cm segment of distal ileum, removed about 10 cm proximal to the caecum was suspended under 0.5 g tension in a 10 ml organ bath containing Tyrode solution (mM: NaCl 137; KCl 2.68; CaCl₂ 1.82; NaHCO₃ 5.9; MgCl₂ 1; NaH₂PO₄ 0.42; glucose 5.6) oxygenated with 95% O₂ 5% CO₂, at 37° C.

[54] BENZIMIDAZOLINE-2-OXO-1-CARBOXYLIC ACID DERIVATIVES USEFUL AS 5-HT RECEPTOR ANTAGONISTS

[75] Inventors: Marco Turconi, Voghera; Arturo Donetti, Milan; Ernesto Montagna, San Giuliano Milanese; Massimo Nicola, Pavia; Annamaria Uberti, Milan; Rosamaria Micheletti, Milan; Antonio Giachetti, Milan, all of Italy

[73] Assignee: Boehringer Ingelheim Italia, Milan, Italy

[21] Appl. No.: 33,675

[22] Filed: Mar. 16, 1993

Related U.S. Application Data

[60] Division of Ser. No. 845,891, Mar. 4, 1992, Pat. No. 5,223,511, which is a continuation-in-part of Ser. No. 768,497, Sep. 30, 1991, abandoned, which is a continuation of Ser. No. 552,353, Jul. 12, 1990, abandoned, which is a continuation of Ser. No. 243,949, Sep. 13, 1988, abandoned.

[30] Foreign Application Priority Data

Sep. 23, 1987 [IT] Italy 21997 A/87

[51] Int. Cl.³ A61K 31/46; C07D 451/12

[52] U.S. Cl. 514/304; 546/126

[58] Field of Search 546/126; 514/304

[56] References Cited

U.S. PATENT DOCUMENTS

4,871,744 10/1989 King et al. 546/126

FOREIGN PATENT DOCUMENTS

0223385 5/1987 European Pat. Off. 546/126

Primary Examiner—C. Warren Ivy

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Attorney, Agent, or Firm—David E. Frankhouser; Alan R. Stempel; Mary-Ellen M. Timbers

[57] ABSTRACT

Pharmacologically active benzimidazoline-2-oxo-1-carboxylic acid compounds which are useful for treating a human host suffering from anxiety.

7 Claims, No Drawings

BENZIMIDAZOLINE-2-OXO-1-CARBOXYLIC ACID DERIVATIVES USEFUL AS 5-HT RECEPTOR ANTAGONISTS

RELATED APPLICATIONS

This is a division of application Ser. No. 845,891, filed Mar. 4, 1992, now U.S. Pat. No. 5,223,511 which is a continuation-in-part of application Ser. No. 768,497, filed Sep. 30, 1991, now abandoned which is a continuation of application Ser. No. 552,353, filed Jul. 12, 1990, now abandoned, which is a continuation of application Ser. No. 243,949, filed Sep. 13, 1988, now abandoned.

FIELD OF THE INVENTION

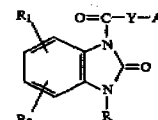
The present invention relates to novel pharmacologically active benzimidazoline-2-oxo-1-carboxylic acid derivatives, to the process for their preparation and to the pharmaceutical compositions containing them. The new compounds are 5-HT receptor antagonists useful as antiemetic agents and as gastric prokinetic agents.

BACKGROUND OF THE INVENTION

Serotonin (5-HT) is known to play a major role both in Central Nervous System (CNS) and in Peripheral Nervous System (PNS). Compounds acting as 5-HT receptor antagonists may be effectively used in the prevention or treatment of migraine, cluster headaches and trigeminal neuralgia. They may also be used in the treatment of certain CNS disorders such as anxiety and psychosis. Since 5-HT antagonists may have a beneficial role on gastrointestinal motility a further use of these compounds is in the treatment of delayed gastric emptying, and related disorders such as dyspepsia, flatulence, oesophageal reflux, peptic ulcer, constipation and irritable bowel syndrome. Very recently it has been also discovered that a number of 5-HT antagonists may be particularly useful in the treatment of chemotherapy induced nausea and emesis (J. R. Fozard-Trends in Pharmacological Sciences 8 44, 1987, and references cited therein).

