A COMPOSITION COMPRISING A COMBINATION OF RECEPTOR AGONISTS AND ANTAGONISTS

The present invention relates to a composition comprising a combination of a) at least one compound with agonist activity to the 5-HT₄ receptor and b) at least one compound with antagonist activity to the 5-HT₁ receptor and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.
A composition comprising a combination of receptor agonists and antagonists

Field of the Invention

The present invention relates to a composition comprising a combination of a) at least one compound with agonist activity to the 5-HT₄ receptor, and b) at least one compound with antagonist activity to the 5-HT₃ receptor, to a composition as defined above for use as a medicament, to the use of said composition in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction in humans or animals, and to a method of treatment of such disorders, wherein said compound is administered.

Background of the Invention

The seven main receptors of the 5-HT (serotonin; 3-(β-aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported to be of significance in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in e.g. WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT₁ type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇ type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., Eur. J. Pharm., 334, 1-23 (1997), which is incorporated herein by reference.

A review of typical agonists and antagonists of various 5-HT receptors is disclosed in R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference.

SU 1 701 320 A1 discloses the use of serotonin for treatment of acute asthma attacks. This reference does not suggest any receptor mechanism for serotonin, which is a compound with both a contracting and a relaxing ef-
fect on the airways, as is further discussed herein below.

In the RBI Handbook or Receptor Classification and Signal Transduction, 3rd Edition, 1998, RBI, One Strathmore Road, Natick, MA 01760-2447, USA, Editor: Keith J. Watling are also 5-HT receptor compounds having agonist or antagonist activity to various receptors disclosed.

Disclosure of the Invention

The present invention is based on the novel finding that certain 5-HT receptors are of utmost importance in regulating bronchoconstriction, that is determining the level of airway constriction.

As used herein, the expression "disorders involving airway constriction", equivalent to the expression "bronchoconstriction disorder", refers to an abnormal increase of the force development of the smooth muscle in human or animal airways, resulting in a reduced diameter in some or all of the airways of the lungs and/or the extrapulmonary airways, such as occurring in asthma, chronic obstructive pulmonary disease, emphysema and chronic bronchitis. Said expression also refers, in a wider sense, to reduction of airflow, more precisely airway diameter, caused by swelling, oedema, plasma extravasation or mucous secretion caused by e.g. asthma or any other disorder related thereto.

The expression "has the capacity of reducing the abnormal airway constriction by at least ...%" used throughout the present patent application means that the compound in question or the composition of compounds in combination as well as the derivatives and pharmaceutically acceptable salts thereof, persistently reduces, in a certain degree, airway constriction caused either by (1) the underlying disease (asthma etc) or (2) the administration of 5-HT or other substances capable of activating constricting 5-HT receptors, e.g. 5-HT_3 receptors. The level of constriction in the airways can, for instance, be de-
terminated by spirometric measurements of the Forced Expiratory Volume (FEV1), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV1 during periods of relatively little obstructive problems.

The present invention relates in one aspect to a composition comprising a combination of compounds comprising a) one or several compounds with agonist activity to the 5-HT4 receptor, and b) one or several compounds with antagonist activity to the 5-HT3 receptor.

In another aspect, the present invention relates to a composition as defined above for use as a medicament.

In still another aspect it relates to the use of said composition in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving airway constriction, such as asthma, chronic obstructive pulmonary disease, emphysema and chronic bronchitis.

In a preferred embodiment said compound with 5-HT4 receptor agonist activity included in the composition is 5-HT or a derivative thereof with agonist activity to the 5-HT4 receptor. The combination of a) one or several 5-HT4 receptor agonist(s), and b) one or several 5-HT3 receptor antagonist(s) increases airway relaxation compared to the use of either compound alone, wherein said combination has the capacity of reducing the abnormal airway constriction by at least 30%, preferably at least 60%, and most preferably at least 90%.

According to the present invention, several known 5-HT3 antagonist compounds are, unexpectedly, able to enhance a 5-HT-induced airway relaxation. The 5-HT3 receptor is a ligand modulated ion channel. Several potent and specific 5-HT3 antagonists exist today, of which ondansetron, tropisetron, granisetron, and dolasetron are commercial pharmaceuticals, but not against disorders involving airway constriction.
Some of the 5-HT₃ receptor antagonists are at the same time 5-HT₄ receptor agonists. However, for a substance to be active as a 5-HT₃ receptor antagonist, the distance from the aromatic center to the basic nitrogen should be about 7,5 Å and no large substituents are tolerated on the basic nitrogen. In contrast, for 5-HT₄ receptor agonists the corresponding distance is about 8 Å, and a large lipophilic group may be bound to the basic nitrogen, thereby obtaining a better binding to 5-HT₄.

The 5-HT₃ antagonists may be divided into certain classes on the basis of chemical structure. Some are unspecific, e.g.

![Chemical structure of a 5-HT₃ antagonist](image)

benzazepines, e.g. mirtazapine

![Chemical structure of mirtazapine](image)
benziazepines, e.g. diltiazem

e.g. perphenazine, chlorpromazine, stemetil.
Some are at the same time 5-HT4 agonists, e.g. benzamides

(cisapride, zacopride, mosapride, metoclopramide, pancopride, BRL 24924, BMY 33462)
2,3-dihydro-benzofuran-7-carboxamides

(e.g. zatosetron=LY 277359, ADR 851);

1,4-benoxazin-8-carboxamides

(e.g. azasetron = Y25130)
benzimidazolones

e.g. itasetron (=DAU 6215);
indazol-3-carboxamides

e.g. N 3389, LY 278584, DAT 582 (= (R) AS-5370)
The latter group reminds most of the specific 5-HT₃
antagonists, which contains the group

in different forms, such as
ondansetron (=GR 38032 F)

alozetron

cilansetron (=KC 9946)

In one group of substances the structure has been inverted and the carbonyl group has been placed on the indoline nitrogen

PK 1052

This substance is unique by being an antagonist against both 5-HT₃ and 5-HT₄ receptors.
BRL 46470A binds to two different positions of the receptor.

A further development is the so-called bisindoles

Another group is the isoquinoline-1-ones

palonosetron (=RS 25259-197)  RS 42358-197

and the quinoline-3-carboxamides

WAY-SEC 579  Mirisetron (=WAY 100579)
Also the quinoline-4-carboxylates are active antagonists

5 e.g. KF 17643

10 e.g. KF 18259

Other compounds are benzimidazolones

20 e.g. droperidol (neurolidol, etc.), itasetron (DAU6215), and the naphtimides

25 e.g. RS 56532

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SUBSTITUTE SHEET (RULE 26)
e.g. RS 56532
A unique single structure is MDL 72222, which also is a specific 5-HT₃ antagonist

Other specific structures are

GK 128

Talipexole

iodophenpropit
thioperamide, and

2-piperidin- and 2-piperazin-benzimidazoles.

According to the present invention, the following
15 compounds can also be used as antagonists to the 5-HT₃ receptor: (R)-zacopride, 2-methyl-5HT, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, 3-((allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-((1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-((dimethylamino)methyl)-3-((1-methyl1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyamezine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazine, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICS 205-930, Imipramine, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KP-20170, Lerasetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Methysergide, Mianserin, MK 212, N-3256, NAN-190, N-methylquipazine, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Pancropride, Phenylbiguanide, Pitozifen, Prochlorperazine (Stemetil), QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanerpin, RP 62203, RS-25259-197, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-
apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperazine; tropanyl-3,5-di-methylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron (=ICS 205-930=Rifenserin), Bemese-tron, L-683,877, LY-278,584 maleate and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect and capability of reducing abnormal airway constriction as specified above.

In the following, an alternative presentation of useful compounds according to the present invention and references thereto is listed.

**N-substituted benzamides**

- Metoclopramide

![Metoclopramide](image)

- QX 222. The compound is an analogue to lidocain®, which is a N-substituted benzamide derivative.

- Cisapride (Cizapride) cis-4-Amino-N-[1-[3-((p-fluorophenoxy)propyl]-3-methoxy-4-piperidyl]-5-chloro-o-anisamide. The compound is also a known 5-HT4 agonist.
cis-4-Amino-N-[1-[3-(α-fluorofenoxi)propyl]-3-metoxi-4-piperidyl]-5-kloro-o-anisamid

- Pancopride ((+)-N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-amino-5-chlorobenzamide)

Pancopride ((+)-N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-amino-5-chlorobenzamide) is a new potent and selective 5-HT3 receptor antagonist, orally and parenterally effective against cytotoxic drug-induced emesis. In vitro, pancopride displayed high affinity (Ki = 0.40 nM) for [3H]GR65630-labelled 5-HT3 recognition sites in membranes from the cortex of rat brains. In vivo, pancopride antagonized 5-HT-induced bradycardia in anaesthetized rats when administered i.v. 5 min (ID50 = 0.56 microgram/kg) or p.o. 60 min (ID50 = 8.7 micrograms/kg) before 5-HT challenge. A single oral dose (10 micrograms/kg) of pancopride produced a significant inhibition of the bradycardic reflex over an 8-h period. Pancopride dose dependently inhibited
the number of vomiting episodes and delayed the on-
set of vomiting induced by cisplatin in dogs (ID50 = 3.6 micrograms/kg i.v. and 7.1 micrograms/kg p.o.). Panco pride was also effective in blocking mechlor-
ethamine- and dacarbazine-induced emesis. Unlike
metoclopramide, panco pride was shown to lack any
measurable antidopaminergic activity both in vitro
and in vivo. These results support clinical data,
indicating that panco pride will be a useful drug for
treating cytostatic-induced emesis in humans.

- (R)-zacopride (R+ zacopride, zacopride) IUPAC name:
  4-amino-N-(1-azabicyclo[2.2.2] oct-3yl)-5-chloro-2-
  methoxy-benzamide.

The differential activities of R (+)- and S(-)-zac-
co pride as 5-HT3 receptor antagonists.
Barnes JM, Barnes NM, Costall B, Domeney AM, Johnson
DN, Kelly ME, Munson HR, Naylor RJ, Young R; Pharma-

R(+)- and S(-)-zacopride were assessed as potential
5-HT3 receptor antagonists in behavioural and bio-
chemical tests. The S(-)isomer was more potent than
the R(+)isomer to antagonise the hyperactivity in-
duced by the injection of amphetamine or the infu-
sion of dopamine into the nucleus accumbens in the
rat. In contrast, the R(+)isomer was more potent to
reduce the aversive behaviour of mice to a brightly
illuminated environment and in a marmoset human

threat test, to facilitate social interaction in
rats, to increase performance in a mouse habituation
test and prevent a scopolamine-induced impairment,
and to antagonise the inhibitory effect of 2-methyl-
5-hydroxytryptamine to reduce [3H]acetylcholine re-
lease in slices of the rat entorhinal cortex. In
binding assays, [3H]S(-)-zacopride and [3H]R(+)-
zacopride labelled homogenous populations of high-
affinity binding sites in the rat entorhinal cortex, R(+)zacopride compete for a further 10 to 20% of the binding of [3H]R(+)/S(-)-zacopride or [3H]R(+)-zacopride in excess of that competed for by (S)(-)zacopride. It is concluded that both isomers of zacopride have potent but different pharmacological activities, with the possibility of different recognition sites to mediate their effects.

- BRL 24682
  The compound is also a known 5-HT4 agonist.

- BRL 24924 [(+/-)-(endo)]-4-amino-5-chloro-2-methoxy-N-(1-azabicyclo-[3.3.1]-non-4-yl) benzamide hydrochloride. The compound is also a known 5-HT4 agonist.


- Renzapride= BRL 24924; see above

- SC-52491 (Azanoradamantane)

- SC-53116 ((1-S,8-S)-4-amino-5-chloro-N-[(hexahydro-1H-pyrrolizin-1-yl) methyl]-2-methoxy-benzamide hydrochloride)

- Batanopride (4-amino-5-chloro-N-[2-(diethylamino)ethyl]2-(1-methyl-2-oxopropoxy) benzamide). Batanopride is also known by the name BMY-25801.

- WAY 100289
Indoles, Indole-1-carboxamides and Imidazole derivatives

- 2-methyl-5-HT

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- 5,7-DHT = 5,7-dihydroxy-tryptamine

- Bisindoles

- Bufotenine = (5-hydroxy-N,N-dimethyltryptamine)

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- BRL 46470A (endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)2,3-dihydro-3,3 dimethyl-indole-1-carboxamide, hydrochloride)

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- BRL 46470 (endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl)

- BRL 47204

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- FK 1052 (\(+\)-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride)

Pharmacological characterization of FK1052, a dihydropyridoindole derivative, as a new serotonin 3 and 4 dual receptor antagonist., Nagakura Y, Kadowaki M, Tokoro K, Tomoi M, Mori J, Kohsaka M; J Pharmacol Exp Ther 1993 May, 265:2:752-8

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\(+\)-8,9-Dihydro-10-dihydro-10-methyl-7-[(5-methyl-4-imidazolyl) methyl]pyrido-[1,2-a]indol-6(7H)-one hydrochloride (FK1052) is a newly designed and synthesized 5-hydroxytryptamine (5-HT)3 receptor antagonist with 5-HT4 receptor antagonistic activity. This compound, as well as ondansetron and granisetron, dose-dependently inhibited the von Bezold-Jarish re-
flex, a 5-HT3 receptor-mediated response, after intravenous (i.v.) and intraduodenal (i.d.) dosing to rats. The ID50 values showed FK1052 (0.28 microgram/kg, i.v., 5.23 micrograms/kg, i.d.) to be more potent than ondansetron (5.23 micrograms/kg, i.v., 170 micrograms/kg, i.d.) and granisetron (0.70 micrograms/kg, i.v., 66 micrograms/kg, i.d.). Furthermore, bioavailabilities of the test drugs by ID50 ratio (i.d./i.v.) showed that FK1052(17) was better absorbed than ondansetron(33) and granisetron(94) and possessed a similar duration of action to that of ondansetron and granisetron. We also examined the effects on 2-methyl-5-HT-, 5-HT- and 5-methoxytryptamine-induced contractions of guinea pig isolated ileum. FK1052, ondansetron and granisetron concentration-dependently inhibited 2-methyl-5-HT, a 5-HT3 agonist-induced contraction. The pA2 values for the 5-HT3 receptor indicated that FK1052 (8.36) was 40 times and three times more potent than ondansetron (6.79) and granisetron (7.86), respectively. FK1052, unlike ondansetron and granisetron, inhibited the 5-HT4-mediated component of concentration-response curve to 5-HT. Furthermore, FK1052 suppressed 5-methoxytryptamine, a 5-HT4 agonist-induced contraction in a concentration-dependent but insurmountable manner.

- RU 24969 (5-methoxy-3(1,2,3,6-tetrahydropyridin-4-y1)-1 H-indole)
- SDZ 206-792

1. The binding characteristics of [3H]ICS 205-930, a potent and selective 5-hydroxytryptamine 5-HT3 receptor antagonist, were investigated in membranes prepared from murine neuroblastoma-glioma NG 108-15 cells. 2. [3H]ICS 205-930 bound rapidly, reversibly and stereoselectively to a homogeneous population of high affinity recognition sites: Bmax = 58 +/- 3 fmol/mg protein, pKD = 9.01 +/- 0.08 (n = 11). Non-linear regression and Scatchard analysis of saturation data suggested the existence of a single class of [3H]ICS 205-930 recognition sites on NG 108-15 cells. The binding was rapid, stable and reversible. The affinity of [3H]ICS 205-930 determined in kinetic studies was in agreement with that obtained under equilibrium conditions. 3. Competition studies performed with a variety of agonists and antagonists also suggested the presence of a homogeneous population of [3H]ICS 205-930 recognition sites. All competition curves were steep and monophasic and were best fit by a 1 receptor site model. [3H]ICS 205-930 binding sites displayed the pharmacological profile of a 5-HT3 receptor. Potent 5-HT3 receptor antagonists showed nanomolar affinities for [3H]ICS 205-930 binding sites with the following rank order of potency: SDZ 206-830 greater than ICS 205-930 greater than SDZ 206-792 greater than BRL 43694 greater than quipazine greater than BRL 24924 greater than SDZ 210-204 greater than MDL 72222 greater than SDZ 210-205. Metoclopramide, mCP and mianserin showed submicromolar affinity.
Ondansetron INN (Ondansetron)

2,3-Dihydro-9-methyl-3-[(2-metylimidazol-1-yl)methyl]karbazol-4(1H)-on

The compound is both an indole derivative and an imidazole. Other imidazole derivatives are listed below.

- **GR 38032 F**

Comparison of the 5-HT3 receptor antagonist properties of ICS 205-930, GR38032F and zacopride., Cohen ML, Bloomquist W, Gidda JS, Lacefield W; *J Pharmacol Exp Ther* 1989 Jan, 248:1:197-201

The well-documented 5-HT3 receptor antagonists, ICS 205-930 and GR38032F, have been compared with regard to their inhibitory activity at 5-HT3 receptors to another gastrokinetic agent, zacopride. Zacopride and ICS 205-930 showed similar affinity (-log kB approximately 8.0), whereas GR38032F showed lower affinity (-log ka approximately 7.0) at 5-HT3 receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as inhibitors of serotonin-induced bradycardia (5-HT3-mediated activation of the von Bezold Jarisch reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS.
205-903, which was approximately 2-fold more potent than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zacopride possessed the longest duration of inhibitory effectiveness in urethane-anesthetized rats with maximal inhibition still apparent 6 hr after oral administration. All three agents inhibited cisplatin-induced emesis after i.v. administration in dogs with zacopride being 10-fold more potent than ICS 205-930 or GR38032F, which were equipotent. These comparative data with three 5-HT3 receptor antagonists indicate that in animals, zacopride was more potent and longer acting than either ICS 205-930 or GR38032F. Furthermore, after oral administration to rats, GR38032F was slightly less potent than ICS 205-930 and possessed the shortest duration of action.