DESCRIPTION OF THE INVENTION

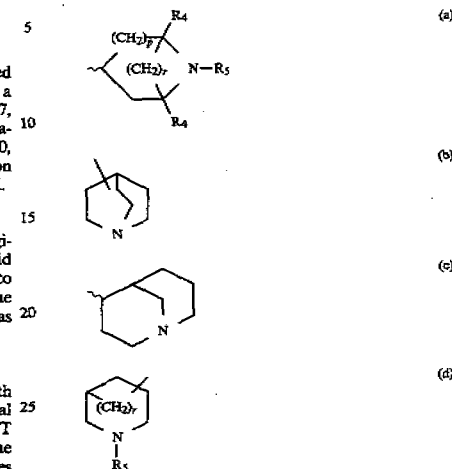
We have now synthesized, and this is the object of the present invention, a novel class of structurally distinct compounds which exhibit a specific 5-HT receptor blocking activity which are useful in the treatment of chemotherapy and radiation induced nausea and emesis and/or of delayed gastric emptying. They are also of value in the treatment of motion sickness, arrhythmia, migraine, cluster headaches, trigeminal neuralgia, anxiety and psychosis. Moreover they are useful in the treatment of gastrointestinal motility disorders such as gastrointestinal hypomotility and related disorders such as dyspepsia, flatulence, oesophageal reflux, peptic ulcer, constipation, irritable bowel syndrome. The compounds, object of the present invention, have the general formula (I)



wherein R is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl; R₁ is hydrogen; R₂ is hydrogen, halogen, or

5,358,954

C₁₋₆ alkoxy; Y is oxygen or N—R₃, in which R₃ is hydrogen; A is a group selected from:



wherein p is 1; r is 0, 2 or 3; R₄ is hydrogen; R₅ is hydrogen. C₁₋₆ alkyl, or R₅ is a group of the formula —CR₆—N—R₇ wherein R₆ is hydrogen, C₁₋₄ alkyl or amino and R₇ is hydrogen or C₁₋₆ alkyl.

For pharmaceutical use the compounds of general formula (I) can be used in the form shown or in the form of tautomers or as physiologically acceptable acid addition salts. The term "acid addition salts" includes salts with inorganic or organic acids. Physiologically acceptable acids used for the salification include, for example, maleic, citric, tartaric, fumaric, methansulphonic, hydrochloric, hydrobromic, iodic, nitric, sulphuric, phosphoric, acetic, benzoic, ascorbic acid. Physiologically acceptable salts include also quaternary derivatives of compounds of formula (I) obtained by reaction of the above compounds with compounds of formula R₈—Q wherein R₈ is C₁₋₆ alkyl, phenyl C₁₋₆ alkyl or C₃₋₇ cycloalkyl C₁₋₄ alkyl and Q is a leaving group such as halogen, p-toluenesulphonate, mesylate. Preferred R₈ groups are methyl, ethyl, n-propyl, iso-propyl and cyclopropylmethyl. Physiologically acceptable salts also include internal salts of compounds of formula (I) such as N-oxides. The compounds of formula (I) and their physiologically acceptable salts may also exist as physiologically acceptable solvates, such as hydrates, which constitute a further aspect of the present invention. It has to be understood that the carbonyl group in position two of the general formula (I) might exist in its enol form when R is hydrogen and that there are also the tautomers of the amidino derivatives of formula (I) wherein R₅ is a group of formula —CR₆—N—R₇ and R₆ and R₇ are as hereinbefore defined. The present invention therefore includes in its scope these tautomeric forms.

Some of the compounds of formula (I) according to the present invention contain chiral or prochiral centres and thus may exist in different stereoisomeric forms including enantiomers of (+) and (–) type or mixtures

of them. The present invention includes in its scope both the individual isomers and the mixtures thereof.