• Alosetron=Lotronex (Glaxo)
The compound is both an indole derivative and an imidazole. Other imidazole derivatives are listed below.


The purpose of this study was to investigate the pharmacological properties of the novel, selective 5-HT3 receptor antagonist, alosetron, and its effects on transit time in both the normal and perturbed small intestine of the rat. Alosetron concentration-dependently inhibited radioligand binding in membranes containing rat and human 5-HT3 receptors with estimated pKi values of 9.8 (n = 3) and 9.4 (n = 6), respectively. In selectivity studies alosetron had little or no significant affinity for any of the many other receptors and ion channels studied. Alosetron potently antagonized the depolarization produced by 5-HT in the rat vagus nerve (estimated pKB value of 9.8, n = 25). In anaesthetized rats, i. v. administration of alosetron inhibited 2-methyl-5-HT induced bradycardia (Bezold Jarisch index) at 1 and 3 microg kg-1, with an agonist dose ratio of approximately 3.0 at 1.0 microg kg-1, = 3-5). Alosetron administered via the duodenum also inhibited this reflex, with duration of action that was significantly longer than that seen with ondansetron (120-60 min, respectively, n = 6). Alosetron had no significant effect on normal small intestinal propulsion in the rat, but fully reversed the increase in intestinal propulsion (96%, n = 3) produced by egg albumin challenge. Alosetron is a highly selective 5-HT3 antagonist which normalizes
perturbed small intestinal propulsion. Previous clinical data in IBS patients together with the transit data provide a good rationale for further studies with alosetron in IBS patients.

- Bemesetron

- Galdansetron

- Dolasetron mesilate =MDL73147 BF= Anzemet. IUPAC name: (2,6,8,9αβ)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate, monohydrate.

- Dolasetron=MDL74156
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- Tropisetron =Navoban®
  IUPAC name: 1aH,5aH - Tropane - 3a - yl-3 - indole-carboxylate

- Zatosetron =LY 277359. The compound is also called LY 19617.


In this study, we have examined the effect of acute and chronic administration of LY 277359, a putative 5-HT3 receptor antagonist, on the number of spontaneously active dopamine cells in the substantia nigra pars compacta (SNC or A9) and ventral tegmental area (VTA or A10). This was accomplished using the standard extracellular single unit recording techniques. The acute administration of LY 277359 (0.1 or 1.0 mg/kg i.p.) produced a significant increase in the number of spontaneously active A10, but not A9, dopamine cells compared to saline controls. The acute administration of 10 mg/kg of LY 277359 did not significantly alter the number of spontaneously active dopamine cells in either area. In contrast to
its acute effects, the administration of 0.1 mg/kg per day of LY 277359 for 21 days decreased the number of spontaneously active A9 and A10 dopamine cells. However, the i.v. administration of (+/-)-apomorphine (50 micrograms/kg) did not reverse LY 277359's action, suggesting that the chronic LY 277359-induced reduction of dopamine cells was not the result of depolarization block. To test whether chronic administration of LY 277359 at a high dose would induce depolarization block of dopamine cells, rats were treated with 1.0 or 10 mg/kg LY 277359. Interestingly, the chronic administration of 1.0 mg/kg LY 277359 increased the number of A10, but not A9 dopamine cells. In contrast, chronic treatment with 10 mg/kg selectively decreased the number of spontaneously active A10 dopamine cells.

- GR65630 (3-[(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)]-1-propanone)

- GR67330

[3H] GR67330, a very high affinity ligand for 5-HT3 receptors.


GR67330 potently inhibited 5-hydroxytryptamine (5-HT)-induced depolarizations of the rat isolated vagus nerve. At the higher concentrations used (0.3 nmol/l-1 nmol/l) this was accompanied by a marked reduction in the maximum response to 5-HT. The calculated pKB value was 10.2. The binding of the tritiated derivative of GR67330 to homogenates of rat entorhinal cortex was examined. Kinetic analysis revealed that specific [3H] GR67330 (0.1 nmol/l) binding was rapid and reversible. Association and disso-
ciation rate constants were 1.48 +/- 0.36 x 10(8) mol/l-1 s-1 and 7.85 +/- 0.41 x 10(-3) s-1 respectively. Equilibrium saturation analysis revealed specific binding was to a single site (Bmax 22.6 +/- 0.21 fmol/mg protein) of high affinity (Kd 0.038 +/- 0.003 nmol/l). At low ligand concentrations, specific binding was up to 90% of total binding. If unlabelled GR67330 was used to define non-specific binding two sites were evident (Kd1 0.066 +/- 0.007 nmol/l, Kd2 20.1 +/- 9.7 nmol/l; Bmax1 31.5 +/- 3.2 fmol/mg protein, Bmax2 1110 +/- 420 fmol/mg protein). [3H] GR67330 binding was inhibited potently by 5-HT3 antagonists and agonists. Ligands for other 5-HT receptors and other neurotransmitter receptors were either only weakly active or inactive at inhibiting binding. Hill numbers for antagonist inhibition of binding were close to unity, except for quipazine which was significantly greater than one. In common with other 5-HT3 binding studies, all 5-HT agonist tested had Hill numbers greater than one (1.51-1.71). GR38032 and GR65630 inhibited a greater proportion of binding than other 5-HT3 antagonists, this additional binding was interpreted as inhibition from a second saturable site unrelated to the 5-HT3 receptor.

ICS 205-930 ((3 Alpha-Tropanyl)-1H-Indole-3-carboxylic acid ester)
Comparison of the 5-HT3 receptor antagonist properties of ICS 205-930, GR38032F and zacopride., Cohen ML, Bloomquist W, Gidda JS, Lacefield W J Pharmacol Exp Ther 1989 Jan, 248:1:197-201

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and ICS 205-930 showed similar affinity (-log kB approximately 8.0), whereas GR38032F showed lower affinity (-log ka approximately 7.0) at 5-HT3 receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as inhibitors of serotonin-induced bradycardia (5-HT3-mediated activation of the von Bezold Jarisch reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS 205-903, which was approximately 2-fold more potent than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zacopride possessed the longest duration of inhibitory effectiveness in urethane-anesthetized rats with maximal inhibition still apparent 6 hr after oral administration. All three agents inhibited cisplatin-induced emesis after i.v. administration in dogs with zacopride being 10-fold more potent than ICS 205-930 or GR38032F, which were equipotent. These comparative data with three 5-HT3 receptor antagonists indicate that in animals, zacopride was more potent and longer acting than either ICS 205-930 or GR38032F. Furthermore, after oral administration to rats, GR38032F was slightly less potent than ICS 205-930 and possessed the shortest duration of action.

- QICS 205-930
3-Tropanyl-indole-3-carboxylate methiodide. It is also called ICS 205-930.

Indalpine (3-[2-(4-piperidinyl)ethyl]-1H-indole)

VA21B7 (3-[2-(4'-piperonylpiperazinyl) indolyl] carboxaldehyde)


VA21B7 (3-[2-(4'-piperonylpiperazinyl) indolyl] carboxaldehyde) was synthesized as a potential 5-HT3 receptor antagonist. Even though VA21B7 showed a higher affinity towards 5-HT3 receptors as compared to other receptors studied, it was not a potent 5-HT3 receptor antagonist either in the periphery or in the brain. In a simple animal model of anxiety such as the two-compartment box in mice, a remarkable anxiolytic-like effect was found at doses of 2-500 micrograms/kg IP and also at low oral doses, in the microgram range. These drug doses did not produce any significant effect on spontaneous motor activity of mice. The anxiolytic profile of VA21B7 was further explored using other models of anxiety in rats such as the elevated plus-maze and punished-drinking. VA21B7 was compared with standard 5-HT3 receptor antagonists such as ondansetron, tropisetron and granisetron, with the 5-HT1A agent buspirone and with diazepam. In the plus-maze, VA21B7 showed an anxiolytic-like profile after doses of 0.25-0.5 mg/kg IP or 2-4 mg/kg PO which did not modify the number of total entries into the open and closed arms of the maze. Diazepam, granisetron and
tropisetron were also effective in this test but not ondansetron and buspirone. VA21B7 was also able to release suppressed behaviour in the punished-drinking test. The dose-response curve was bell-shaped with a peak at 2-4 mg/kg. At variance with other studies, 5-HT3 receptor antagonists also increased the number of shocks taken in this test and the dose-response curve was also bell-shaped. VA21B7 was not anticonvulsant like diazepam, its anxiolytic action in the light/dark test was not flumazenil-sensitive and there was no rebound anxiogenic effect on withdrawal from chronic VA21B7 treatment for 15 consecutive days. Moreover, VA21B7 was not amnesic like the benzodiazepines but low doses of 2-4 mg/kg reduced the memory deficits induced in rats by scopolamine. Much higher doses were necessary to decrease spontaneous motor activity in rats. Since VA21B7 appears to be well tolerated in rodents at high doses, we think that it is of potential interest as an anxiolytic in humans.

**Benzimidazolones, benzimidazoles and other imidazoles**

The common chemical structure of a benzimidazolone is:

![Chemical Structure](image)

- Iodophenpropit (4-(1H-imidazol-4-yl-methyl)-piperidine)
- BIMU 1 (endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride)
• 2-piperazin-benzimidazole

• 2-piperidin-benzimidazole

• Cilansetron (1-10-[(2-methyl-1H-imidazol-1-yl)methyl]-5,6,8,9,10,11-hexahydro-4H-pyrido [3,2,1-jk]carbazol-11-one hydrochloride)

• GK 128 (2-[(2-methylimidazol-1-y1)methyl]benzo[i]-thiochromen-1-one monohydrochloride hemihydrate)

Effect of a novel 5-hydroxytryptamine3 (5-HT3) receptor antagonist, GK-128, on 5-HT3 receptors mediating contractions and relaxations in guinea-pig distal colon.

Ito C, Kawamura R, Isobe Y, Tsuchida K, Muramatsu M, Higuchi S;

*Gen Pharmacol* 1997 Sep, 29:3:353-9

We investigated 5-hydroxytryptamine3 (5-HT3) receptor-mediating contractions and relaxations in the guinea-pig isolated distal colon using various 5-HT3 receptor agonists and antagonists, including GK-128 (2-[(2-methylimidazol-1-yl) methyl] benzo[f] thiochromen-1-one monohydrochloride hemihydrate).

2. Selective 5-HT3 receptor agonists, 2-methyl-5-HT and m-chlorophenylbiguanide, produced spantide-insensitive contraction and atropine-insensitive contraction and the relaxation. These agonists showed a small, but significant, difference of potency between contraction and relaxation. 3. GK-128 competitively blocked both 2-methyl-5-HT- and m-chlorophenylbiguanide-induced responses with similar potency. The affinities of GK-128 for spantide-insensitive contraction and atropine-insensitive contraction were ten-fold higher than for relaxation. 4. Other selective 5-HT3 receptor antagonists, azasetron and tropisetron, also exhibited higher af-
finity in contraction than in relaxation, but the extent of their affinity differences was smaller than that observed in GK-128. In contrast, grani-setron, ramosetron and ondansetron exhibited no significant differences in their affinity values among the three responses. 5. These results suggest that the 5-HT3 receptors which mediate contraction and relaxation in the guinea-pig distal colon may not be the same, and that GK-128 is a 5-HT3 receptor antagonist with a stronger potency for contraction.

- Droperidol. Ingår i Dridol, Janssen-Cilag

**Droperidol**

\[ \text{INN (Droperidol)} \]

\[ 1-\{1-(3-(4-Fluorobenzyloxy)propyl)-1,2,3,6-tetrahydro-4-pyridyl]-1,3-dihydro-2H-benimidazol-2-on \]

- **KAE-393/YM-114**

\((R)-5-[(2,3-dihydro-1-indolyl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole\)


YM114 (KAE-393), \((R)-5-[(2,3-dihydro-1-indolyl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole hydrochloride, is a derivative of YM060, a potent 5-
HT3 receptor antagonist. We investigated the effects of YM114 on 5-HT3 receptors, both in vitro and in vivo, and on bowel dysfunction induced by restraint stress, 5-HT and thyrotropin-releasing hormone (TRH), and compared them with the effect of trimebutine. YM114 dose dependently inhibited the reduction in heart rate induced by 5-HT (30 micrograms/kg i.v.) in rats (ED50 = 0.31 micrograms/kg i.v.), and the potency of YM114 was almost the same as that of the racemate. The S-form of YM114 also inhibited 5-HT-induced bradycardia, but 1350 times less potent than the R-form. YM114 and its S-form inhibited [3H]GR65630 binding to N1E-115 cell membranes in a concentration-dependent manner with Ki values of 0.341 and 616 nM, respectively, showing the isomeric activity ratio (R-/S-form) of YM114 to be much greater (1800). YM114 antagonized 5-HT-induced depolarization of the nodose ganglion (EC50 = 1.39 nM). Trimebutine (1 mg/kg i.v.) failed to inhibit 5-HT-induced bradycardia, implying that it does not possess 5-HT3 receptor antagonistic activity. YM114 significantly and dose dependently prevented restraint stress-, 5-HT- and TRH-induced increases in fecal pellet output, and restraint stress- and 5-HT-induced diarrhea in rats and mice (ED50 = 6.9, 72.5, 154.6, 9.7 and 52.4 micrograms/kg p.o., respectively). Trimebutine significantly prevented stress- and 5-HT-induced diarrhea (ED50 = 29.4 and 87.3 mg/kg p.o., respectively), but only partially affected stress-, 5-HT- and TRH-induced increases in fecal pellet output. Thus, YM114 is a potent and stereoselective 5-HT3 receptor antagonist with much greater protective effects against stress-induced defecation than trimebutine hydrochloride.

- Itasetron=DAU6215 ((3-alpha-tropanyl)1H-benzimidazolone-3-carboxamide chloride) Intravenous ita-
setron: establishing the effective dose range for
the prophylactic control of acute emesis in cancer
patients undergoing high-dose cisplatin chemothera-
py. .. Patoia L, Del Favero A, Giglietti A, Malacarne
P, Donati D, Indelli M, Bensi G, Palladino MA,
Cigarini P, Kempe R, Voigt T; Clin Oncol (R Coll Ra-
diol) 1999, 11:2:99-104

Nausea and vomiting induced by chemotherapy are a
major cause of distress to patients and reduce com-
pliance with potentially beneficial treatment. Ita-
setron hydrochloride is a new 5-hydroxytryptamine3
(5-HT3) antagonist with potent antiemetic prop-
ties. It is more potent than ondansetron in animal
models and in early clinical studies it demonstrates
a long half-life and does not undergo hepatic bio-
transformation before elimination. The aim of this
open, uncontrolled study was to establish the effec-
tive dose range of itasetron hydrochloride given in-
travenously (i.v.) to patients due to receive high-
dose cisplatin chemotherapy (50-120 mg/m2) for the
first time. Thirty-nine patients were enrolled in
the trial and received a single i.v. infusion of
itasetron hydrochloride at a dose of 17-280 mi-
crog/kg body weight before commencing the cisplatin
infusion (median dose 90-110 mg/m2). Antiemetic pro-
tection was demonstrated by doses in the range of
35-280 microg/kg. The 17 microg/kg dose was not ef-
effective. Treatment failure (>5 emetic episodes/24
hours) was reported in only six (16%) of the 38
evaluable patients over all treatment groups. Ad-
verse events were generally mild or moderate and of
a similar type and incidence to those of current 5-
HT3 antagonists. Physicians' and patients' assess-
ments of efficacy and tolerability of itasetron hy-
drochloride were similar, the majority rating the
treatment as 'good' or 'very good'. In conclusion,
Itasetron hydrochloride is effective in the dose range 35-280 microg/kg in preventing cisplatin-induced emesis. Taken together with results from a larger dose-finding study, a dose corresponding to 35 microg/kg (equivalent to 2.5 mg itasetron, calculated as free base) has been pursued in Phase III studies with the i.v. formulation.

- Lerisetron


A series of 2-piperazinylbenzimidazole derivatives were prepared and evaluated as 5-HT3 receptor antagonists. Their 5-HT3 receptor affinities were evaluated by radioligand binding assays, and their abilities to inhibit the 5-HT-induced Bezold-Jarisch reflex in anesthetized rats were determined. Compound 7e (lerisetron, pKi = 9.2) exhibited higher affinity for the 5-HT3 receptor than did tropisetron and granisetron, while compound 7q (pKi = 7.5) had very low affinity for this receptor, showing that substitution on the N1 atom of the benzimidazole ring is essential for affinity and activity. The effect of substitution on the aromatic ring of benzimidazole by several substituents in different positions is also discussed. A strong correlation between the 5-HT3 antagonistic activity of the studied compounds and the position of substitution on the aromatic ring was established. Thus, while the 4-methoxy derivative 7m showed weak affinity for the 5-HT3 receptor (pKi = 6.7), the 7-methoxy derivative 7n exhibited the highest affinity (pKi = 9.4). Compounds 7e and 7n are now under further investigation.
as drugs for the treatment of nausea and emesis evoked by cancer chemotherapy and radiation.