It has to be understood that, when mixtures of optical isomers are present, they may be separated according to the classic resolution methods based on their different physico-chemical properties, e.g. by fractional crystallization of their acid addition salts with a suitable optically active acid or by the chromatographic separation with a suitable mixture of solvents.

In the present invention the term A of formula (a) means 3-linked 8-azabicyclo [3.2.1]octane or 3-linked 9-azabicyclo cyclo [3.3.1]nonane or 2-linked 7-azabicyclo [2.2.1]heptane, 4-linked piperidine, the one of formula (b) means 3 or 4-linked 1-azabicyclo [2.2.2]octane, the one of formula (c) means 4-linked 1-azabicyclo [3.3.1]nonane and the one of formula (d) means 5-linked 2-azabicyclo [2.2.2]octane. The term halogen means fluorine, chlorine, bromine or iodine. It has also to be understood that in compounds of formula (I) the azabicyclic moieties of group A may be endo or exo substituted.

Compounds of formula (I) containing the pure endo or exo moieties may be prepared starting from the appropriate precursors or by separating mixtures of the endo or exo isomers not stereospecifically synthesized, by conventional methods such as e.g.: chromatography.

Preferred compounds of formula I, based upon their activity as 5-HT receptor blocking agents, are those wherein:

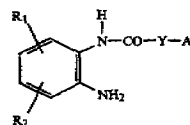
A is endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, R₁ and R₂ are H, R is H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl and Y is oxygen or NH;

A is 1-azabicyclo[2.2.2]oct-3-yl, R₁ and R₂ are H, R is H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl and Y is oxygen or NH;

A is endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl, R₁ and R₂ are H, R is H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl and Y is oxygen or NH; or,

A is endo-1-azabicyclo[3.3.1]non-4-yl, R₁ and R₂ are H, R is H, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl and Y is oxygen or NH.

The compounds of general formula (I) when R is H may be prepared by reacting a compound of general formula (II)

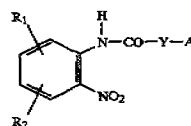


wherein R₁, R₂, Y and A are as hereinbefore defined, with a reactive carbonyl derivative of formula (III)



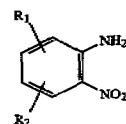
wherein X and X' are leaving groups which may each be, for example, halogen, halogenated alkoxy, alkoxy or a heterocycle. Preferred groups are chlorine, trichloromethoxy, methoxy, ethoxy or imidazolyl. The reaction may be conveniently carried out in aprotic solvents such as benzene, toluene, ethylacetate, acetonitrile, tetrahydrofuran, methylene chloride, chloroform, carbon-tetrachloride or dimethyl-formamide at a temperature ranging from 0° to 100° C., preferably at 5° C.,

at room temperature or at the boiling point of the solvent of choice. The presence of an acid acceptor such as triethylamine may be beneficial in some instances. Compounds of general formula (II), used as starting materials in the above mentioned process, may be prepared by reducing a compound of formula (IV)

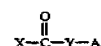


wherein R₁, R₂, Y and A are as hereinbefore defined, with hydrogen or a hydrogen donor such as ammonium formate, cyclohexene, cyclohexadiene, or hydrazine. The reduction is preferably carried out with hydrogen in the presence of a suitable catalyst, preferably 5% or 10% Pd/C or Raney nickel in the presence of a suitable solvent such as methanol, ethanol, toluene, water or a mixture of them. The same reduction may be conveniently carried out with iron in acidic medium or in the presence of FeCl₃ with Zn in acetic or hydrochloric acid, with SnCl₂ in hydrochloric acid or with other reducing agents such as titanium trichloride, ferrous sulphate, hydrogen sulphide or its salts, sodium hydrosulphite.

Compounds of general formula (IV) may be prepared by reacting a compound of general formula (V)



wherein R₁ and R₂ are as hereinbefore defined, with a reactive intermediate of general formula (VI)



wherein X, Y and A are as hereinbefore defined. The reaction is carried out in an aprotic solvent such as tetrahydrofuran, acetonitrile, chloroform, toluene, chlorobenzene or without solvents, and optionally in the presence of an acid acceptor, preferably in pyridine at a temperature ranging from 20° to 100° C. preferably at 20° or at 80° C.

Compounds of general formula (V) are either commercially available or may be conveniently prepared according to known procedures. For example, 5-fluoro-2-nitro-aniline is prepared according to Courtin Helv. Chim. Acta 65,546 (1982), 5-methoxy-2-nitro-aniline is prepared according to Morrin Acheson R. et al. J. Chem. Soc., Perkin Trans 1, 1117 (1978). Compounds of general formula (VI) may be prepared by reacting a compound of general formula (VII)

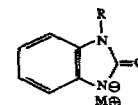


wherein A and Y are as hereinbefore defined, preferably Y is an oxygen atom, with a compound of formula

(III), wherein X and X' are as hereinbefore defined, preferably halogen and halogenated alkoxy. The reaction is carried out in aprotic solvents such as tetrahydrofuran, acetonitrile, methylene chloride or chloroform at a temperature between 10° C. and the boiling point of the solvent of choice, preferably at room temperature. Compounds of general formula (VI) are preferably isolated as hydrochloride salts.

Compounds of general formula (VII) are either commercially available or may be prepared according to known procedures, for example, endo-9-methyl-9-azabicyclo[3.3.1]nonan-3-ol is prepared according to C. L. Zirkle et al. J. Org. Chem. 26, 395 (1961), endo-8-phenyl-methyl-8-azabicyclo[3.2.1]octan-3-ol is prepared according to Nador et al. Arzneim Forsch 12, 305 (1962).

The compounds of general formula (I), wherein R₁ and R₂ are both hydrogen atoms and R, Y and A are as hereinbefore defined, may conveniently be obtained by reacting a compound of formula (VIII)

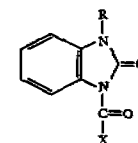


wherein M is a metal atom, such as sodium, potassium or lithium, preferably sodium with a compound of formula (VI). The reaction is preferably carried out in a polar aprotic solvent, such as dimethyl formamide or tetrahydrofuran at a temperature ranging from 0° to 100° C., preferably at room temperature.

Compound (VIII) is generated "in situ" from the corresponding hydrogen compounds by means of sodium, potassium, sodium hydride, potassium hydride, potassium tert-butyrate, butyllithium, lithium diisopropylamide, preferably sodium hydride.

Compounds which can be used to prepare the hydrogen compounds of formula (VIII) are either commercially available or may be prepared according to Z. Eckstein et al. J. Chem. Engineering Data 28, 279 (1983), or the references cited therein.

The compounds of general formula (I), wherein R₁ and R₂ are both hydrogen atoms and R, Y and A are as hereinbefore defined, may be also prepared by reacting a reactive compound of general formula (IX)

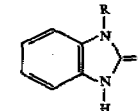


wherein R and X are as hereinbefore defined, with a compound of formula (X)



wherein Z is a hydrogen atom, a metal preferably Li, Na or K, Y and A are as hereinbefore defined. The reaction is carried out in an aprotic solvent such as tetrahydrofuran, chloroform, acetonitrile, o-dichlorobenzene and optionally in the presence of an acid acceptor such as pyridine or triethylamine, preferably pyridine, at a temperature ranging from 0° to 200° C., preferably between 20° and 160° C. Compounds of general

formula (IX), used as starting materials in the above mentioned process, wherein R is hereinbefore defined and X is chlorine, may be prepared according to the method described by W. H. W. Lunn U.S. Pat. No. 4,061,861. Alternatively the same compounds may be prepared by reacting a compound of general formula (XI)



wherein R is as hereinbefore defined, with a compound of general formula (III), wherein X and X' are as hereinbefore defined, preferably they are halogen and halogenated alkoxy. The reaction is preferably carried out in an inert solvent, such as tetrahydrofuran, dioxane or dichlorobenzene optionally in the presence of charcoal at temperature between 50° C. and 150° C., preferably at the boiling point of the solvent. Compounds of general formula (XI) are either commercially available or they may be prepared according to Z. Eckstein et al. J. Chem. Engineering Data 28, 279 (1983).