- Lurosetron

- Mirisetron =WAY100579

- Ramosetron =YM 060. \((R)-5-[(1\text{-methyl}-3\text{-indolyl})\text{-carbonyl}]-4,5,6,7\text{-tetrahydro-1H-benzimidazole hydrochloride}\)

*Indazole carboxamide derivatives*

The compounds have the general structure.

\[
\begin{array}{c}
\text{NH} \\
\text{CO}
\end{array}
\]

- AS5370 ((+/-)-N-[1\text{-methyl}-4-(3\text{-methyl-benzyl})\text{-hexahydro-1H-1,4-diazepin-6-yl}]-1H- indazole-3-carboxamide dihydrochloride). The compound is also a diazepin derivative.

- DAT582 (the compound is the R- enantiomer of compound AS5370) 5-HT3 receptor antagonist effects of DAT582, (R) enantiomer of AS-5370.


The serotonin 5-HT3 receptor antagonist effects of DAT-582, the (R) enantiomer of AS-5370 ((+/-)-N-[1-methyl-4-(3-methyl-benzyl)hexahydro-1H-1,4-diazepin-6-yl]-1H- indazole-3-carboxamide dihydrochloride), and its antipode were compared with those of AS-5370
and existing 5-HT3 receptor antagonists. In anesthetized rats, DAT-582 antagonized 2-methyl-5-HT-induced bradycardia with an ED50 value of 0.25 microgram/kg i.v., whereas the (S) enantiomer was without effect even at 1000 micrograms/kg i.v. In antagonizing the bradycardia, DAT-582 was as potent as granisetron, slightly more potent than AS-5370, and 2, 5 and 18 times more potent than ondansetron, ICS 205-903 and renzapride, respectively, although it was less potent than zacopride. DAT-582 inhibited cisplatin (10 mg/kg i.v.)-induced emesis in ferrets with an ED50 value of 3.2 micrograms/kg i.v. twice. The antiemetic activity of DAT-582 was more potent than that of the existing 5-HT3 receptor antagonists examined, except zacopride. In contrast, the (S) enantiomer had little effect at 1000 micrograms/kg i.v. twice. In isolated guinea-pig ileum, DAT-582 inhibited 5-HT-induced contractions with an IC50 value of 91 nM, whereas the (S) enantiomer hardly inhibited them even at 1000 nM. These results suggest that DAT-582, the (R) enantiomer of AS-5370, potently and selectively blocks 5-HT3 receptors.

- N-3389 (N-3389 (endo-3,9-dimethyl-3,9- diazabicyclo[3,3,1]non-7-yl 1H-indazole-3-carboxamide dihydrochloride)


The antagonistic activities of compound N-3389 (endo-3,9-dimethyl-3,9- diazabicyclo[3,3,1]non-7-yl 1H-indazole-3-carboxamide dihydrochloride) at 5-HT3 and 5-HT4 receptors were examined using in vitro and
in vivo assays. N-3389 showed potent 5-HT3 receptor antagonistic activities in a radioligand binding assay (pKi = 8.77), against 2-methyl-5-HT (2-Me-5-HT)-induced bradycardia in rats (ED50 = 0.73 micrograms/kg i.v., 38 micrograms/kg p.o.) and against 2-Me-5-HT-induced contraction in longitudinal muscle myenteric plexus preparations of guinea-pig ileum (IC50 = 3.2 x 10(-8) M). As a preliminary to investigating the effect of N-3389 on 5-HT4 receptors, we examined the contraction induced by 5-HT in guinea-pig ileum preparations. We confirmed that 5-HT (10(-8)-10(-5) M) induced biphasic contractions in the preparations. Furthermore, 5-HT3 receptor antagonism inhibited the late phase of the contraction induced by high concentrations of 5-HT (3 x 10(-6)-10(-5) M), whereas 5-HT4 receptor antagonism inhibited the early phase of the contraction induced by low concentrations of 5-HT (10(-8)-10(-6) M). N-3389 (10(-7)-10(-5) M) inhibited both phases of contraction induced by 5-HT. In addition, N-3389 (3 x 10(-7)-3 x 10(-6) M) was found to inhibit the increase of electrically stimulated twitch responses induced by 5-HT (10(-8) M) longitudinal muscle myenteric plexus preparation of the guinea-pig ileum. These results suggest that N-3389 acts as a 5-HT3 and 5-HT4 receptor antagonist.

- BRL 43694=Kytril® =Granisetron

Granisetronum INN (Granisetron)
1-Methyl-N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1H-indazol-3-karboxamid

\[ \text{Granisetronum INN (Granisetron)} \]
\[ 1-\text{Methyl-N-(endo-9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1H-indazol-3-karboxamid} \]

The activity of BRL 43694 (granisetron) was investigated using established models of 5-HT3 receptor activity. In guinea-pig isolated ileum, BRL 43694 antagonised the contractions evoked by relatively high concentrations of 5-HT (pA2 = 8.1 +/- 0.2). However, except in high concentrations, BRL 43694 did not affect the contractions of similar preparations of ileum, evoked by electrical field stimulation (cholinergically mediated), the nicotinic agonist dimethylphenylpiperazinium (DMPP) or by cholecystokinin octapeptide. Similarly, BRL 43694 did not affect electrically evoked, cholinergically mediated contractions of rat or human isolated stomach. In other models of 5-HT3 receptor activity (rabbit isolated heart, Bezold-Jarisch reflex in anaesthetised rats), potent antagonism by BRL 43694 was demonstrated. In radioligand binding studies on rat brain membranes, BRL 43694 had little or no affinity for 5-HT1A, 5-HT1B, 5-HT2 or for many other binding sites. BRL 43694 may therefore be a potent and selective 5-HT3 receptor antagonist.

- Litoxetine=SL81.0385

The selective 5HT uptake inhibitor, litoxetine (SL 81.0385), currently under development as an antidepressant was shown to have antiemetic properties in the ferret. Litoxetine (at 1 and 10 mg/kg i.v.) dose dependently reduced the number of retches and vomiting as well as the number of emetic episodes induced by cisplatin (10 mg/kg i.v.) and delayed the onset of emesis. Fluoxetine (at 1 or 10 mg/kg i.v.) failed to inhibit cisplatin-induced emetic responses and, in contrast, significantly increased the number of retches and vomiting and accelerated the onset of emesis. The possibility that the antiemetic effects of litoxetine may be mediated through an interaction with 5HT3 receptors was studied using [3H]quipazine or [3H]BRL 43694 to label the 5HT3 receptor. Litoxetine has moderate affinity for cerebral 5HT3 receptors (Ki = 85 nM), while fluoxetine, similar to other 5HT uptake inhibitors, has only negligible affinity for this receptor (Ki = 6.5 microM). It is proposed that litoxetine inhibits cisplatin-induced emetic responses due to its moderate 5HT3 antagonist properties. The clinical use of the majority of serotonergic antidepressants (e.g. fluoxetine, fluvoxamine etc.) is associated with gastrointestinal discomfort (particularly nausea and vomiting) as a major side-effect. If nausea and vomiting associated with the use of 5HT uptake inhibitors are due to stimulation of 5HT3 receptors, the concomitant 5HT3 antagonism of litoxetine may limit the gastrointestinal side-effects of this novel antidepressant and thus offer an important advantage.

- **LY 278584** ((1-methyl-N-(8-methyl-8-azabicyclo-[3.2.1.]oct-3-yl)-1H-indazole-3-carboxamide)

Specific [3H]LY278584 binding to 5-HT3 recognition sites in rat cerebral cortex.
Wong DT, Robertson DW, Reid LR; *Eur J Pharmacol* 1989 Jul 4, 166:1:107-10

Binding of [3H]LY278584 a 1-methyl-indazole-carboxamide, to putative 5-HT3 recognition sites in membranes isolated from cerebral cortex of rat brain, is examined. Specific binding of [3H]LY278584 accounts for 83-93% of total binding. The unlabelled LY278584 has 500 times greater affinity for [3H]LY278584 recognition sites than its 2-methyl analogue (LY278989), and their potencies parallel their antagonism of the peripheral 5-HT3 receptors. Moreover, the order of potencies of other known antagonists of 5-HT3 receptors supports the conclusion that 3H]LY278584 binds to putative 5-HT3 receptors in cortical membranes.

- LY-278,584 maleate, see above.

- LY258-458

- LY 278989
  
  Specific [3H]LY278584 binding to 5-HT3 recognition sites in rat cerebral cortex.

Wong DT, Robertson DW, Reid LR; *Eur J Pharmacol* 1989 Jul 4, 166:1:107-10

Binding of [3H]LY278584 a 1-methyl-indazole-carboxamide, to putative 5-HT3 recognition sites in membranes isolated from cerebral cortex of rat brain, is examined. Specific binding of [3H]LY278584 accounts for 83-93% of total binding. The unlabelled LY278584 has 500 times greater affinity for [3H]LY278584 recognition sites than its 2-methyl analogue (LY278989), and their potencies parallel their antagonism of the peripheral 5-HT3 receptors. Moreover, the order of potencies of other known an-
agonists of 5-HT3 receptors supports the conclusion that [3H]LY278584 binds to putative 5-HT3 receptors in cortical membranes.

- LY-211-000

Benzofuranes, benzooxazines, benzo(di)azepines, bensothiazepines

A general structure for these classes of compounds is:

- 2,3-dihydro-benzofuran-7-carboxamides. X1=C, X2=O; five-membered ring system.

- RG 12915 ([4-[(N-(1-azabicyclo[2.2.2.]octan-3-(S)-yl)]2-chloro-cis 5a-(S)-9a-(S)-5a,6,7,8,9,9a-hexahydrobenzofuran-2-carboxamide hydrochloride])

- ADR 851 [4-amino-5-chloro-2,3-dihydro-N-(pyrrolidin-2-ylmethyl)benzofuran-7-carboxamide]

- ADR-882
42


5

The present study examined analgesia produced by S and R isomers of the novel 5-HT3 receptor antagonists, ADR-851 and ADR-882 (0.1-10 mg/kg s.c.) against acute thermal, mechanical and formalin-induced inflammatory pain in rats. Neither isomer of ADR-851 or ADR-882 was analgesic in the thermal or mechanical test. Similarly, neither S or R forms of ADR-882 produced significant anti-nociception in the formalin test. In contrast, ADR-851R produced significant analgesia at 3 and 10 mg/kg doses in this test, while ADR-851S produced significant analgesia only at 1 mg/kg.

- RP 62203 (2-[3-(4-(4-fluorophenyl)-piperazinyl)]-propyl)naphto[1,8-ca]isothiazole-1,1-dioxide)

- Clozapine. Ingår i Leponex, Novartis

*Clozapinum INN (Klozapin)*

8-Kloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepin
• Amitryptiline

**Amitriptylinum** INN (Amitriptylin)

5-(3-Dimethylaminopropyliden)-10,11-dihydro-5H-
-dibens[a,d]cyclohepten

• Cyproheptadine. Is the active ingredient of Periactin, MSD

• Diltiazem

Is the active ingredient in Cardizem, Pharmacia Corporation

**Diltiazemum** INN (Diltiazem)

(2S,3S)-3-(Acetyloxi)-5-[2-(dimethylamino)ethyl]-2-(4-metoxifenyl)-2,3-
-dihydro-1,5-bensotiazepin-4(5H)-on
- Imipramin

5-(3-Dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[b,f]azepin

- Mianserin

- Mirtazapine (1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a] pyrido [2,3-c] benzazepine)

- Pizotifen

**Pizotifenum INN (Pizotifen)**

4-(1-Methyl-4-piperidyliden)-9,10-dihydro-4H-benzo-[4,5]cyclohepta[1,2-b]tiofen
Quinolines, quinolicines and isoquinolines

The common structure of quinoline is:

![Quinoline structure](image)

5 Isoquinoline and quinolizine are isomers of quinoline.

- Quinoline-3-carboxamides
- Quinoline-4-carboxylates

10 - Isoquinoline-1-one (isomer till quinolin-1-one)

- SEC 579

15 - RS 56532 \((\text{S})\)-6-amino-5-chloro-2-\((1\text{-azabicyclo[2,2,2]octan-3-yl})\) 2,3-dihydro-1H-benz[de]-isoquinoline-1,3-dione hydrochloride

- 3-\((1\text{-piperazinyl})\)-2-quinoxalinecarbonitrile

20 - 3-\((4\text{-allylpiperazin-1-yl})\)-2-quinoxalinecarbonitrile

- KF 17643 \((\text{endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl-2-}(n\text{-propyloxy})-4\text{-quinolinecarboxylate})\)

25 - KF 18259 \((\text{endo-}(8\text{-methyl-8-aza-bicyclo[3.2.1]oct-3-yl})-1\text{-isobutyl}-2\text{-oxo-1,2-dihydro-4-quinoline-monoxy-4-quinolinecarboxylate hydrochloride})\)

30 - KF 20170 \((\text{endo-N-}(8\text{-methyl-8-aza-bicyclo[3.2.1]oct-3-yl})-4\text{-hydroxy-3- quinolinecarboxamide})\)
• Palonosetron=RS 25259-197
  (3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-
  2,3,3a,4,5,6-hexahydro-1-oxo-1H-benzo[de]-
  isoquinoline-hydrochloride

• Quipazine (2-(1-piperazinyl)-Quinoline)

• N-methylquipazin

• 4-Ph-N-Me-quipazine

• RS-42358-197 [(S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-
  2,4,5,6-tetrahydro-1 H-benzo[de]isoquinolin-1-one
  hydrochloride]

• RS-056812-198 (R)-N-(quinuclidin-3-yl)-2-(1-methyl-
  1 H-indol-3-yl)-2-oxo-acetamide

• RS-25259-197 [(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-
  yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benzo[de]-
  isoquinoline-hydrochloride]

The interaction of RS 25259-197, a potent and selec-
tive antagonist, with 5-HT3 receptors, in vitro.

Wong EH, Clark R, Leung E, Louzy D, Bonhaus DW,
Jakeman L, Parnes H, Whiting RL, Eglen RM, Br J

A series of isoquinolines have been identified as 5-
HT3 receptor antagonists. One of these, RS 25259-197
[(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-
2,3,3a,4,5,6-hexahydro-1-oxo-1H-benzo[de]iso-
quinoline-hydrochloride], has two chiral centres.
The remaining three enantiomers are denoted as
RS 25259-198 (R,R), RS 25233-197 (S,R) and RS 25233-
198 (R,S). 2. At 5-HT3 receptors mediating contrac-
tion of guinea-pig isolated ileum, RS 25259-197 an-
agonized contractile responses to 5-HT in an unsurmountable fashion and the apparent affinity (pKB), estimated at 10 nM, was 8.8 +/- 0.2. In this tissue, the -log KB values for the other three enantiomers were 6.7 +/- 0.3 (R,R), 6.7 +/- 0.1 (S,R) and 7.4 +/- 0.1 (R,S), respectively. The apparent affinities of RS 25259-197 and RS 25259-198, RS 25233-197 and RS 25233-198 at 5-HT3 receptors in membranes from NG-108-15 cells were evaluated by a [3H]-quipazine binding assay. The -log Ki values were 10.5 +/- 0.2, 8.4 +/- 0.1, 8.6 +/- 0.1 and 9.5 +/- 0.1, respectively, with Hill coefficients not significantly different from unity. Thus, at these 5-HT3 receptors, the rank order of apparent affinities was (S,S) > (R,S) > (S,R) = (R,R). 3. RS 25259-197 displaced the binding of the selective 5-HT3 receptor ligand, [3H]-RS 42358-197, in membranes from NG-108-15 cells, rat cerebral cortex, rabbit ileal myenteric plexus and guinea-pig ileal myenteric plexus, with affinity (pKi) values of 10.1 +/- 0.1, 10.2 +/- 0.1, 10.1 +/- 0.1 and 8.3 +/- 0.2, respectively.

Phenthiazines and Benzoazazines

- Chlorpromazine

Chlorpromazinum INN (Klorpromazin)
10-(3-Dimethylaminopropyl)-2-klorofentiazin

- Cyamemazine (10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile)
• Fluphenazin

Fluphenazinum INN (Flufenazin)
10-[3-(4-(2-Hydroxyethyl)-1-piperazinyl)propyl]-2-
-trifluoromethylpentiazin

• Prochlorperazine=Stemetil

• KB-6933 (6-amino-5-chloro-1-isopropyl-2-(4-methyl-1-
piperazinyl)benzimidazole dimaleate)

• Perphenazine. Ingår i Trilafon. Cl istället för CF₃ i
formeln för Flufenazine

• Trifluoperazine
• Azasetron=Y25130 (+-)-N-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide monohydrochloride

Pharmacokinetics of azasetron (Serotone), a selective 5-HT3 receptor antagonist.
Tsukagoshi S *Gan To Kagaku Ryoho* 1999 Jun, 26:7:1001-8

5-HT3 receptor antagonists have been established in a number of clinical trials as effective agents in the management of nausea and vomiting induced by cancer chemotherapy including cisplatin. Azasetron (Serotone) is a potent and selective 5-HT3 receptor antagonist, and classified as benzamide derivative. It has a different chemical structure from indole-type 5-HT3 receptor antagonists such as granisetron, ondansetron, ramosetron and tropisetron. The major difference is found in the pharmacokinetic profiles. Approximately 60-70% of azasetron administered i.v. and orally is excreted in urine as the unmetabolized form. Also, orally-administered azasetron has shown to be absorbed and/or secreted by the saturable transport mechanism in the small intestine, resulting in good bioavailability as approximately 90%. In this report, the relationship between the structure of 5-HT3 receptor antagonists (especially azasetron) and their pharmacokinetics were described.