Compounds of general formula (X), used as starting materials in the above mentioned process, wherein Z is a metal atom as hereinbefore defined, may be conveniently prepared by reacting a compound of general formula (VII)



wherein Y and A are as hereinbefore defined, with a metal, a metal hydride or a strong base such as, for example, sodium hydride, potassium hydride, metallic sodium or potassium, potassium t-butyrate, butyl lithium, lithium diisopropylamide, preferably sodium hydride or butyl lithium in an aprotic solvent such as tetrahydrofuran, diethyl ether or dimethylformamide.

The reaction is preferably carried out at a temperature between -78° C. to room temperature. Compounds of formula (VII) are either commercially available or may be prepared according to known procedures (c.f., for example, C. L. Zirkle et al. J. Org. Chem. 26, 395 (1961); J. Med. Chem. 16, 853 (1973); S. Archer J. Am. Chem. Soc. 79, 41 (1957); Chemical Abstract 94, 65477 (1981); European Patent Application 94,742 (1983); E. F. Elslager J. Med. Chem. 17, 75 (1974); G. Kraiss et al. Tetrahedron Lett. 12, 57 (1971); P. Dorstert et al. Eur. J. Med. Chem. 19, 105 (1984). It has to be understood that compounds of general formula (I) containing an R, R₁, R₂, R₃ and R₅ group which may give rise to another R, R₁, R₂, R₃ and R₅ group, are useful novel intermediates. Some of these transformations may also occur in the intermediates for compounds of general formula (I). Some examples of such conversions, which obviously are not exhaustive of all possibilities, are:

- 1) a nitro group may be transformed into an amino group by reduction;
- 2) an amino group may be transformed into a C₁₋₆ acylamino group by acylation with a suitable carboxylic acid derivative;
- 3) an amino group may be transformed into a C₁₋₄ alkyl N-mono or di-substituted group by alkylation;
- 4) an amino group may be transformed into a C₁₋₆ alkoxy carbonyl amino group by reaction with a

- 7 suitable reactive C₁₋₆ alkyl carbonic acid monoester derivative;
- 5) a carboxyl group may be transformed into a C₁₋₆ alkoxy carbonyl group, or into a carbamoyl group optionally C₁₋₄ alkyl N-mono or di-substituted by reaction of a suitable reactive carboxylic acid derivative with appropriate alcohols and amines;
- 6) a carbamoyl group may be transformed into a cyano group by dehydration;
- 7) a C₁₋₆ alkyl thio or a C₁₋₆ alkyl sulphanyl group may be transformed into a C₁₋₆ alkyl sulphanyl or a C₁₋₆ alkylsulphonyl group by oxidation;
- 8) an aromatic hydrogen group may be transformed into a nitro group by nitration;
- 9) a hydrogen group may be transformed into a halogen group by halogenation;
- 10) a secondary amide group, optionally conjugated with other carboxamidic moieties, may be transformed into a C₁₋₆ N-alkyl tertiary amide group by alkylation;
- 11) a secondary amine group may be transformed into an amidino derivative by reaction with appropriate reactive compounds such as e.g. ethyl formimidate, ethyl acetimidate or cyanamide;
- 12) a tertiary amino group may be transformed into a quaternary ammonium derivative by reaction with a suitable alkylating agent such as methyl bromide or methyl iodide;
- 13) a tertiary amidic group optionally conjugated with other carboxamidic moieties may be transformed into a secondary amidic group by removing an optionally C₁₋₆ alkoxy substituted benzyl.

These transformations are well known to any expert of the branch.

The compounds of general formula (I) prepared according to the process as above described may optionally be converted with inorganic or organic acids into the corresponding physiologically compatible acid addition salts, for example, by conventional methods such as by reacting the compound, as base, with a solution of the corresponding acid in a suitable solvent. Particularly preferred acids include for example hydrochloric, hydrobromic, sulphuric, acetic, citric, tartaric acids.

Particularly preferred compounds, according to the present invention are the following:

N-(1-azabicyclo[2.2.2]oct-3-yl)-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 28).

N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-3-methyl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 31).

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 26).

N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 27).

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-methyl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxamide (Compound 32).

2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid (endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl) ester (Compound 19).

N-(endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide (Compound 45).

3-Ethyl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl) ester (Compound 60).

2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid (endo-8-amidino-8-azabicyclo[3.2.1]oct-3-yl) ester (Compound 44).

As already mentioned hereinbefore the new compounds of formula (I), according to the present invention, have useful pharmacological properties owing to their ability to antagonize the physiological 5-HT effects in warm-blooded animals. Therefore the new compounds are commercially viable in the prevention and in the treatment of disorders wherein 5-HT receptors are involved such as chemotherapy or radiation induced nausea and emesis, delayed gastric emptying, psychosis, and anxiety.

The following tests show that the compounds according to the present invention have favorable characteristics in these respects.

PHARMACOLOGY

Bezold-Jarisch Reflex in Anaesthetized Rats

Rats (250-275 g) were anaesthetized with urethane (1.25 g/kg i.p.). Blood pressure was recorded from the left femoral artery by means of a pressure transducer (Statham) and heart rate was recorded by feeding a cardiometer with the blood pressure signal.

The Bezold-Jarisch effect was elicited by rapid bolus intravenous injection of 5-HT (20 µg/kg). Increasing doses of antagonists were injected 5 min before 5-HT to evaluate their effect on the initial abrupt cardiac slowing and associated fall in blood pressure resulting from the reflex vagal stimulation. ED₅₀ values were calculated by linear regression analysis of the data expressed as percentage inhibition.

The obtained potency of the compounds, object of the present invention, is reported in the table I.

TABLE I

Compound	Bradycardia ED ₅₀ (µg/kg, i.v.)	Hypotension ED ₅₀ (µg/kg, i.v.)
1	5.4	5.9
19	3.4	6.8
24	5.7	7.8
25	12.0	6.5
26	0.3	0.4
27	0.35	0.51
28	1.0	1.5
31	0.49	1.97
32	1.7	2.2
37	3.7	3.9
44	0.0003	0.0004
45	1.7	1.0
47	1.7	2.2
48	4.7	6.4
50	6.1	5.8
51	0.4	1.3
52	0.3	1.1
54	0.6	2.0
56	1.3	1.4
57	4.0	3.1
60	3.2	5.2

Guinea Pig Ileum Longitudinal Muscle-Myenteric Plexus

Male guinea pigs (Dunkin Hartley, 450-550 g) were killed by cervical dislocation. A 2 cm segment of distal ileum removed about 10 cm proximal to the caecum was suspended under 0.5 g tension in a 10 ml organ bath containing Tyrode solution (mM: NaCl 137; KCl 2.68; CaCl₂ 1.82; NaHCO₃ 5.9; MgCl₂ 1; NaH₂PO₄ 0.42; glucose 5.6) oxygenated with 95% O₂ 5% CO₂ at 37° C. Responses were registered with an isotonic transducer on a polygraph (Basile).

Electrical field stimulation (EFS) was performed with bipolar platinum electrodes, with 0.5 msec pulses at 0.1 Hz frequency, supramaximal voltage. When contractions had stabilized, cumulative concentration-response curves were constructed for the compounds under investigation, by adding increasing concentration at 5 min intervals.

The effect of compounds of EFS evoked contractions was evaluated as percentage of the contraction height measured before addition of compounds.

The compounds, object of the present invention, strengthened the contractions induced by electrical stimulation in the guinea pig ileum in the concentration range 10⁻¹⁰ - 10⁻⁸M, while having no effect on muscle tone.