• 5-((Dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole

• 1,4-Benzoxazin-8-Carboxamide
Other compounds, including piperidines, piperazines, al-
kaloïdes, benzoates and ureas

- Anpirtoline (6-Chloro-2-[piperidinyl-4-thio]-pyridine)

- Ritanserin

- NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-butyl] piperazine)

- Naphtimidese.

- TFMP (1-(3-trifluoromethylphenyl)piperazine)

- Ifenprodil (dl-erythro-4-benzyl-alpha-(4-hydroxy-
phenyl)-beta-methyl-1-piperidine-ethanol tartrate) 
(ifenprodil tartrate)

- MCPP (Meta-chlorophenylpiperazine) (mCPP)

- MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine )

- Metergoline ([(8{BETA})-1,6-dimethylergolin-8-
yl)methyl]-Carbamic acid phenylmethyl ester)

- Methysergide (1-methyl-D-lysergic acid butanolamide)

- S-apomorfin

- Tropanyl-3,5-dimethylbenzoate

- Trimebutine, ett 3,4,5-trimetoxybenzoate derivat.
• TMB-8 (8-(N,N-diethylamino)octyl 3,4,5-trimethoxybenzoate)

• Phenylbiguanide


The aims of the present study were to confirm the modulation by 5-HT3 receptors of the electrically evoked release of tritium from slices preloaded with [3H]-5-HT of guinea-pig frontal cortex, hippocampus and hypothalamus, and to assess their functional role in 5-HT release. 2. The selective 5-HT3 agonist, 2-methyl-5-HT, introduced 8 min before the electrical stimulation, enhanced in a concentration-dependent manner the evoked release of [3H]-5-HT in the three brain regions studied. The 5-HT3 agonists, phenylbiguanide and m-chlorophenyl-biguanide, did not enhance the release of tritium in frontal cortex and hypothalamus slices. 3. In hypothalamus slices, this response was lost when 2-methyl-5-HT was introduced 20 min before the stimulation, thus indicating that these 5-HT3 receptors desensitize rapidly. When 2-methyl-5-HT was added 20-min before the first stimulation period to desensitize the 5-HT3 receptors, removed for 24 min, and then re-introduced 8 min before the second stimulation period, the enhancing effect of 2-methyl-5-HT was restored, thus indicating that these 5-HT3 receptors can rapidly regain normal sensitivity. 4. The enhancing effect of 2-methyl-5-HT was attenuated by the 5-HT3 receptor antagonists m-chloro-phenylpiperazine = quipazine = ondansetron > or = ICS 205-930 = BRL 24924 >
MDL 72222 = zacopride. 5. The 5-HT reuptake blocker, paroxetine, enhanced the electrically evoked release of tritium when introduced 8 min before stimulation; this effect of paroxetine was blocked by ICS 205-930, thus indicating that these 5-HT3 receptors can be activated by endogenous 5-HT. 6. In the absence of electrical stimulation, 2-methyl-5-HT (10 microM) produced a marked enhancement of the basal release of [3H]-5-HT which was calcium-dependent and blocked by S-zacopride but not by paroxetine. 7. The enhancing effect of 2-methyl-5-HT was dependent both on the frequency of stimulation, as indicated by the attenuated effect of 120 stimulations delivered at 1 Hz instead of 5 Hz, and on the duration of the stimulation, as indicated by the more pronounced effect of pulses delivered at 5 Hz for 24 s instead of 72 s or 120 s. McNeil-A-343 (4-[(m-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride).

- MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3-yl-3,5-dichlorobenzoate)

MDL 72222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors. Fozard JR Naunyn Schmiedebergs Arch Pharmacol 1984 May, 326:1:36-44

The properties of MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3-yl-3,5-dichlorobenzoate), a novel compound with potent and selective blocking actions at certain excitatory 5-hydroxytryptamine (5-HT) receptors on mammalian peripheral neurones, are described. On the rabbit isolated heart, MDL 72222 was a potent antagonist of responses mediated through the receptors for 5-HT present on the terminal sympathetic fibres. The threshold for antagonism was approximately 0.1 nM and the negative logarithm of
the molar concentration of MDL 72222 which reduced the
chronotropic response of the isolated rabbit
heart to twice an ED50 of 5-HT to that of the ED50
was 9.27. MDL 72222 was also highly selective since
responses to the nicotine receptor agonist, dimeth-
ethylphenylpiperazinum iodine (DMPP), were inhibited
only at concentrations more than 1000 times those
necessary to inhibit 5-HT. In the anaesthetized rat,
MDL 72222 produced marked blockade of the Bezold-
Jarisch effect of 5-HT. Again, inhibition was selec-
tive since much higher doses of MDL 72222 failed to
alter the response to electrical stimulation of the
efferent vagus nerves. In contrast, MDL 72222 proved
only a weak and essentially non-selective antagonist
of responses mediated by the 5-HT M-receptor present
on the cholinergic nerves of the guinea-pig ileum.
MDL 72222 does not block smooth muscle contractile
responses elicited by oxytocin or mediated through
5-HT D-receptors, muscarinic or nicotinic cholino-
ectors or histamine H1-receptors except at rela-
tively high concentrations.

- MDL 72699 MDL 72699 är kvartenåra saltet av MDL
72222.

- Mepyramine (N,N-dimethyl N'-(methoxy-4 benzyl)-N'-
(pyridyl-2)ethylenediamine).

- Galanolactone= Gingerol

The irregularly shaped roots (rhizomes) of ginger
(zingiber officinale) are used extensively in Chi-
nese, Indian, and Japanese cultures where they are
believed to have anti-inflammatory, analgesic, cho-
lesterol-lowering, and antithrombotic properties.
Al-though ginger has been evaluated for the treat-
ment of nausea and vomiting associated with hyper-
emesis gravidarum, anesthesia, and chemotherapy,
this review will focus on ginger for motion sickness.

- Talipexole
Additional compounds

- YM 26103-2
- YM 26308-2
- M-840 ([3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5-yl]-methyl)trimethyl-ammonium iodide

Ref. A mechanism of 5-HT3 receptor mediation is involved etiologically in the psychological stress lesion the stomach of the mouse. J Pharmacol Exp Ther, 1994 Oct, 271:1, 100-6

The role of brain amines, possibly involved in psychological stress, was evaluated and we postulate that the 5-hydroxytryptamine 5-HT3 receptors in the central nervous system are involved in the gastric lesion formation by psychological stress. The stress was in a communication box paradigm, in which each nonshocked mouse (responder) was placed in a Plexiglas compartment adjacent to mice receiving electrical shocks (sender). The responder mice revealed rather depressed gastric secretion, but developed gastric lesions which are significantly attenuated by pretreatment of dl-p-chlorophenylalanine methyl ester HCl (PCPA; 200-400 mg/kg p.o.), but not 6-hydroxydopamine (6-OH-DA; 60 micrograms/body i.c.v. or 80 mg/kg i.p. 1 hr after a 20-mg/kg i.p. dose of desipramine). Oral treatment with GR38032F (0.01-1 mg/kg), ICS205-930 (0.01-20 mg/kg), MDL72222 (0.01-1 mg/kg), metoclopramide (0.1-100 mg/kg), ketanserin (0.01-10 mg/kg) and sulpiride (32-320 mg/kg) dose-dependently attenuated the psychological stress lesion formation, and the activity was arranged in the order of their in vitro binding affinities for the 5-HT3, but not 5-HT1A or 5-HT2 receptors. In contrast, a peripherally acting 5-HT3 antagonist, M-840 ([3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5-yl]...
y1]-methyl]trimethyl-ammonium iodide), dopamine acting compounds, haloperidol and FR64822 [N-(4-pyridylcarbamoyl)amino-1,2,3,6-tetrahydropyridine], and antisecretory drugs, atropine and famotidine, minimally affected the lesion formation.

- SDZ ICT 322, an indole-3-carboxylic acid scopine ester

- MD-354

MD-354. We were intrigued by the novel 5-HT3 agonist phenylbiguanide. It seemed quite selective for 5-HT3 receptors, but displayed rather low affinity (Ki >1,000 nM). In a prior study with Dr. S. Peroutka, we had investigated the SAFIR of various arylpiperazines at 5-HT3 receptors. Arylpiperazines, as mentioned earlier, are relatively nonselective agents; however, many bind at 5-HT3 receptors with significantly higher affinity than phenylbiguanide. We identified some structural similarities between the arylpiperazines and phenylbiguanide and, in collaboration with Milt Teitler, made a series of hybrid analogs that we hoped would bind with higher affinity than phenylbiguanide. Two such analogs were meta- chlorophenylbiguanide (mCPBG) and 2-naphthylbiguanide (Ki = 10-20 nM); both displayed significantly higher affinity than phenylbiguanide. Although we reported these compounds in abstract form, a full paper http://www.phc.vcu.edu/rag/serotonin/-seven on mCPBG independently appeared by another group of investigators at the same time. It was not until a few years later that we finally published a full paper on these agents. However, in the course of our studies, we identified a novel class of 5-HT3 agonists: the arylguanides. MD-354, for example, was found to bind at 5-HT3 receptors with high affinity (Ki ca.
35 nM) and to display agonist actions in several assay systems.

\[
\text{MD-354}
\]

- S 21007 (21007 [5-(4-benzyl piperazin-1-yl)4H pyrrolo [1,2-a]thieno[3,2-e]pyrazine]).

Interaction of S 21007 with 5-HT3 receptors. In vitro and in vivo characterization.

The interaction of S 21007 [5-(4-benzyl piperazin-1-yl)4H pyrrolo [1,2-a]thieno[3,2-e]pyrazine] with serotonin 5-HT3 receptors was investigated using biochemical, electrophysiological and functional assays. Binding studies using membranes from N1E-115 neuroblastoma cells showed that S 21007 is a selective high affinity (IC50 = 2.8 nM) 5-HT3 receptor ligand. As expected of an agonist, S 21007 stimulated the uptake of [14C]guanidinium (EC50 approximately 10 nM) in NG 108-15 cells exposed to substance P, and this effect could be prevented by the potent 5-HT3 receptor antagonist ondansetron. In addition, like 5-HT and other 5-HT3 receptor agonists (phenylbiguanide and 3-chloro-phenylbiguanide), S 21007 (EC50 = 27 microM) produced a rapid inward current in N1E-115 cells. The 5-HT3 receptor agonist action of S 21007 was also demonstrated in urethane-
anaesthetized rats as this drug (120 micrograms/kg i.v.) triggered the Bezold-Jarisch reflex (rapid fall in heart rate), and this action could be prevented by pretreatment with the potent 5-HT3 receptor antagonist zacopride. Finally, in line with its 5-HT3 receptor agonist properties, S 21007 also triggered emesis in the ferret. Evidence for 5-HT3 receptor antagonist-like properties of S 21007 was also obtained in some of these experiments since previous exposure to this compound prevented both the 5-HT-induced current in N1E-115 cells and the Bezold-Jarisch reflex elicited by an i.v. bolus of 5-HT (30 micrograms/kg) in urethane-anaesthetized rats. These data suggest that S 21007 is a selective 5-HT3 receptor agonist which can exhibit antagonist-like properties either by triggering a long lasting receptor desensitization or by a partial agonist activity at 5-HT3 receptors in some tissues.

Further, in the following patent publications more compounds useful according to the present invention are presented.
N-substituted benzamides


or a pharmaceutically acceptable salt thereof wherein n is 0 or 1; Ar can be
R<sup>1</sup> is alkoxy of 1 to 6 carbon atoms; and
R<sup>2</sup> and R<sup>3</sup> are the same or different and are hydrogen, halogen, CF<sub>3</sub>, hydroxy, C<sub>1-6</sub> alkoxy, C<sub>2-7</sub> acryl, amino, amino substituted by one or two C<sub>1-6</sub> alkyl groups, C<sub>2-7</sub> acylamino, aminocarbonyl or aminosulfonyl, optionally substituted by one or two C<sub>1-6</sub> alkyl groups, C<sub>1-6</sub> alkyl sulfonyl or nitro groups;
wherein X can be NR, S, or O;
Y can be CH or N;
R is H, alkyl or aryl; and
m is 1 or 2.

The structure is a benzamide with Ar=Ph-CONH-. 

A compound of the formula or a pharmaceutically acceptable salt thereof wherein n is = or 1; and Ar is an aromatic amide moiety, which compound exhibits prokinetic activity and is a 5-HT<sub>3</sub> antagonist.

- EP0430190 (November 1990, Syntex, Inc) New tricyclic compounds in which
the dashed line denotes an optional double bond;
n is 1, 2 or 3;
p is 0, 1, 2 or 3;
q is 0, 1 or 2;
each R¹ is independently selected from halogen, hydroxy, lower C₁₋₆ alkoxy (optionally substituted with phenyl), lower C₁₋₆ alkyl, nitro, amino, amino-carbonyl, (lower C₁₋₆ alkyl)amino, di(lower C₁₋₆ alkyl)amino, and (lower C₁₋₆ alkanoyl)amino;
each R² is lower C₁₋₆ alkyl; and
R³ is selected from

\[ (CH₂)ᵣ NR⁴ \]  
\[ (CH₂)ᵧ \]  
\[ (CH₂)ᵤ \]  
\[ (CH₂)ᵣ N-R³ \]  

in which
u, x, y and z are all independently an integer from 1 to 3; and
R⁴ and R⁵ are independently C₁₋₇ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₂ alkyl, or a group
(CH₂)ₜR₆ where t is 1 or 2 and R₆ is thiethyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C₁₋₄ alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C₁₋₄ alkyl (optionally substituted by hydroxy, C₁₋₄ alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy); or

a pharmaceutically acceptable salt thereof or an N-oxide thereof; or

an individual isomer or mixture of isomers thereof.

The present invention is directed to new pharmaceutically active compounds with 5-HT₃ receptor antagonist activity of Formula I: in which the dashed line denoted an optional double bond; n is 1, 2 or 3; p is 0, 1, 2 or 3; q is 0, 1 or 2; each R₁ is halogen, hydroxy, alkoxy (optionally substituted with phenyl), alkyl, nitro, amino, amino carbonyl, (alkyl)amino, di(alkyl)amino, and (alkanoyl)amino; each R₂ is alkyl; and R₃ is in which u, x, y and z are all independently an integer from 1 to 3; and R₄ and R₅ are independently alkyl, cycloalkyl, cycloalkylalkyl, or a group (CH₂)ₜR₆ where t is 1 or 2 and R₆ is thiethyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from alkyl, alkoxy, trifluoromethy1 or halogen, or is phenyl optionally substituted by alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and alkyl (optionally substituted).

Indoles, Indole-1-carboxamides and Imidazole derivatives
• EP0721949 (September 1993, Tokyo Tanabe Company Limited) Indoline compound and 5-HT3 receptor antagonist containing the same as active ingredient.

\[
\begin{align*}
\text{R}^3 & \text{N} \\
\text{R}^1 & \text{R}^2 \\
\end{align*}
\]

wherein \( \text{R}^1 \) represents the group

\[
\begin{align*}
\text{N} & \text{H} \\
\text{N} & \text{H} \\
\end{align*}
\]

\( \text{R}^2 \) represents a phenyl group which may be substituted or an aromatic heterocyclic group, and \( \text{R}^3 \) represents hydrogen, a halogen, or a lower alkyl group, hydroxyl group, lower alkoxy group, carbamoyl group or lower alkoxy carbonyl group, or a physiologically acceptable salt thereof, or its solvate.

An indoline compound represented by general formula (I); a physiologically acceptable salt thereof; solvates of these compounds; and a 5-HT3 receptor antagonist containing the same as the active ingredient. In formula (I) \( \text{R}^1 \) represents the group (a) or (b),
R2 represents optionally substituted phenyl or heteroaryl; and R3 represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, carbamoyl or lower alkoxy carbonyl. The compound has a potent antagonism against 5-HT3 receptors in the intestinal tract as compared with the known 5-HT3 receptor antagonists and is excellent in the persistence of the activity. Hence it is useful for preventing or treating vomiting or nausea induced by chemotherapy or radiation, irritable bowel syndrome and diarrhea.

- EP0711299 (May 1994, Pharmacia S.p.A) Azabicycloalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One As SHT 3 Antagonists

![Chemical Structure](attachment:image.png)

wherein

each of R, R₁ and R₂, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C₁-C₆ alkyl, CF₃, C₁-C₆ alkoxy, C₁-C₆ alkylthio, formyl, C₂-C₆ alkanoyl, carboxy, C₁-C₆ alkoxy carbonyl, nitro, -N(R₄ R₅) in which each of R₄ and R₅ independently is hydrogen, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl; or a (R₆ R₇)N-SO₂ group, in which each of R₄ and R₇ independently is hydrogen or C₁-C₆ alkyl; R₃ is a group a)
or b)

wherein
n is an integer of 1 or 2 and \( R_8 \) is hydrogen, \( C_1-C_6 \) alkyl unsubstituted or substituted by phenyl, \( C_2-C_4 \) alkenyl, \( C_2-C_4 \) alkynyl, formyl or \( C_2-C_6 \) alkanoyl; and the pharmaceutically acceptable salts thereof.

Novel 5-HT3 receptor antagonist compounds having general formula (I) wherein each of \( R, R_1 \) and \( R_2 \), which may be the same or different, is hydrogen, halogen, hydroxy, cyano, \( C_1-C_6 \) alkyl, \( CF_3 \), \( C_1-C_6 \) alkoxy, \( C_1-C_6 \) alkylthio, formyl, \( C_2-C_6 \) alkanoyl, carboxy, \( C_1-C_6 \) alkyl-carbonyl, nitro, \(-N(R_4 R_5)\) in which each of \( R_4 \) and \( R_5 \) independently is hydrogen, \( C_1-C_6 \) alkyl, formyl or \( C_2-C_6 \) alkanoyl; or a \((R_6 R_7)N-SO_2\) group, in which each of \( R_6 \) and \( R_7 \) independently is hydrogen or \( C_1-C_6 \) alkyl; \( R_3 \) is a group (a) or (b) wherein \( n \) is an integer of 1 or 2 and \( R_8 \) is hydrogen, \( C_1-C_6 \) alkyl unsubstituted or substituted by phenyl, \( C_2-C_4 \) alkenyl, \( C_2-C_4 \) alkynyl, formyl or \( C_2-C_6 \) alkanoyl; and the pharmaceutically acceptable salts thereof, are provided.

- EP0711293 (May 1994, Pharmacia S.p.A) Imidaxoylalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One And Their Use As Therapeutic Agents.
wherein
n, 1, 2 or 3 is;
each of R, R₁ and R₂, which may be the same or different, is hydrogen, halogen, hydroxy, cyano C₁-C₆ alkyl, CF₃, C₁-C₆ alkoxy, C₁-C₆ alkylthio, formyl, C₂-C₆ alkanoyl, carboxy, C₁-C₆ alkoxy carbonyl, nitro, -N(R₄)R₅ in which each of R₄ and R₅ independently is hydrogen, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl; or a R₆(R₇)N-SO₂ group, in which each of R₆ and R₇ independently is hydrogen or C₁-C₆ alkyl; R₃ is an imidazolyl group having the formula

a) 

or b) 

wherein each of R₆ and R₁₀, which may be the same or different, is hydrogen or C₁-C₆ alkyl, R₉ is hydrogen, C₁-C₆ alkyl or a nitrogen protection group chosen from triphenylmethyl, t-butyloxy carbonyl, benzy-
loxyecarbonyl, acetyl, formyl, di(p-methoxyphenyl)-methyl and (p-methoxyphenyl)diphenylmethyl; and the pharmaceutically acceptable salts thereof.

Novel 5-HT3 receptor antagonist compounds having formula (I), wherein n is 1, 2 or 3; each of R, R1 and R2, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C1-C6 alkyl, CF3, C1-C6 alkoxy, C1-C6 alkylthio, formyl, C2-C6 alkanoyl, carboxy, C1-C6 alkoxy-carbonyl, nitro, -N(R4 R5), in which each of R4 and R5 independently is hydrogen, C1-C6 alkyl, formyl or C2-C6 alkanoyl; or a (R6 R7)N-SO2 group, in which each of R6 and R7 independently is hydrogen or C1-C6 alkyl; R3 is an imidazolyl group of formula (a) or (b), wherein each of R8 and R10 which may be the same or different is hydrogen or C1-C6 alkyl, R9 is hydrogen, C1-C6 alkyl or a nitrogen protecting group; and the pharmaceutically acceptable salts thereof, are disclosed.


This invention relates to the novel salt 6-fluoro-2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one methane sulphonate, to solvates of this salt, to pharmaceutical compositions containing it and to its use in medicine as 5-HT3 receptor antagonists.
• EP0364274 (October 1989, Glaxo Group Ltd) Imidazole derivatives.

wherein Im represents an imidazolyl group of the formula:

and one of the groups represented by R³, R⁴ and R⁵ is a hydrogen atom, or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₆ alkenyl, phenyl or phenyl C₁₋₃ alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆ alkyl group;

R¹ and R² each represent a hydrogen atom, or together with the carbon atoms to which they are attached form a phenyl ring;

X represents an oxygen or a sulphur atom, or a group NR⁶, wherein R⁶ represents a C₁₋₆ alkyl group;
Z-Y represents the group CH-CH₂ or C=CH;
and physiologically acceptable salts and solvates thereof, which comprises:
(A) for the production of a compound of formula (I) in which Z-Y represents the group CH-CH₂, hydrogenating a compound of formula (II):

![Chemical Diagram]

or a protected derivative thereof, followed if necessary by removal of any protecting groups present; or

(B) for the production of a compound of formula (I) in which Z-Y represents the group C=CH, reacting a compound of formula (II), or a protected derivative thereof, with an organic acid or a mineral acid, followed if necessary by removal of any protecting groups present; or

(C) converting a compound of general formula (I) into another compound of formula (I) using conventional techniques; or

(D) removing protecting group(s) from a protected form of a compound of formula (I); and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer; and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

The invention provides imidazole derivatives of the general formula (I) wherein Im represents an imidazolyl group of the formula: and one of the groups represented by R₃, R₄ and R₅ is a hydrogen atom, or
a C1-C6 alkyl, C3-7 cycloalkyl, C3-6 alkenyl, phenyl or phenyl C1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C1-6 alkyl group; R1 and R2 each represent a hydrogen atom, or together with the carbon atoms to which they are attached form a phenyl ring; X represents an oxygen or a sulphur atom, or a group NR6, wherein R6 represents a C1-6 alkyl group; Z-Y represents the group CH-CH2 or C=CH; and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine at 5-HT3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety and nausea and vomiting.


A γ-carboline of the formula I

[Chemical structure]

or pharmaceutically acceptable acid addition salt and/or hydrate thereof for use in a method of treatment or prophylaxis of diseases or conditions induced by the action of 5-hydroxytryptamine on 5-hydroxytryptamine 3-receptors in a mammal, including man.

The present invention provides γ-carbolines of the formula: or non-toxic acid additional salts thereof
and/or hydrates thereof, for use as 5-HT3 receptor antagonists. The present invention also provides pharmaceutical compositions comprising compounds of the formula I.


Compounds of the general formula (I)

wherein \( n \) represents 2 or 3;
Im represents an imidazolyl group of the formula:

wherein one of the groups represented by \( R^1, R^2 \) and \( R^3 \) is a hydrogen atom or a \( C_{1-6} \) alkyl, \( C_3-7 \) cycloalkyl, \( C_3-6 \) alkenyl, phenyl or phenyl \( C_{1-3} \) alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a \( C_{1-6} \) alkyl group;
Y represents a group \(-(CH_2)_m-\), wherein \(m\) represents 2, 3 or 4; or Y represents a group \(-X(CH_2)_p-\), C\(_{1-6}\) alkyl group, and X is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof.

The invention provides lactam derivatives of the general formula (I) wherein \(n\) represents 2 or 3; Im represents an imidazolyl group of the formula:

wherein one of the groups represented by \(R_1\), \(R_2\) and \(R_3\) is a hydrogen atom or a C\(_{1-6}\) alkyl, C\(_{3-7}\) cycloalkyl, C\(_{3-6}\) alkenyl, phenyl or phenyl C\(_{1-3}\) alkyl-group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C\(_{1-6}\) alkyl group; Y represents a group \(-(CH_2)_m-\), wherein \(m\) represents 2, 3 or 4; or Y represents a group \(-X(CH_2)_p-\), wherein \(p\) represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR\(_4\), where \(R_4\) is a C\(_{1-6}\) alkyl group, and X is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine at 5-HT\(_3\) receptors and are useful, for example in the treatment of psychotic disorders, anxiety and nausea and vomiting.

- RU2059623 Tetrahydrobenzimidazole derivatives or its pharmaceutically acceptable salt.

tetrahydrobenzimidazole derivative of the formula

![Chemical Structure](attachment:image.png) and a pharmaceutical
composition containing an effective amount of compound

and a pharmaceutically acceptable carrier showing activity of a 5-HT3 receptor antagonist.


The invention relates to tetracyclic ketones of the general formula (I)

wherein
n represents 1, 2 or 3;
Im represents an imidazolyl group of the formula:
wherein one of the groups represented by $R^1$, $R^2$ and $R^3$ is a hydrogen atom or a $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{3-6}$ alkenyl, phenyl or phenyl $C_{1-3}$ alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a $C_{1-6}$ alkyl group;

$Y$ represents a group $-(CH_2)_m-$, wherein $m$ represents 2, 3 or 4; or a group $-X(CH_2)_p-$, where $p$ represents 2 or 3, $X$ represents an oxygen or a sulphur atom or a group $NR^4$, where $R^4$ is a $C_{1-6}$ alkyl group, and $X$ is attached to the benzene ring moiety of the molecule;

and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT$_3$ receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

The invention relates to tetracyclic ketones of the general formula (I)##STR1## wherein $n$ represents 1, 2 or 3; $Im$ represents an imidazolyl group of the formula: ##STR2## wherein one of the groups represented by $R$.sup.1, $R$.sup.2 and $R$.sup.3 is a hydrogen atom or a $C$.sub.1-6 alkyl, $C$.sub.3-7 cycloalkyl, $C$.sub.3-6 alkenyl, phenyl or phenyl $C$.sub.1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a $C$.sub.1-6 alkyl group; $Y$ represents a group $-(CH$.sub.2$)_m-$, where $m$ represents 2, 3 or 4, or a group $-X(CH$.sub.2$)_p-$, where $p$ represents 2 or 3, $X$ represents an oxygen or a sulphur atom or a group $NR$.sup.4, where $R$.sup.4 is a $C$.sub.1-6 alkyl group, and $X$ is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof. The compounds are potent...
and selective antagonists of the effect of 5-HT at 5-HT sub.3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

*Indazole carboxamide derivatives*


\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\end{array}
\]

(A)

A 5-HT3 antagonist containing a novel N,N'-disubstituted amide derivative having a potent and selective 5-HT3 receptor antagonistism, represented by general formula (I), a hydrate thereof, or an acid addition salt thereof, wherein R1 represents hydrogen or lower alkyl; R2 and R3 may be the same or different from each other and each represents hydrogen, lower alkyl, lower alkenyl, aryl-substituted lower alkyl which may be substituted, acyl or lower alkoxy carbonyl; R4 represents hydrogen, lower alkyl or lower alkoxy; A represents CH or N; and n represents 1, 2 or 3.

- EP0558923 (January 1992, Nisshin Flour Milling Co., Ltd.) Diazabicyclo derivatives as 5-HT3 antagonists

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R} \\
\text{R}' \\
\end{array}
\]

(A)
wherein
R<sup>1</sup> is alkyl, 3-methyl-2-butanyl, cyclopropylylmethyl, 
2-propynyl, cyanomethyl, 2-oxopropyl, 2-hydroxypropyl, 
2-pyridylmethyl, methoxycarbonylmethyl, 2-
ethoxyethyl, isobutoxycarbonyl, or 4,6-diamino-2-
triazinylmethyl;
R<sup>2</sup> is hydrogen; and
R<sup>3</sup> and R<sup>4</sup> are methyl.

Diazabicyclo derivatives of formula (I) and pharmaceutically acceptable salts thereof: wherein R<sup>1</sup> is 
hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, oxoalkyl, alkoxy-
cabonylalkyl, alkoxy carbonyl, acyl, dialkylaminooalkyl, hydroxyalkyl, haloalkyl, cyanoalkyl, heterocyc-
cloalkyl, aryl, heteroarylalkyl or arylalkyl, the 
aryl group and the aryl moiety being optionally sub-
stituted by alkoxy, nitro, alkyl, amino or halo; R<sup>2</sup> 
is hydrogen or alkyl; R<sup>3</sup> and R<sup>4</sup> may be the same or 
different and each is hydrogen, alkyl, alkenyl, 
acyl, alkoxyalkyl or arylalkyl wherein the aryl moi-
ety is optionally substituted by alkoxy, nitro, al-
kyl, amino or halo; with the proviso that when R<sup>2</sup> is 
hydrogen and both R<sup>3</sup> and R<sup>4</sup> are methyl, R<sup>1</sup> does not 
represent hydrogen, alkyl, unsubstituted benzyl or 
dimethylaminoethyl; having 5-HT3 receptor antagonist 
activity.

Quinolines and Isoquinolines

• WO9964421 (June 1999, Arena Pharmaceuticals, Inc) Acet-
ethylcholine enhancers.

An acetylcholine enhancer selected from the group 
consisting of the chemical compounds represented by 
the following structures:
Disclosed herein are quinoline derivatives having dual mechanistic properties, referred to in this patent documents as "acetylcholine enhancers", i.e., compounds which evidence acetylcholinesterase (AChE) inhibition activity, and 5-HT3 receptor antagonist activity. A particularly preferred compound is 2-[2-(1-benzylpiperizin-4-yl)ethyl]-2,3-dihydro-9-methoxy-1H-pyrrolo[3,4-b]quinolin-1-one hemifumarate, referred to herein as Compound A ("Cm.A").

A compound of formula (I), or a pharmaceutically acceptable salt thereof:

\[
\text{CO-}E-Z
\]

wherein

E is NH or O,

R\textsubscript{1} is hydrogen, halogen, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy, hydroxy or nitro;

Z is an azacyclic or azabicyclic side chain; and

i) the group CO-E-Z is in the 1-position and either R\textsubscript{2} is in the 3-position and is hydrogen, C\textsubscript{1-6} alkyl or C\textsubscript{1-6} alkoxy, or R\textsubscript{2} is in the 4-position and is hydrogen, halogen, CF\textsubscript{3}, C\textsubscript{1-6} alkyl, C\textsubscript{1-7} acyl, C\textsubscript{1-7} acylamino, phenyl optionally substituted by one or two C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C\textsubscript{1-6} alkyl or C\textsubscript{3-8} cycloalkyl groups or by C\textsubscript{4-5} polymethylene or by phenyl, C\textsubscript{1-6} alkylsulphonyl, C\textsubscript{1-6} alkylsulphinyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkylthio, hydroxy or nitro; or

ii) the group CO-E-Z is in the 3-position and either R\textsubscript{2} is in the 1-position and is hydrogen, C\textsubscript{1-6} alkyl or C\textsubscript{1-6} alkoxy, or R\textsubscript{2} is in the 4-position and is hydrogen or C\textsubscript{1-6} alkoxy;

having 5-HT\textsubscript{3} receptor antagonist activity.
Isoquinoline derivatives (I) having 5-HT3 receptor antagonist activity, a process for their preparation and their use as pharmaceuticals. In formula (I) E is NH or O, R1 is hydrogen, halogen, alkyl, alkoxy, hydroxy or nitro; Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c) wherein; p is 1 or 2; q is 1 to 3; r is 1 to 3; R3 or R4 is hydrogen or alkyl, and Y is a group -CH2-X-CH2- wherein X is -CH2-, oxygen, sulphur or X is a bond; and (I) when the group CO-E-Z is in the 1-position and either R2 is in the 3-position and is hydrogen, alkyl, or alkoxy, or R2 is in the 4-position and is hydrogen CF3, alkyl, acyl, acylamino (substituted) phenyl or (substituted) amino, (substituted) aminocarbonyl or (substituted) aminosulphonyl; (II) the group CO-E-Z is in the 3-position and either R2 is in the 1-position and is hydrogen, alkyl or alkoxy or R2 is in the 4-position and is hydrogen or alkoxy.

- EP0628043 (February 1992, Merrell Dow Pharmaceutical Inc) 2,6-Methano-2H-Quinolizin As 5-HT3-Receptor Antagonist

A compound of the formula:

![Chemical structure diagram]

where

R is hydrogen or alkyl;
$R_1$ is hydrogen, amino, mono- and di-alkylamino, acylamino, halo or haloalkyl;
$R_2$ is hydrogen, halo, sulfamyl, mono- and di-alkylsulfamyl or haloalkyl;
$R'$ and $R''$ are independently hydrogen or alkyl;
vicinal $R'$ and/or $R''$ groups may form a $C=C$ double bond;
geminal $R$ and $R'$ and $R$ and $R''$ groups may be $-(CH_2)_n-$
where $n$ is 2 to 6;

$Z$ is

where $m$ is 0-2, $n$ is 1-2 and $X$ is $N$ or $S$; or pharmaceutically acceptable salts thereof.

This invention relates to 5-chloro-2,3-dihydro-2,2-
dimethylbenzofuran-7-carboxylic acid-octahydro-3-
hydroxy-2,6-methano-2H-quinolizin-8-yl ester (I), a novel 5-HT3-receptor antagonists, its method of preparation, and to its end-use application in the
treatment of radio- and chemo-therapeutically-induced nausea and vomiting, in the treatment of pain associated with migraine, in the treatment of cognitive disorders, in treating hallucinatory endogenous psychoses of the type manifested in patients suffering from schizophrenia and mania, for irritable bowel syndrome, and to combat drug abuse.


\[
\begin{align*}
\text{(R}^1\text{)}_q \quad \text{(R}^2\text{)}_m \quad \text{(R}^3\text{)}_n
\end{align*}
\]

wherein each substituent \( R^1 \) is the same or different and is hydrogen, halogen, \( C_{1-4} \) alkyl, \( C_{1-4} \) alkoxy or a group of formula:

\(-\text{NR}^4\text{R}^5\)

wherein \( R^4 \) is hydrogen, \( C_{1-4} \) alkyl or \( C_{2-4} \) alkanoyl and \( R^5 \) is hydrogen, \( C_{1-4} \) alkyl or benzyl;
each substituent \( R^2 \) is the same or different and is hydrogen or \( C_{1-4} \) alkyl;
each substituent \( R^3 \) is the same or different and is hydrogen or \( C_{1-4} \) alkyl;

1 is 1, 2, 3 or 4;
m is 1 or 2;
n is 1 or 2 and
is a single bond or double bond; or a non-toxic acid addition salt thereof or a hydrate thereof.

Isoquinolinone derivatives of the formula: wherein R1 is hydrogen, C1-4 alkyl, C1-4 alkoxy or a group of formula: -NR4R5 wherein R4 is hydrogen, halogen, C1-4 alkyl or C2-4 alkanoyl and R5 is hydrogen, C1-4 alkyl or benzyl; R² is hydrogen or C1-4 alkyl; R³ is hydrogen or C1-4 alkyl; 1 is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2 and --- is a single bond or double bond an non-toxic acid addition salts thereof and are useful for the prevention and/or treatment of diseases induced when 5-HT acts on 5-HT3 receptors (especially vomiting induced by the administration of an anti-cancer agent).

Benzofuranes, Benzooxazines and Benzo(di)azepines


\[
\begin{array}{c}
\text{X} \\
\text{Y} \\
\text{R} \\
\text{CH}_2
\end{array}
\]

where

X is hydrogen, halo, sulfamyl, alkylsulfamyl or alkylsulfonyl;

Y is hydrogen, amino, mono- or di-alkylamino or halo;
Z is

\[(CR_1R_2)_y-N\]

3-quinuclidine, 4-quinuclidine, 4-(1-azabicyclo[3.3.1]nonane), 3-(9-methylazabicyclo[3.3.1]nonane) or 4-[3-methoxy-1-(3-[4-fluorophenoxy]propyl)piperidine];

\(R, R_1, R_2, R_3 \text{ and } R_4\) are independently: hydrogen or alkyl;

\(x\) is 2 or 3;

\(y\) is 1 to 4;

and pharmaceutically acceptable salts thereof.

This invention relates to benzoxazine and benzoxazepine carboxamide compounds which exhibit 5-HT\(_{1A}\) antagonist properties including CNS, anti-emetic and gastric prokinetic activity and which are void of any significant D\(_{2}\) receptor binding affinity.

This invention also relates to pharmaceutical compositions and methods for the treatment of gastrointestinal and mental disorders using said compounds.

- IL 107654 Use of substituted N-3,4-dihydro-4-oxo-2,2-pyrimidyl)amino alkyl-4-piperidinyl 2,2-dimethyl-7-benzofuran and benzopyrancarboxamide.

A pharmaceutically acceptable acid addition salt form or a stereochemically isomeric form thereof,

\(R_1\) and \(R_2\) represent hydrogen, or
R1 and R2 taken together from a bivalent radical of formula
-CH=CH-CH=CH-(a)
-CH=C(Cl)-CH=CH-(b) or
-CH=CH-C(Cl)=CH-(c);
n represents 2, 3 or 4;
R3 represents hydrogen or methoxy;
m represents 1 or 2;
R4 represents hydrogen, amino or Cl,3alkylcarbonyl-
aminoo; and
R5 represents hydrogen or halo,
for the manufacture of a medicament for treating 5-
HT3-mediated disorders.

• US5288731 (August 1992, Rhone-Poulenc Rorer Pharmaceuticals Inc) 2,6-Methano-2H-1-Benzoxacincarboxylic
acids, esters and amides.

and its steroisomers, enantiomers, diasteroisomers
and racemic mixtures with an amine of the formula
H₂N-Z;
where
R₁ is hydrogen, an amino or alkylamino optionally
substituted with a protecting group halo or haloalkyl;
R₂ is hydrogen, halo, sulfamyl, mono- and di-alkyl-
sulfamyl or haloalkyl;
R' and R'' are hydrogen or alkyl; and Z is:
and its racemic mixtures and stereospecific isomers.

Novel compounds which are 2,6-methano-2H-1-benzoxocincaboxamides having 5-HT.sub.3-antagonist properties including unique CNS, antiemetic and gastric prokinetic activities and which are void of any significant D.sub.2 receptor binding affinity, therapeutic compositions and methods of treatment of disorders which result from 5-HT.sub.3 activity using said compounds. Processes for their preparation and the preparation of their intermediates are also disclosed.

- WO9209284 2,6-Methano-2-H-1-benzoxacincarboxamides as 5-HT3 antagonists.

Other 5-HT3 antagonist compounds

- EP0611370 (October 1992, Smithkline Beecham Plc) Pyridine-3-Carboxylic Acid Esters Or Amides Useful As 5-HT3 Antagonists.

A compound of formula (I), or a pharmaceutically acceptable salt thereof:

```
CO-L-Z
R_1
R_2
R_3
```

(I)
wherein
R₁ is C₁₋₆ alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cycloalkyl C₁₋₄ alkoxy;
R₂ is hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino optionally substituted by one or two C₁₋₆ alkyl groups;
R₃ is hydrogen, halo or C₁₋₆ alkyl;
L is O or NH; and
Z is a di-azacyclic or azabicyclic side chain; having 5-HT₃ receptor antagonist activity.

Compounds of formula (I) and pharmaceutically acceptable salts thereof wherein R₁ is C₁₋₆ alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cycloalkyl C₁₋₄ alkoxy; R₂ is hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy or amino optionally substituted by one or two C₁₋₆ alkyl groups; R₃ is hydrogen, halo or C₁₋₆ alkyl; L is O or NH; and Z is a di-azacyclic or azabicyclic side chain; having 5-HT₃ receptor antagonist activity.

- EP0607233 (October 1991, Smithkline Beecham Plc) 3,9-Diazabicyclo(3.3.1)Nonane Derivatives With 5-HT₃ Receptor Antagonist Activity

A compound of formula (I), or a pharmaceutically acceptable salt thereof:
wherein
X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;
A is a linking moiety;
Z is a carboxylic acyl group; and
R is hydrogen or methyl;
having 5-HT₃ receptor antagonist activity.

Compounds of formula (I), and pharmaceutically acceptable salts thereof, wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is a linking moiety; Z is a carboxylic acyl group; and R is hydrogen or methyl; having 5-HT₃ receptor antagonist activity.

A compound of formula (I) or a pharmaceutically acceptable salt thereof:

wherein
A₁, A₂, A₃ and the carbon atoms to which they are attached form a 5- or 6-membered non-aromatic heterocyclic ring containing at least one -O-, -CO- or -N-;
R₁ and R₂ are hydrogen or C₁₋₆ alkyl;  
Y is hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ alkoxy;  
L is O or NH;  
Z is an azabicyclic side chain;  
5  
having 5-HT₃ receptor antagonist activity.

Compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein A₁, A₂, A₃ and the carbon atoms to which they are attached form a 5- or 6-membered non-aromatic heterocyclic ring containing at least one -O-, -CO- or -N-; R₁ and R₂ are hydrogen or C₁₋₆ alkyl; Y is hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ alkoxy; L is O or NH; Z is an azabicyclic side chain; having 5-HT₃ receptor antagonist activity.

- US4808588 (July 1987, Beecham Group) Heterocyclic ureas and carbonates useful as pharmaceuticals.

![Chemical Structure](image)

wherein

Het is monocyclic heteroaryl having two adjacent carbon atoms, a and b, depicted in formula (I) selected from the group consisting of pyridine, pyrimidine, pyrazine, pyrrole, imidazole, thiophene, furan, oxazole and thiazole;

R₁ and R₂ are independently selected from hydrogen, halogen, CF₃, C₁₋₆ alkyl and C₁₋₆ alkoxy;

R₃ is hydroxy, C₁₋₆ alkoxy, C₃₋₇ alkenyl-methoxy, phenoxy or phenyl C₁₋₄ alkoxy in which either phenyl
moiety may be substituted by one or two C₁-₆ alkyl, C₁-₆ alkoxy or halo; CO₂R₆ wherein R₆ is hydrogen or C₁-₆ alkyl, CONR₇R₈ or SO₂NR₇R₈ wherein R₇ and R₈ are independently hydrogen or C₁-₆ alkyl or together are C₄-₆ polymethylene, NO₂, (CH₂)ₙOR₉ wherein n is 1 or 2 and R₉ is C₁-₆ alkyl or S(O)ₙR₁₀ wherein n is 0, 1 or 2 and R₁₀ is C₁-₆ alkyl; L is NH or O; Z is a group of formula (a), (b) or (c):

(a)

(b)

(c)

wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R₄ or R₅ is C₁-₄ alkyl.

Compounds of formula (I), or a pharmaceutically acceptable salt thereof: #STR1## wherein: H is monocyclic heteroaryl having two adjacent carbons atoms, a and b, depicted in formula (I); p₁ R.sub.1 and R.sub.2 are independently selected from hydro-
gen, halogen, CF.sub.3, C.sub.1-6 alkyl and C.sub.1-6 Alkoxy; R.sub.3 is hydroxy, C.sub.1-6 alkoxy, C.sub.3-7 alkenyl-methoxy, phenoxy or phenyl C.sub.1-4 alkoxy in which either phenyl moiety may be substituted by one or two C.sub.1-6 alkyl, C.sub.1-6 alkoxy or halo; Co.sub.2 R.sub.6 wherein R.sub.6 is hydrogen or C.sub.1-6 alkyl, CONR.sub.7 R.sub.8 or SO.sub.2 NR.sub.7 R.sub.8 wherein R.sub.7 and R.sub.8 are independently hydrogen or C.sub.1-6 alkyl or together are C.sub.4-6 polymethylene, NO.sub.2, (CH.sub.2).sub.m OR.sub.9 wherein m is 1 or 2 and R.sub.9 is C.sub.1-6 alkyl or S(O).sub.n R.sub.10 wherein n is 0, 1 or 2 and R.sub.10 is C.sub.1-6 alkyl; L is NH or O; Z is a group of formula (a), (b) or (c); ##STR2## wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R.sub.4 or R.sub.5 is C.sub.1-4 alkyl; having 5-HT.sub.3 antagonist activity, a process for their preparation and their use as pharmaceuticals.

The most preferred 5-HT₃ receptor antagonists for the present indications are tropanyl 3,5-dimethylbenzoate, MDL 72222, SDZ 216-525, ICI 169369, Zacopride, Tropisetron, Ramosetron, Ondansetron, Granisetron, Azasetron, Dolasetron, and Cilansetron.

Several known substances are able to stimulate the relaxing 5-HT₄ receptor, without significantly activating the constricting 5-HT₃ receptor, thereby causing airway relaxation. Such agonist compounds are exemplified below.

Most of the different 5-HT₄ agonists can be referred to specific groups, where each group contains a common structural element. The largest group, and also the basis for several others, are the benzamides. They all contain the structural element 4-amino-5-chloro-2-methoxy benzamide and are further developments of the first 5-HT₄ agonist, metoclopramide, with the structural formula:
Another common feature is a basic nitrogen in a side chain from the amide nitrogen. This basic nitrogen is often a part of a sterically locked system. Examples of substances from this group are: BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506 (N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]-ethyl]-methanesulfonamide monohydrochloride), Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116 (4-amino-5-chloro-N-[[1S, 7aS]-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxybenzamide), SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, Zacopride, Zelmac (SDZ HTF919; tegaserod).

Thus, a structure-activity relation study performed indicates that a benzene ring and a basic nitrogen in the same plane as the ring and at a distance of 8±1 Å from the center of the benzene ring is required. The nitrogen should be locked in that position with a view to obtaining selectivity for the 5-HT₄ receptor. A lipophilic group on the basic nitrogen also seems to be important for the agonistic action. Further, a heteroatom with a free electron pair close to the indole nitrogen in tryptamine seems to give a positive effect.
Benzoic acid esters are modifications of the benzamide theme:

\[
\text{O} \quad \text{O-R} \\
\text{Cl} \quad \text{NH}_2
\]

The only difference is that the amide group has been replaced with an ester group. Examples are ML 10302 (4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)-ethylester), RS 57639, and SR 59768.

Another variant of the basic theme is to introduce the methoxy group into a ring, thereby arriving at a 2,3-dihydró-bensofuran-7-carboxamide group. Examples are ADR 932, Prucalopride (=R 093877); and SK-951.

Benzofurananes and benzotiophenes are also contemplated,
as well as the benzodioxan

Still another variant is based on the discovery that the benzoic acid antagonist RS 23597 (an ester) was transformed to an agonist if it was converted to a ketone

e.g. RS 67333 and RS 17017.

The basic concept also applies for naphtalimides, e.g. RS 56532.
Benzindolones are also contemplated.

The amide function may also be replaced with an oxadiazol ring.

e.g. YM-53389

Benzimidazolone-1-carboxamides

e.g. BIMU 1, BIMU 8 (2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride), DAU 6215, and DAU 6236, are also contemplated.

The carboxamides
are also contemplated.

Some indols are also useful as 5-HT₄ agonists, e.g. 5-methoxytryptamine, 2-methylserotonin, and 5-hydroxy-N,N-di-methyltryptamine.

It should be noted that many of these substances may be quaternized on the nitrogen in the side chain without losing the activity.

Benzokinoliones

According to the present invention, the following compounds can also be used as agonists to the 5-HT₄ receptor: 5-carboxamidotryptamine (5-CT), with the structural formula:

5-HT, 3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-(2S,4S)-1-ethyl-2-hydroxy-methyl-4-pyrrolidinyl)benzamide (e.g. TKS 159), thiophene
carboxamide derivatives 3 (a-j), 5. azabicyclo(x.y.z)
derivatives, 2-piperazinylbenzoxazole derivatives,
2-piperazinyl-benzothiazole derivatives (e.g. VB20B7),
Sandoz compound 1b, cleopride, 2-piperidinmethylethers
of benzimidazole, zelmac, 2-[1-(4-piperonyl)piperazinyl]-
benzothiazole, benzopyranes,
substituted dihydrobenzofuran derivatives with the
following structure (see EP 0 766 680)

wherein

R₁, R₂ and R₃ are, each independently, hydrogen,
C₁-C₆ alkyl, halogen, hydroxy, C₁-C₄ alkoxy, amino,
C₁-C₄ alkylamino or C₁-C₄ di-alkylamino;
X is O, NH or CH₂;
Z is a group (a), (b), (c) or (d)

(a)

(b)
wherein

n is 1, 2, 3 or 4;

m is zero or 1;

q is zero, 1 or 2;

R₄ is hydrogen, C₁-C₆ alkyl, benzyl, cyclohexylmethyl or -CH₂-CH₂-SO₂NH-R₆ in which R₆ is C₁-C₆ alkyl or benzyl;

R₅ is C₁-C₆ alkyl; and

T is halogen;

provided that, when Z is defined under (c), then X is 0 or CH₂; or a pharmaceutically acceptable salt thereof, for use as a 5-HT₄ receptor agonist.

Compounds with the following indazole structure:

(see JP 08169830)
This 5-HT$_4$ receptor agonist contains a new diazabicyclo derivative of formula I (R is a 4-6C cycloalkyl) or its pharmaceutically permissible salt as an active component. The compound of formula I is especially preferably N-(endo-3,9-dimethyl-3,9-diazabicyclo[3,3,1]non-7-yl)-1-cyclobutylindazol-3-carboxamide. The 5-HT$_4$ receptor agonist is especially an agent for the yl)-1-cyclobutylindazol-3-carboxamide. The 5-HT$_4$ receptor agonist is especially an agent for the oxadiazole derivatives (see WO95/32965).

An oxadiazole derivative represented by general formula (I) and useful as a 5-HT4 receptor agonist, a pharmaceutically acceptable salt thereof, or a medicinal com-
position thereof wherein one of R1 and R2 represents (a) and the other represents -A-Het; A represents a mere bond or lower alkylene; Het represents a monocyclic, fused or cross-linked heterocyclic group containing at least one nitrogen atom and bonded to A at the ring carbon atom; and R3 represents lower alkyl, lower alkenyl or lower alkyynyl.

4-amino-5-chloro-2-methoxybenzoic esters (see WO95/25100)

\[
\text{structure image}
\]

wherein \(n\) is 1 or 2, R represents a hydrogen or halogen atom or a cyano, hydroxy, (C1-C4)alkyl, (C1-C4)-alkoxy, carboxy, (C1-C4)alkoxycarbonyl, aminocarbonyl, mono(C1-C4)alkylaminocarbonyl, di(C1-C4)alkylamino-carbonyl, mono(C1-C4)alkylamino, di(C1-C4)alkylamino, (C1-C5)alcanoylamino or (C1-C5)alcanoyl group, and when R is a hydrogen atom the dashed line may represent a double bond, as well as pharmaceutically acceptable salts or solvates and quaternary ammonium salts for the preparation of medicaments having 5-HT4 agonistic action.

Oxazabicyclo derivatives (see EP 0 623 621)

\[
\text{structure image}
\]
wherein R is a hydrogen atom, a halogen atom, a halo(C₁-C₆)alkyl group, a (C₁-C₆)alkoxy group, a nitro group, a hydroxyl group or an amino group, n is 1 or 2, the R groups being the same or different when n is 2, and Ar represents a radical of formula (II), (III), (IV), (V), (VI), (VII) or (VIII).
wherein

Ra to Re are independently a hydrogen atom, a halogen atom, a hydroxyl group, a \((C_1-C_6)\)alkoxy group or a \((C_1-C_8)\)alkyl group;

R_1 is a hydrogen atom, a \((C_1-C_8)\)alkyl group, a \((C_3-C_8)\)alkenyl group, a \((C_3-C_8)\)alkynyl group, a \((C_3-C_8)\)cycloalkyl group, a \((C_3-C_6)\)cycoalky\((C_1-C_6)\)-alkyl group, a \((C_1-C_6)\)alkoxy\((C_2-C_5)\)alkyl group, a \((C_3-C_6)\)oxoalkyl group, a \((C_1-C_6)\)alkoxycarbonyl\((C_1-C_6)\)alkyl group, a \((C_1-C_6)\)alkoxycarbonyl group, a \((C_1-C_6)\)alkanoyl group, a di\((C_1-C_6)\)alkylamino\((C_2-C_6)\)-alkyl group, a hydroxy\((C_2-C_6)\)alkyl group, a halo \((C_1-C_6)\)alkyl group, a cyano\((C_1-C_6)\)alkyl group, 4,6-diamino-2-triazinylmethyl group or a benzyl group optionally substituted by one or two substituents selected from the group consisting of halogen,

\((C_1-C_6)\)alkoxy, nitro, hydroxyl and amino;

Z is CH or N;

R_2, R_3, R_5, R_6, R_9, R_{10} and R_{11} are independently a hydrogen atom or a \((C_1-C_6)\)alkyl group;

R_4 is a \((C_1-C_6)\)alkyl group, a pyridyl group or a phenyl group optionally substituted by halogen, \(C_1-C_6\) alkyl, \(C_1-C_6\) alkoxy or trifluoromethyl;

Q is N, S or O;

X is a halogen atom;

Y is NH_2 or a phthalimido group;

R_7 is a hydrogen atom;

R_8 is a hydrogen atom or a \((C_1-C_4)\)alkyl group; or R_7 and R_8 together form a single bond.
Compounds having the following structure (see EP 0 908 459)

wherein
A-D is C=N or N-C=O;
n is 1, 2, 3, 4 or 5;
R is hydrogen, halo, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, C₁-C₄ alkylthio, cyano, trifluoromethyl, carboxamido, mono or di(C₁-C₄ alkyl) carboxamido;
R¹ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or substituted C₃-C₆ cycloalkyl;
R² and R³ are each hydrogen or taken together form a bridge of 1 to 4 methylene units;
X is OR⁴ or NR⁴R⁵;
R⁴ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, phenyl, substituted phenyl, (C₁-C₆ alkyl)CO, benzoyl, substituted benzyol, tricyclo[3.3.1.¹³.⁷]decan-1-oyl, or S(O)₂R⁶;
R⁵ is hydrogen or R⁴ and R⁵ together with the nitrogen to which they are attached form a 1-pyrrolidiny1, 1-piperaziny1, 1,2,3,4-tetrahydro-2-isoquinolinyl, 2,3-dihydro-1-indoliny1, 4-morpholiiny1, 1-piperidy1, 1-hexamethyleneminy1, or phthalimidyl ring;
R⁶ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, phenyl, or substituted phenyl; or a pharmaceutically acceptable salt thereof.
Benzamide derivatives having the following structures

having the substituents specified in WO 97/10207

having the substituents specified in WO95/18104.

and

(see JP11001472)

(II)
This novel compound is represented by formula I [\(R^1\) is a halogen; \(R^2\) is H, a lower alkyl; \(R^3\) is H, a lower alkyl, a lower alkanoyl; \(R^4\) is a lower alkoxy; \(a\) is 1 or 2; \(b\) is 2 or 3; \(i\) is 1 or 2; \(j\) is 2 or 3; \(k\) is 0, 1, 2; \(X\) is \(-(CH_2)_m-\) (m is 1 or 2); \(A\) is a group of formula II or formula III (p is 1, 2, 3; q is 0, 1, 2, 3; \(r\) is 0, 1, 2; \(R^{5a}\) is H, a lower alkyl; \(R^{5b}\) is H, a lower alkyl)], typically 4-amino-N-[1-[1-(3-aminopropyl)-4-piperidinyl-methyl]-5-chloro-2-methoxybenzamide.

Indazolecarboxamides (see WO 96/33713)

wherein:

\(R\) is hydrogen, \(C_1-C_6\) alkyl, \(C_3-C_6\) cycloalkyl;

\(R^1\) is hydrogen, halo, \(C_1-C_4\) alkyl, hydroxy, \(C_1-C_4\) alkoxy or alkylthio, cyano, trifluoromethyl, carbox-amido, mono- or di(\(C_1-C_4\) alkyl)carboxamido;
m, n and o are independently 0-5, provided that the sum of m, n and o is 2-5;
R² is hydrogen or C₁-C₄ alkyl;
R³ and R⁴ combine with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperazinyl, 1,2,3,4-tetrahydro-isoquinoliny1, 2,3-dihydro-1-indoliny1, 4-morpholiny1, 1-piperidiny1 or 1-hexamethylenemiminy1, substituted with phenyl, naphthyl, (phenyl or naphthyl)(C₁-C₃ alkyl), (phenyl or naphthyl)(C₁-C₃ alkanoyl), amino, mono- or di(C₄-C₄ alkyl)amino, or a group of the formula -NH-Y-R⁵; provided that a piperazinyl or morpholiny1 group may not be substituted with amino, mono- or di(C₁-C₄ alkyl)amino, or -NH-Y-R⁵;
wherein a phenyl or naphthyl group is unsubstituted or substituted with 1-3 halo, C₁-C₃ alkyl or C₁-C₃ alkoxy groups;
Y is carbonyl, sulfonyl, aminocarbonyl or oxycarbonyl;

(+)-norcisapride of formula (I) and compounds (V), and its pharmaceutically acceptable acid additions salts; compounds of formula (V), wherein the piperidine ring has the absolute configuration (3S, 4R) and PG is methoxy-carbonyl, ethyloxycarbonyl, tert-butyloxycarbonyl or phenylmethyl. (see WO 99/02496)

\[ \text{(I)} \]
Thiophene carboxamide, 5-HT4 agonist


New thiophene carboxamide derivatives 3(a-j) were synthesized as serotonin 5-HT4 receptor agonists. Preliminary results showed that the compounds 3a, 3d, 3e and 3f caused concentration dependent relaxation of carbachol-induced contraction in tunica muscularis mucosae in rat oesophagus.

\[ R^2R^3 \]

or the pharmaceutically acceptable salt thereof, wherein

- \( Z \) is oxygen, \( S(O) \) wherein \( m \) is 0, 1 or 2; or NO
- \( Q \) is hydrogen, \( (C_1-C_6) \)alkyl or phenyl;
- \( X \) is hydrogen, chloro, fluoro, bromo, iodo, hydroxy, nitro, cyano, \( (C_1-C_6) \)alkyl, trifluoromethyl, \( (C_1-C_6) \)alkoxy, \( (C_1-C_6) \)alcohol \( S(O) \) wherein \( a \) is 0, 1 or 2; or phenyl wherein the phenyl group is optionally substituted by hydrogen, halo, hydroxy, nitro, cyano, \( (C_1-C_6) \)alkyl, trifluoromethyl, \( (C_1-C_6) \)alkoxy, or \( (C_1-C_6) \)alkyl \( S(O) \) wherein \( b \) is 0, 1 or 2;
Y is

or

wherein M is oxygen or sulfur;
X² is hydrogen fluoro, chloro, trifluoromethyl,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy or (C₁-C₆)alkyl S(0)c
wherein c is 0, 1 or 2;
R¹ is a group of formulas
wherein the broken line represents an optional double bond;

5 p is 1, 2 or 3;
E is oxygen or S(O)₆ wherein d is 0, 1 or 2;
R⁸ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl optionally substituted with
(C₁-C₆)alkoxy or one to three fluorine atoms, or
10 [(C₁-C₄)alkyl]aryl wherein the aryl moiety is phenyl, naphthyl, or heteroaryl(CH₂)q-, wherein the heteroaryl moiety is selected from the group consisting of pyridyl, pyrimidyl, benzoazolyl, benzothiazolyl, benzisoxazolyl and benzisothiazolyl and q is zero,
one, two, three or four, and wherein said aryl and heteroaryl moieties may optionally be substituted with one or more substituents independently selected from the group consisting of chloro, fluoro, bromo, iodo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl,
15 cyano and (C₁-C₆)alkyl S(O)ₑ wherein e is 0, 1 or 2;
R⁷ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, [(C₁-C₄)alkyl]aryl wherein the aryl moiety is phenyl, naphthyl, or heteroaryl-(CH₂)r-, wherein the heteroaryl moiety is selected from the group consisting of pyridyl, pyrimidyl, benzoazolyl, benzothiazolyl, benzisoxazolyl and benzothiazolyl and r is zero, one, two, three or four, and wherein said aryl and heteroaryl moieties may optionally be substituted with one or more substituents independently selected from the group consisting of chloro, fluoro, bromo, iodo, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, -C(=O)-(C₁-C₆)alkyl, cyano and (C₁-C₆)alkyl S(O)ₑ wherein e is 0, 1 or 2;
20 or R⁶ and R⁷ taken together form a 2 to 4 carbon chain;
R⁸ is hydrogen or (C₁-C₃)alkyl;
$R^9$ is hydrogen or ($C_1$-$C_6$)alkyl;

or $R^8$ and $R^9$, together with the nitrogen atom to which they are attached, form a 5 to 7 membered heteroalkyl ring that may contain from zero to four heteroatoms selected from nitrogen, sulfur and oxygen;

$R^{10}$ is hydrogen or ($C_1$-$C_6$)alkyl;

$R^2$ is hydrogen, ($C_1$-$C_4$)alkyl, phenyl or naphthyl, wherein said phenyl or naphthyl may optionally be substituted with one or more substituents independently selected from chloro, fluoro, bromo, iodo, ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, trifluoromethyl, cyano and ($C_1$-$C_6$)alkyl $S(O)g$ wherein $g$ is 0, 1 or 2; and

$R^3$ is $-(CH_2)_tB$, wherein $t$ is zero, one, two or three and $B$ is hydrogen, phenyl, naphthyl or a 5 or 6 membered heteroaryl group containing from one to four heteroatoms in the ring, and wherein each of the foregoing phenyl, naphthyl and heteroaryl groups may optionally be substituted with one or more substituents independently selected from chloro, fluoro, bromo, iodo, ($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)-alkoxy-($C_1$-$C_6$)alkyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, COOH and ($C_1$-$C_6$)alkyl $S(O)h$ wherein $h$ is 0, 1 or 2.
Piperazinyl benzothiazole, 5-HT4 agonist


This study describes the in-vitro interaction of the gastrokinetic agent 2[1-(4-piperonyl)piperazinyl]-benzothiazole (VB20B7) with the 5-hydroxytryptamine 5-HT3 and 5-HT4 receptor subtypes, using functional as well as radioligand binding studies. The benzamide derivative cisapride was used as a comparison. In radioligand binding assays VB20B7 showed, like cisapride, a weak affinity at 5-HT3 receptors from rat cerebral cortex. The new compound lacked any affinity at other 5-HT receptors or at dopaminergic D2 receptors, whereas cisapride showed high affinity for the 5-HT4 receptors from guinea-pig hippocampus and moderate affinity at dopaminergic D2 receptors. In the non-stimulated guinea-pig ileum, the concentration-response curves to the specific 5-HT3 agonist 2-Me-5-HT and to 5-HT were shifted to the right by VB20B7. In the rat oesophagus tunica muscularis mucosae preparation (TMM), VB20B7 was evaluated for its activity at 5-HT4 receptors: VB20B7 behaved as a 5-HT4 receptor agonist, inducing a concentration-dependent relaxation of the preparation precontracted with carbachol. In this preparation, VB20B7 and cisapride were able to stimulate adenylate cyclase activity, an effect probably mediated through activation of 5-HT4 receptors, as can be inferred from the blockade by the 5-HT4 antagonist, tropisetron, of the enhanced cAMP formation. However, consistent with the lack of affinity at central 5-HT4 recep-
tors, VB20B7 did not stimulate cAMP formation in guinea-pig hippocampal slices. VB20B7 also caused an increase in the twitch response of the transmurally stimulated guinea-pig ileum, although at a concentration higher than cisapride. This effect was blocked by desensitisation of the 5-HT4 receptor with 5-MeOT and also by the 5-HT4 receptor antagonist tropisetron. Both VB20B7 and cisapride increased the K(+)evoked acetylcholine release in this preparation. The results show that VB20B7 possesses affinity for 5-HT4 receptors located in the rat TMM and guinea-pig ileum preparations, but is devoid of affinity at central 5-HT4 receptors. In addition, VB20B7 shows low to moderate affinity at both central and peripheral (enteric) 5-HT3 receptors. The interaction of VB20B7 with the peripheral 5-HT4 and 5-HT3 receptors may be relevant for the gastrokinetic effects of the new compound.


WO 95/32965


A small set of 2-4-[3-(4-aryl/heteroaryl-pipera- zinyl)propoxy]phenyl-2H-benzo tri azoles and cores-
ponding N-oxides were prepared. The synthesized compounds were able to bind on some serotonin (5-HT1A, 5-HT2A) and dopamine (D2, D3) receptors, while displaying poor or no affinity for 5-HT1B, 5-HT2C, 5-HT3 and 5-HT4 subtypes. The strong contribution of the N-oxide function for the binding on 5-HT1A, D2 and D3 receptors is noteworthy. For 2-4-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propoxy]phenyl-2H-benzotriazole-1-oxide (4b), the binding constants (Ki) were 11.9 (5-HT1A) and 10.5 nM (D3). In a general pharmacological screening, the 2-4-[3-(4-phenyl-1-piperazinyl)propoxy]phenyl-2H-benzotriazole (3a) exhibited only very weak activities, with the exception of protecting mice from cyanide-induced hypoxia.

Arylcarbamates


A series of carbamate derivatives (7) of 2-(1-piperidinyl)ethyl 4-amino-5-chloro-2-methoxybenzoates, which have been described as potent agonists and antagonists of 5-HT4 receptors, were synthesized. They were evaluated using radioligand binding assays with [3H]GR 113808, a 5-HT4 receptor selective ligand, in the rat striatum and the electrically stimulated myenteric plexus longitudinal muscle of the guinea pig. In contrast to the previously described ester derivatives, a drop in the affinity for 5-HT4 receptors was observed and the compounds were inactive as agonists in the guinea pig ileum preparation. Unexpectedly, the ortho-substituted carbamates 8b,c (R' =H, R0=MeO or EtO, R"=H) had nanomolar affinity for 5-HT4 receptors (Ki = 8.9 +/-0.5 and
2.6 +/- 0.4 nM, respectively). As reported previously, the cis- or trans-3,5-dimethyl substitution of piperidine (8n,o) was particularly favorable (Ki = 1.1 +/- 0.6 nM for both isomers). 8c is an antagonist equipotent to the 5-HT4 receptor antagonist SDZ 205-557 (1).

The most interesting 5-HT4 receptor agonists for the present indications are VB20B7, RS67333, BIMU 1, BIMU 8, 5-methoxytryptamine, Zacopride, RS56532, Mosapride, Pan-copride, Itasetron, BRL 24924, and SC 53116.
Further 5-HT4 agonist structures useful according to the present invention

2-piperidinmethyleneethers of bensimidazol

oxadiazalon based substance

kinolines

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, particularly bensopyranes.
The present invention relates to a composition comprising a combination of compounds comprising a) at least one compound with agonist activity to the 5-HT\textsubscript{4} receptor, and b) at least one compound with antagonist activity to the 5-HT\textsubscript{3} receptor, e.g. for use as a medicament. The present invention also relates to the use of said composition for the manufacture of a medicament intended for treatment of disorders involving airway constriction, as defined above, whereby said composition has the strong bronchorelaxing effect of 5-HT but substantially no constrictor effect. The administration of the composition can be simultaneous or sequential. The compounds with agonist activity to the 5-HT\textsubscript{4} receptor included in said composition may also be unspecific, e.g. 5-HT.

In said combination of compounds with 5-HT\textsubscript{4} agonist and 5-HT\textsubscript{3} antagonist activity, the relative amount of either compound may vary. Typically, the 5-HT\textsubscript{4} agonist is given in a somewhat larger concentration than the 5-HT\textsubscript{3} antagonist.

The most preferred compositions according to the present invention are the following, in each example named in the following order:

- 5-HT\textsubscript{4}-receptor agonist, 5-HT\textsubscript{3}-receptor antagonist, VB20B7 and tropanyl 3,5-dimethylbenzoate
- VB20B7 and MDL 72222
- RS67333 and tropanyl 3,5-dimethylbenzoate
- RS67333 and MDL 72222
- Zacopride and tropanyl 3,5-dimethylbenzoate
- Zacopride and MDL 72222
- RS56532 and tropanyl 3,5-dimethylbenzoate
- RS56532 and MDL 72222
- Itasetron and tropanyl 3,5-dimethylbenzoate
- Itasetron and MDL 72222
- VB20B7 and SDZ 216-525
- RS67333 and SDZ 216-525
- RS67333 and 3(1-piperazinyl)-2-quinoxalinecarbonitrile
- VB20B7 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile

5 - RS67333 and tropanyl 3,5-dimethylbenzoate
- RS67333 and VB20B7
- RS67333 and 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole, and
- VB20B7 and 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole

The most preferred combinations are
- VB20B7 and tropanyl 3,5-dimethylbenzoate
- RS67333 and tropanyl 3,5-dimethylbenzoate

15 - Zacopride and tropanyl 3,5-dimethylbenzoate
- VB20B7 and 3-(1-piperazinyl)-2-quinoxalinecarbonitrile
- RS67333 and VB20B7
- VB20B7 and 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole

The present invention also relates to a method for treatment of disorders involving airway constriction, wherein said method comprises the administration to a human or animal patient of a therapeutically effective amount of a composition comprising a combination of a) a compound with agonist activity to the 5-HT₄ receptor, and b) a compound with antagonist activity to the 5-HT₃ receptor. Preferably, said method relates to the treatment of asthma, chronic bronchitis, emphysema and chronic obstructive pulmonary disease.

Brief Description of the Drawing

Fig. 1 depicts the effects of 5-HT and the selective 5-HT₄ agonist RS 67333 on the spontaneous tone in a human airway preparation in vitro. Note that 5-HT only gives a transient relaxation, while the selective 5-HT₄ agonist causes a strong sustained relaxation effect.
Detailed Description of the Invention

As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT₄ receptor, this sustained relaxing effect is achieved because the contractile 5-HT₃ receptor is not affected; only the relaxing 5-HT₄ receptor is activated. In the case of antagonists to the 5-HT₃ receptor, this effect is achieved due to direct blocking of the 5-HT₃ receptor, whereby the unspecific agonists to the 5-HT₄ receptor, such as 5-HT, can act without also causing contraction by the 5-HT₃ receptor.

It should be noted that the medicament prepared according to present invention in each embodiment may optionally include two or more of the above outlined compounds.

Further, in the embodiment when the compound having 5-HT₃ antagonist activity is administered, optionally together with complementary serotonin or derivatives thereof, a serotonin uptake inhibitor can be added with a view to amplifying the relaxing effect, e.g. fluoxetine, citalopram, paroxetine, sertralin, and fluvoxamine.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition adapted either for administration via the respiratory tract or for oral, intravenous, intramuscular, intrathecal, topical, intraperitoneal or subcutaneous administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.
Moreover, said medicament is preferably administered via the respiratory tract in the form of e.g. an aerosol or an air-suspended fine powder. However, in some cases useful alternative administration forms are tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories.

The subject-matter of the present invention was in ter alia deduced from animal experiments, where a specific behavior of the airway smooth muscle called “spontaneous tone” was examined. The spontaneous tone, which involves a spontaneous continuous contraction in the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "Regulation of spontaneous tone in guinea pig trachea" by S. Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and this oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead displays a strong, smooth type of tone.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from a specific type of airway epithelium cells, so called neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin (5-HT), which activates 5-HT₁, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇ as well as 5-HT₂ receptors, in particular 5-HT₂, 5-HT₃, and 5-HT₄ receptors.
Additional experiments have shown that when a small dose (1 μM) serotonin (5-HT) was added to denuded guinea-pig airway smooth muscle preparations displaying a strong, smooth spontaneous tone, the average force level was increased significantly, i.e. a transient contraction was observed. A contractile effect of serotonin (5-HT) on airways (smooth muscle) has previously been reported, see e.g. Skogvall, S., Korsgren, M., Grampp, W., J. Appl. Phys., 86:789-798, 1999. However, when a large dose (100 μM) of 5-HT was used, the spontaneous tone was, after a transient contraction, significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal pre-treatment level when the preparations were again exposed to control, drug-free conditions. Thus, it has now surprisingly been shown that serotonin causes a contraction of guinea-pig airways at low concentrations and relaxation at high concentrations, i.e. a dual effect.

Similar experiments have also been performed on human airway preparations from patients undergoing lobectomy or pulmectomy due to lung cancer. In humans, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig: even as low a concentration as 1 μM 5-HT induced a significant relaxation in preparations displaying a spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, examinations on spontaneous tone on human in vitro preparations have shown that 5-HT indeed causes a contraction also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline (pre-treatment). The relaxation, which has a maximum after 10-15 min, disappears gradually during the following 30-45 min (see Fig 1). In guinea pig trachea, the...
first 5-HT-induced effect is a contraction which reaches a maximum after approximately 10 min, and this is followed, within approximately 30 min, by a considerable reduction of tone, i.e. a relaxation below the pre-treatment level. The transient nature of the 5-HT relaxation in human airways is most likely caused by a simultaneous activation of the fast relaxing 5-HT₄ receptor, and an activation of the slower contracting receptor, which in human airways surprisingly has been found to be the 5-HT₃ receptor. This is clear, because activation of the relaxing 5-HT₄ receptor by a substance that lacks 5-HT₃ receptor activating properties (such as RS 67333), results in a relaxation that is persistent and not transient (see Fig. 1).

It has previously been suggested that 5-HT may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. serotonin, may be of use as an addition to standard beta₂ receptor stimulation for the treatment of acute asthma attacks. However, from the presently described experiments it seems clear that 5-HT alone is unsuitable, i.e. not effective or useful, for the treatment of said diseases, e.g. asthmatic disorders, because of the only transient relaxing effect by 5-HT (see Fig. 1).

Also, reports from other groups indicate that 5-HT if anything tends to induce a weak bronchoconstriction rather than a relaxation in asthmatics (see e.g. Dupont et al. 1999, Eur Resp J 14:642-649 and Takahashi et al. 1995, Am J Respir Crit Care Med 152:377-380, which are incorporated herein by reference). If instead, according to the present invention, a composition comprising a combination of compounds that stimulates the relaxing 5-HT₄ receptor and blocks the contracting 5-HT₃ receptor is given, the relaxing effect is persistent, and not transient. The action of this combination at two different receptors causes a greater airway relaxation than an action at only one receptor. I should be noted that more
than one of the 5-HT₄ receptor agonists and more than one of the 5-HT₃ receptor antagonists may be included in such a composition. A reduced effect, however still satisfactory is attained, by the administration of only the 5-HT₃ receptor antagonist.

In summary, it has now been discovered that agonist action on the 5-HT₄ receptor results in a relaxing effect, whereas agonist action on 5-HT₃ receptors results in a contractile effect. In conclusion, the dual effect of 5-HT is most likely a result of its agonist action on the relaxing 5-HT₄ receptor as well as on the contracting 5-HT₃ receptor.

It was also deduced from these experiments that compounds having agonist activity to the 5-HT₄ receptor, while having only low or no agonist activity to a 5-HT₃ receptor, therefore are useful as agents for treatment of disorders involving airway constriction, as defined above.

In the above mentioned experiments it has been shown that compounds having antagonist activity to a 5-HT₃ receptor are useful as agents for treatment of disorders involving airway constriction, since they are capable of blocking the contractile effect of a compound having agonist activity to a 5-HT₃ receptor. Administration of serotonin, a serotonin reuptake inhibitor or any other substance having 5-HT₄ receptor agonist activity in combination with a 5-HT₃ receptor antagonist results in a much better relaxation of the bronchi, compared to administration of only one of those compounds.
1. A composition comprising a combination of a) at least one compound with agonist activity to the 5-HT$_4$ receptor, and b) at least one compound with antagonist activity to the 5-HT$_3$ receptor.

2. A composition according to claim 1, wherein said composition has the capacity of reducing pathological airway constriction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said combination is chosen from the following groups of 5-HT$_4$ agonists and 5-HT$_3$ antagonists, or derivatives or pharmaceutically acceptable salts thereof:

   a) 5-HT$_4$ receptor agonists: serotonin (5-HT), benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopramide, with the structural formula:

   ![Structure](image)

   having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, Zacopride, and Zelmac (SDZ HTF919; tegaserod);
benzoic acid esters:

preferably ML 10302, RS 57639, and SR 59768;

a 2,3-dihydro-benzofuran-7-carboxamide compound,
preferably ADR 932, Prucalopride (=R 093877), and SK-951;

benzofuranes and benzothiophenes,
the benzodioxan

the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone

e.g. preferably RS 67333 and RS 17017; naphtalimides, preferably RS 56532;

benzindolone;
compounds in which the amide function has been replaced with an oxadiazol ring;

preferably YM-53389;
benzimidazolone-1-carboxamides

preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;
the carboxamides

indols, preferably 5-methoxytryptamine, 2-methylserotonin, and 5-hydroxy-N,N-di-methyltryptamine;
compounds quaternized on the nitrogen in the side chain:
benzokinolinones

5-carboxamidotryptamine (5-CT), with the structural formula:

5-HT, 3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxy-methyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac, 2-[1-(4-piperonyl)piperazinyl]benzothiazole, benzpyranes,
substituted dihydrobenzofuran derivates with the following structure:

wherein R1-R3, X and Z are groups that can be substituted;

compounds with the following indazole structure:

oxidiazole derivatives

4-amino-5-chloro-2-methoxybenzoic esters

oxazabicyclo derivatives
compounds having the following structure

benzamide derivatives having the following structures

\[ \text{I} \]

\[ \text{II} \]

\[ \text{III} \]
indazolecarboxamides

$$\text{I}$$

\(+\)-norcisapride of formula (I) and compounds (V), and its pharmaceutically acceptable acid additions salts; compounds of formula (V) wherein the piperidine ring has the absolute configuration (3S, 4R) and PG is methyloxy-carbonyl, ethyloxy carbonyl, tert-butyloxy carbonyl or phenylmethyl;

$$\text{I}$$

$$\text{V}$$
Further 5-HT4 agonist structures useful according to the present invention

2-piperidinmethylethers of benzimidazol

oxadiazalon based substance

kinolines

SUBSTITUTE SHEET (RULE 26)
benzopyranes.
b) 5-HT\textsubscript{3} receptor antagonists

benzazepines, preferably mirtazapine

benztiazepines, preferably diltiazem

and fentiazines
preferably perphenazine, chlorpromazine, stemetil; compounds also having 5-HT₄ receptor agonist activity, preferably benzamides (cisapride, zacopride, mosapride, metoclopramide, pancopride, BRL 24924, BMY 33462)

and

WAY 100289

2,3-dihydro-benzofuran-7-carboxamides

(preferably zatosetron=LY 277359, ADR 851); 1,4-bensoxazin-8-carboxamides

SUBSTITUTE SHEET (RULE 26)
preferably azasetron (=Y25130); benzimidazolones

preferably itaset indazol-3-carboxamides

preferably N 3389, LY 278584, DAT 582 (=R)AS-5370; wherein the latter group reminds most of the specific 5-HT₃ antagonists, which contains the group
in different forms, such as

ondansetron

alosetron
cilansetron (=KC 9946)
substances the structure of which has been inverted and
the carbonyl group has been placed on the indoline nitrogen

FK 1052

also being an antagonist against both 5-HT₃ and 5-HT₄ receptors,
5 bisindoles

10 YM 114

15 isoquinoline-1-ones

20 palonosetron (=RS 25259-197) RS 42358-197

25 and the quinoline-3-carboxamides

30 WAY-SEC 579

35 Mirisetron (=WAY 100579),
quinoline-4-carboxylates

preferably KF 17643

preferably KF 18259;

benzimidazolones

preferably droperidol (neurolidol), itasetron (DAU6215), and the naphtimides
preferably RS 56532;

MDL 72222, which also is a specific 5-HT₃ antagonist;

; and

GK 128

Talipexole
(R)-zacopride, 2-methyl-5HT, 3-[(1-piperazinyl)-2-quinoxalinecarbonitrile, 3-[(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-[(dimethylamino)methyl]-3-[(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-[(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirto-line, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Flu-phenazine, Galdansetron, GR 38032 F, GR 67330, Grani-setron (=Kytril=BRL 43694), GR-H, GYK1-48903, ICS 205-930, Imipramine, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Ketanserin, Leris-etron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Methysergide, Mianserin, MK 212, N-3256, NAN-190, N-methylquipazin, 3-[(1-piperazinyl)-2-quinoxalinecarbonitrile, 2-piperidin- and 2-piperazin-benzimidazoles; and also
nitrile, ONO-3051, Pancopride, Phenylbiguanide, Pitolizifen, Prochlorperazine (Stemetil), QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-25259-197), RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMP, TMB 8, trifluoperazine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron (=ICS 205-930 =Rifenserin), Bemesetron, L-683,877, LY-278,584 maleate and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect.

3. Composition according to claim 2, wherein it comprises a combination of compounds selected from one of the following combinations of 5-HT₄-receptor agonists and 5-HT₃-receptor antagonists, wherein the 5-HT₄ receptor agonist is mentioned first:

- VB20B7 and tropanyl 3,5-dimethylbenzoate
- VB20B7 and MDL 72222
- RS67333 and tropanyl 3,5-dimethylbenzoate
- RS67333 and MDL 72222
- Zacopride and tropanyl 3,5-dimethylbenzoate
- Zacopride and MDL 72222
- RS56532 and tropanyl 3,5-dimethylbenzoate
- RS56532 and MDL 72222
- Itasetron and tropanyl 3,5-dimethylbenzoate
- Itasetron and MDL 72222
- VB20B7 and SDZ 216-525
- RS67333 and SDZ 216-525
- RS67333 and 3(1-piperazinyl)-2-quinoxalinecarboxanitile
# INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/SE 00/02612

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC7:** A61K 31/395, A61K 31/4045, A61P 11/06, A61P 11/08

According to International Patent Classification (IPC) or to both national classification and IPC.

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC7:** A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
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<td>Am J Respir Crit Care Med, Volume 152, 1995, Tsuneyuki Takahashi et al, <em>&quot;5-Hydroxytryptamine Facilitates Cholinergic Bronchoconstriction in Human and Guinea Pig Airways&quot;</em> page 377 - page 380</td>
<td>1-6</td>
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</tbody>
</table>

[ ] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

- "T" document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search: 16 May 2001

Date of mailing of the international search report: 17-05-2001

Name and mailing address of the ISA/Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/EÖ

Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)
<table>
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<td>X</td>
<td>The Journal of Pharmacology and Experimental Therapeutics, Volume 257, No 1, 1991, Carl K. Buckner et al, &quot;A Pharmacologic Examination of Receptors Mediating Serotonin-Induced Bronchoconstriction in the Anesthetized Guinea Pig&quot; page 26 - page 34</td>
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<td>P,X</td>
<td>WO 0076500 A2 (RESPIRATORIUS AB), 21 December 2000 (21.12.00), see part. claims 13-16</td>
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<td>A</td>
<td>US 5399562 A (DANIEL P. BECKER ET AL), 21 March 1995 (21.03.95)</td>
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Form PCT/ISA/210 (continuation of second sheet) (July 1998)
Claim 6 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

Claim 1 and depending parts of claims 4-6 relate to a composition of compounds defined by reference to a desirable characteristic or property, namely that at least one compound has agonist activity to the 5-HT4 receptor and that at least one compound has antagonist activity to the 5-HT3 receptor. The mentioned claims cover all compounds having this characteristic or property. Claim 2 (which is dependent of claim 1) and depending parts of claims 4-6 are restricted to specific compounds. However, these claims relate to a very great number of structurally different compounds whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, claims 1-2 and 4-6 so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Further expressions such as "compound with agonist activity to the 5-HT4 receptor", "compound with antagonist activity to a 5-HT3 receptor" and "disorders involving airway constriction" are not clear and concise. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Consequently, the search has mainly been carried out for those parts which appear to be clear, supported and disclosed, namely claim 3 and those parts of claims 4-6 relating to claim 3.

The applicant's attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search during any Chapter II procedure.
**INTERNATIONAL SEARCH REPORT**

**Box I**  
Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. **☒** Claims Nos.: 6  
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   see next sheet

2. **☒** Claims Nos.: 1–2, 4–6  
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   
   see next sheet

3. **☐** Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II**  
Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:  

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

**Remark on Protest**  

☐ The additional search fees were accompanied by the applicant’s protest.

☐ No protest accompanied the payment of additional search fees.
<table>
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<td>WO 8904660 A1</td>
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