Antiemetic Activity

Beagle dogs of both sexes (8-12 kg b.w.) were administered cisplatin (3 mg/kg) by intravenous route. Number of emetic episodes was counted during 5 hrs after cisplatin administration. 5 min before cisplatin, animals were given saline (control animals) or a dose of antagonist (treated animals) by i.v. route. In each experiment with an antagonist, protection was calculated as percentage inhibition of the number of emetic episodes in the treated animal compared to the average value obtained in the control group. Linear regression analysis was applied, and the dose reducing by 50% the number of emetic episodes in the control group (ED₅₀) was estimated.

The potency (ED₅₀, µg/kg i.v.) of tested compounds, is shown below:

Compound 26	21.5 µg/kg
Compound 45	3.7 µg/kg
Compound 50	1.3 µg/kg
Compound 1	146.0 µg/kg
Compound 27	3.6 µg/kg
Compound 47	4.4 µg/kg
Compound 80	3.7 µg/kg

Gastric Emptying Properties

This model provides evidence of a facilitation of gastrointestinal peristalsis which may be of benefit in pathological situations related to gastrointestinal motility (Costall and Naylot, Scand. J. Gastroenterology 25, 769-787, 1990).

Male rats fasted for 24 hours before the experiments, were administered amberlite pellets by stomach gavage. The test drugs were administered intraperitoneally immediately after the gastric gavage. The animals were killed 60 min after pellets administration; the stomach was carefully removed and opened and the pellets remaining inside were counted. ED₅₀ value (i.e. the dose that reduces by 50% the number of pellets retained in the stomach of control group) and relative confidence

limits (P<0.05) were calculated. The results of the test are set in the following table:

Compound	ED ₅₀ µg/kg i.p.	95% c.i.
26	44.7	17.7-68.0
45	11.0	7.0-19.0
50	34.4	26.1-45.3
1	107.9	16.6-701.1
27	39.4	21.8-161.9
28	229.0	47.6-1879.4
47	6.4	2.3-17.5
48	3.9	1.2-12.9
60	163.2	92.5-288.0

Anxiolytic Properties

Method: light/dark exploratory test in mice.

The procedure is as described in Jones et al. (Br. J. Pharmacol. 93:985-993, 1988) and is based on the aversion of mice to wide, brightly lit areas. The apparatus is an open-topped box divided into a small and large area by a partition which has a hole at floor level. The small compartment, painted black, is illuminated with red light and the large compartment, painted white, is illuminated by white light. Control animals spend most of their time in the dark area. Animals treated with anxiolytic drugs spend a longer time in the bright area.

Results: tested compounds induced animals to spend a longer time in the bright area, as reported in the following table:

Treatment	Dose mg/kg	Time (sec)	
		dark	light
VEHICLE	—	132 ± 48	48 ± 22
COMPOUND 28	0.001	97 ± 33*	84 ± 33*
VEHICLE	—	109 ± 12	71 ± 12
COMPOUND 45	0.001	50 ± 32*	128 ± 30*
COMPOUND 50	0.01	58 ± 61*	122 ± 61*
VEHICLE	—	126 ± 8	54 ± 8
COMPOUND 48	0.003	114 ± 24*	66 ± 24*
VEHICLE	—	125 ± 11	55 ± 11
COMPOUND 31	0.001	106 ± 5*	74 ± 5*

Values represent mean±S.D. from 8-10 mice. Compounds were administered i.p. 45 before testing.

Anova test: * P<0.05; + trend of difference vs vehicle, not significant.

Antipsychotic Properties

The chronic treatment with typical antipsychotic drugs causes a decrease in the number of spontaneously active dopaminergic neurones in the Ventral Tegmental Area of rat brain (Bunney and Grace, Life Sci. 23: 1715, 1978). Method: the number of spontaneously active dopaminergic neurones in the Ventral Tegmental Area was detected as described by Bunney and Grace (Life Sci. 23: 1715, 1978) in rats treated for 21 days with compound 26.

Results:

Compound 26 (15 µg/kg s.c., twice daily, for 21 days) significantly reduced the number of spontaneously active dopaminergic cells in the Ventral Tegmental Area: