

SUBSTITUTED BENZAMIDES

This invention relates to substituted benzamides.

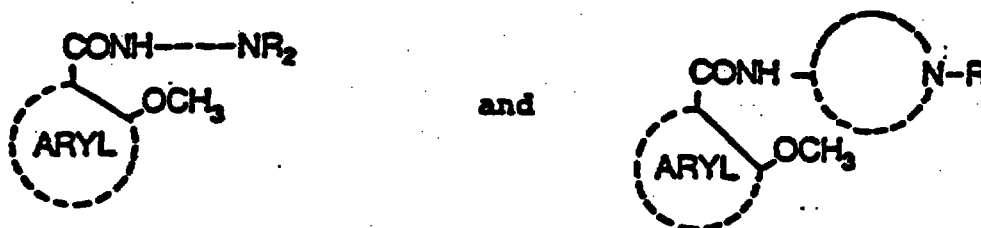
Emesis is a common and serious problem in patients receiving cancer chemotherapeutic agents. In a significant number of patients, nausea and vomiting is so severe that they discontinue their course of chemotherapeutic treatment prior to its completion. Although no known antiemetic agent is totally effective in alleviating the emesis associated with chemotherapy,

there are a large number of compounds (many based on the substituted benzamide structure) which have good antiemetic activity.

Although the complete mechanism of action of antiemetic agents is not known, the effective antiemetic agents are generally dopaminergic antagonists. Indeed, screening for potential antiemetic agents typically is conducted via tests designed to determine dopaminergic blockage, e.g. spiperone binding tests in vitro and apomorphine emesis tests in dogs. As a result of their dopaminergic antagonism and/or central nervous system depression, known antiemetic agents have undesirable side effects such as sedation, dystonic reactions, diarrhea and akathisia.

We have surprisingly found a group of substituted benzamide antiemetic agents with a high specificity of action, which are not dopaminergic antagonists and which are free of the undesirable side effects of the presently known antiemetic agents.

An excellent, modern review article on the variously substituted benzamides and their pharmacological activities is found in "Chemical Regulation of Biological Mechanisms", A. M. Creighton and S. Turner, editors, Royal Society of London (1982), in the chapter entitled "Substituted Benzamides as Dopamine Antagonists", by M. S. Hadley (Pages 140-153). It states that this class of compounds is defined by the formulae

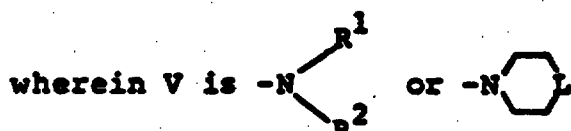
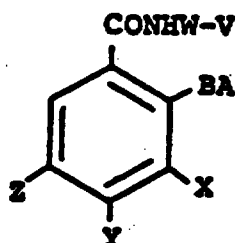


in which the aryl ring is most commonly the phenyl ring and where "a methoxy group ortho to the benzamide moiety is almost invariably present." It points out that the diverse actions of

the substituted benzamides can be considered as being a consequence of the compounds being dopamine antagonists.

Representative prior art patents disclosing N-substituted benzamides, having various substituents on the phenyl ring, include the following.

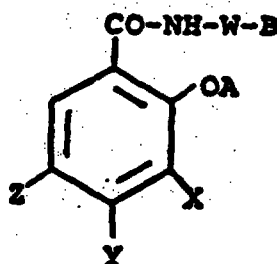
U.S. Patent No. 3,219,528, issued November 23, 1965 to M. L. Thominet, discloses substituted benzamides of the formula



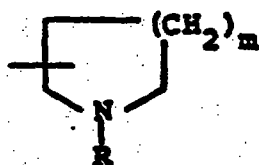
in which R^1 and R^2 are alkyl, L is oxygen, methylene or NR in which R is hydrogen, alkyl or alkylsulfamoyl; W is alkylene; A is alkyl; B is sulfur or oxygen; and X, Y and Z are hydrogen, halogen, alkoxy, nitro, amino, alkylamino, dialkylamino, (lower)acyl, (lower)acylamino, cyano, alkylmercapto, sulfamoyl, alkylsulfamoyl, dialkylsulfamoyl or halomethyl. The compounds are apomorphine antagonists and are stated to be antiemetic agents. U.S. Patents Nos. 3,177,252, issued April 6, 1965, and 3,312,739, issued April 4, 1967, are related and have similar disclosures.

United Kingdom Patent No. 1,500,105, published February

8, 1978, discloses substituted benzamides of the formula



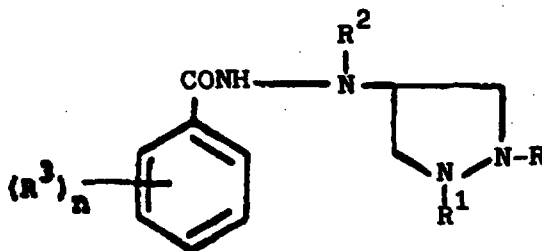
wherein A is hydrogen, C_{1-5} alkyl or C_{2-5} alkenyl; X is hydrogen, C_{1-5} alkoxy, C_{2-5} alkyl, C_{2-5} alkenyloxy or C_{2-5} alkenyl; Y is hydrogen, halogen, nitro, C_{1-5} alkyl, C_{1-5} alkoxy, amino or substituted amino; Z is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkylsulfonyl or a group of the formula $-SO_2NR^1R^2$ in which R^1 and R^2 are the same or different and are hydrogen or a C_{1-5} alkyl group, or $-NR^1R^2$ is a heterocyclic ring optionally containing another heteroatom; W is a C_{1-5} straight or branched chain alkylene group; B is $-NR^3R^4$ in which R^3 is C_{1-5} alkyl and R^4 is C_{1-5} hydroxyalkyl, or B is a nitrogen-attached heterocyclic ring optionally containing a second nitrogen atom and optionally having a substituent, or B is a racemic, dextrorotatory or levorotatory heterocyclic ring of the formula



in which R is C_{1-5} alkyl containing a reactive function such as hydroxy, mercapto, oxo, thioxo, oxa or thia; and m is 1, 2 or 3; and acid addition salts, oxides and quaternary ammonium salts thereof. The compounds are stated to be apomorphine antagonists and to have valuable therapeutic properties, particularly as antiemetics.

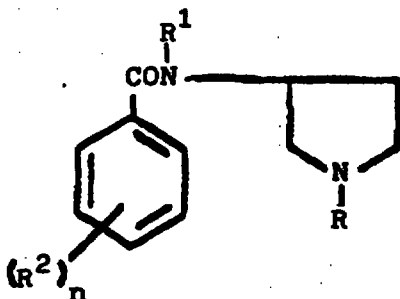
U.S. Patent 4,207,327, issued June 10, 1980 to C. D.

Lunsford et al., discloses compounds of the formula

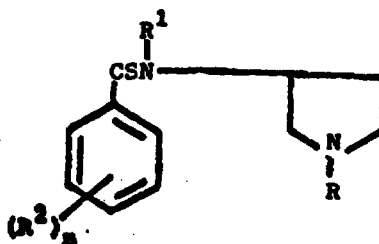


wherein R is alkyl, cycloalkyl or phenylalkyl; R¹ is alkyl, cycloalkyl or phenylalkyl; R² is hydrogen, alkyl or phenyl; and R³ is hydroxy, cyano, nitro, amino, fluoro, chloro, bromo, trifluoromethyl, alkyl, alkoxy, sulfamoyl or acetamido, and each R³ may be the same or different. The compounds are stated to have antiemetic and gastric emptying properties.

U.S. Patent 3,966,957, issued June 29, 1976 to Cale, Jr., et al., discloses substituted benzamides of the formula



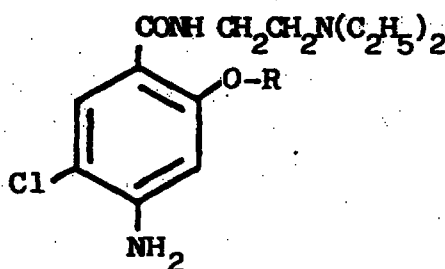
wherein R is cycloalkyl, phenyl or phenylalkyl; R¹ is hydrogen, C₁₋₈ alkyl or phenyl; R² is halogen, alkyl, alkoxy, amino, nitro, alkylamino, dialkylamino, mercaptomethyl, acetamido, sulfamoyl, cyano, hydroxy, benzyloxy or trifluoromethyl; and n is 0-3; and substituted thiobenzamides of the formula



wherein R is cycloalkyl, R¹ is hydrogen, or C₁₋₈ alkyl; R² is

nitro, amino, halogen, sulfamoyl or alkoxy; and n is 0-3; and pharmaceutically acceptable acid addition salts thereof. U.S. Patent No. 3,963,745 is related and has a substantially identical disclosure. The compounds are stated to be apomorphine antagonists and to be useful as antiemetics. Certain of the compounds were stated to reduce catalepsy in rats.

The compounds of this invention are those of the formula



wherein

R is cyclohexane-1-ol-2-yl; 3-methoxybut-1-yl; or 3-hydroxybut-1-yl. Also included are non-toxic pharmaceutically acceptable salts, hydrates, solvates or quaternary ammonium salts of these compounds.

The physiology and neuropharmacology of emesis, and particularly chemotherapy-induced emesis, is not completely understood. The control mechanism for emesis consists of two distinct units in the medulla, the emetic center and the chemoreceptor trigger zone (CTZ). The emetic center, which is the final common pathway for all emetic stimuli, is located in the lateral reticular formation of the fourth ventricle. The CTZ is also located in the floor of the fourth ventricle, in the area postrema, and appears to be activated by chemical stimuli in the blood or cerebrospinal fluid. When stimulated, receptors, such as dopamine receptors, in the CTZ generate impulses which are transmitted to the emetic center, and emesis results. Reflex-induced vomiting may also be caused by irritation (and resulting

stimuli) from the gastrointestinal tract or stimulation of receptors in the central nervous system. The cortex of the brain is believed to be another source of emesis. Thus, the familiar problem of anticipatory vomiting in patients receiving chemotherapy clearly is not associated with exogenous chemical stimulation. It is believed that anticipatory vomiting is mediated initially by the cortex which may then stimulate the medullary emetic center.

There are a number of commercially available antiemetic drugs at the present time, such as metoclopramide, bromopride, alizapride, clebopride, domperidone and nabilone. Metoclopramide is a leading compound and is utilized extensively in combination with cisplatin, which is an effective but highly emetogenic chemotherapeutic agent.

Presently available substituted benzamide antiemetic agents are generally dopaminergic antagonists and, indeed, are believed to exert their antiemetic activity by blocking dopamine receptors in the CTZ. Screening tests for potential antiemetic agents have historically involved tests which determine dopaminergic antagonist activity, e.g. spiperone binding tests in vitro, and the reduction of apomorphine-induced vomiting in the dog or cat.

The principal adverse effects of known substituted benzamide antiemetic agents are due to their dopamine blocking activity, and include akathisia, acute dystonia, Parkinsonian features and tardive dyskinesia, often along with nervous system depression.

The compounds of the present invention are effective antiemetic agents but are not dopaminergic antagonists, as shown by both in vitro tests (spiperone binding) and in vivo tests (apomorphine emesis in the dog). Thus, the compounds of Formula I have good antiemetic activity (particularly against chemotherapy-induced emesis) with a high specificity of action, but with none of the side effect liabilities (such as described

above) that are associated with the dopaminergic antagonist class of substituted benzamide antiemetic agents.

Many of the commercially available substituted benzamide antiemetic agents (such as metoclopramide) also have gastrokinetic activity and are useful in the treatment of disorders related to impaired gastrointestinal motility, such as retarded gastric emptying, dyspepsia, flatulence, esophageal reflux and the like.

Again, because they are not dopaminergic antagonists, the compounds of this invention do not have the above-mentioned side-effect liabilities of the commercially available substituted benzamides such as metoclopramide or clebopride.

The compounds of this invention may be administered either orally, parenterally or by suppository. When utilized as an antiemetic in the case of patients receiving cancer chemotherapeutic agents such as cisplatin, it preferably is given as an intravenous infusion diluted in a larger volume of parenteral solution (such as Dextrose - 5% in water, Dextrose - 5% in 0.45% sodium chloride, Ringer's Injection or Lactated Ringer's Injection). When utilized as a gastrokinetic agent, the compounds preferably are given orally if the symptoms are not severe. With severe symptoms, therapy preferably should begin with i.m. or i.v. administration until the severe symptoms subside, at which time oral administration may be instituted.

The dosage of the compounds of this invention depend on the purpose for which they are taken (antiemetic or gastrokinetic), the particular compound administered, the age, weight and general health of the patient, as well as the severity of the malady, and is within the discretion of the physician.

When taken for gastrokinetic purposes, the compounds of this invention are generally administered at a dosage of from 1 to 100 mg and preferably from 5 to 50 mg, from 2 to 5 times a day and preferably four times a day, e.g. before each meal and at bedtime.

For the prevention of nausea and vomiting associated with emetogenic cancer chemotherapeutic agents, the compounds of this invention are generally administered (diluted in a larger volume of parenteral solution) at a dosage of from 0.1 to 50 mg/kg and preferably from 0.5 to 10 mg/kg, given several times per day. The particular dose to be used depends on the factors mentioned

above, as well as the emetogenicity of the cancer chemotherapeutic agent. In general, the first dose should be given prior to the administration of the cancer chemotherapeutic agent, e.g. 30 minutes, and then every 2-8 hours after administration of the chemotherapeutic agent, until the symptoms of nausea and vomiting subside or become less severe, e.g. for 12 to 24 hours.

Tablets and capsules for oral use preferably are in unit dosage form, and may contain conventional excipients such as binding agents, fillers, tableting lubricants, disintegrants, wetting agents and the like. The tablets may, if desired, be film coated by conventional techniques. Liquid preparations for oral use may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be a dry product for reconstitution with water or other suitable vehicle before use. Liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicle (including edible oils), preservatives, as well as flavoring and/or coloring agents.

For parenteral administration, the compounds of this invention are combined with a sterile vehicle. Depending on the vehicle and concentration of active ingredient, the dosage form may be a solution or suspension. The vehicle normally will comprise sterile water, at least in large part, although saline solutions, glucose solutions and the like may be utilized. Injectable suspensions also may be used, in which case conventional suspending agents may be employed. Conventional preservatives, buffering agents and the like also may be added to the parenteral dosage forms.

For solid dosage forms, either the free base or a salt of the compounds of Formula I may be used. In the case of aqueous solutions, either oral or parenteral, it is often preferred to utilize a salt of the compounds of this invention, due to the usual greater solubility of the salts in aqueous solutions.

It is especially advantageous to formulate the above pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form refers to physically discrete units suitable as unitary doses, each unit containing a predetermined quantity of active ingredient, calculated to produce the desired effect, in association with the desired pharmaceutical carrier.

This invention also includes pharmaceutical compositions for the alleviation of nausea and vomiting, which comprises an effective antiemetic amount of at least one compound of this invention, or a salt, hydrate or solvate thereof, plus a pharmaceutically acceptable carrier.

This invention also includes pharmaceutical compositions for the treatment of disorders related to impaired gastric motility, which comprise an effective gastric motility facilitating amount of at least one compound of this invention, or a salt, hydrate or solvate thereof and a pharmaceutically acceptable carrier.

The invention also relates to an effective antiemetic amount of at least one compound of this invention, or a salt, hydrate, or solvate thereof, in a pharmaceutically accepted carrier for use through the systemic administration to a warm-blooded mammal in alleviating nausea and vomiting in said mammal. The invention also relates to an effective gastric motility facilitating amount of at least one compound of this invention, or a salt, hydrate or solvate thereof, in a pharmaceutically acceptable carrier for use through the systemic administration to a warm-blooded mammal in treating disorders related to impaired gastric motility.

The term systemic administration as used herein refers generally to oral, rectal, and parenteral, which routes further include intranasal administration, sublingual administration, administration via the buccal cavity, and transdermal administration as well as the more common intramuscular, intravenous and subcutaneous routes.

A preferred use for compounds of the present invention relates to their use in alleviating nausea and vomiting in cancer patients who are undergoing cancer therapy such as chemotherapy and/or radiation treatment. It is further intended that in cases of chemotherapeutic treatments with anti-cancer agents, such as cisplatin, for example that a selected compound of this invention and a selected anti-cancer chemotherapeutic agent may be co-administered to the patient and that to facilitate such co-administration pharmaceutical compositions for effecting such treatment

would be utilized and such compositions will contain at least one compound of the present invention in combination with the selected cancer chemotherapeutic agent and a pharmaceutical carrier. It is envisaged that the compounds of this invention would be useful against nausea and vomiting associated with certain medical procedures, post-operative trauma, motion-sickness related disorders, and general nausea and vomiting of unknown origin.

The following Examples and Preparation illustrate the compounds of this invention and their preparation.

Example 1

cis- and trans-4-Amino-5-chloro-2-(cyclohexane-1-ol-2-yl)oxy-N-[(2-diethylamino)ethyl] benzamides

A solution of 4-amino-5-chloro-2-(cyclohexanone-2-yl)oxy-N-[(2-diethylamino)ethyl]- benzamide (3.3 g; 8.7 mmoles) in absolute ethanol (50 ml) was cooled to 0°C and sodium borohydride (0.5 g, 13.2 mmoles) was added portionwise over 15 minutes. The resulting mixture was heated to reflux for 3 hours and then quenched with 1N HCl. Extraction with CH₂Cl₂ (4X) resulted in a mixture of cis and trans cyclohexyl alcohols which were separated by silica gel chromatography to yield pure 4-amino-5-chloro-2-(trans,1,2-cyclohexane-1-ol-2-yl)oxy-N-[2-(diethylamino)-ethyl]benzamide [NMR (CDCl₃) δ 8.4 (br s, 1H); 8.0 (s, 1H); 6.3 (s, 1H); 4.3 (s, 2H); 3.9 (dt, 1H); 3.7 (br m, 2H); 3.4 (m, 1H); 2.7 (m, 6H); 1.7 (br d, 1H); 1.43-1.10 (br m, 8H); 1.03 (t, 6H)] and 4-amino-5-chloro-2-(cis,1,2-cyclohexane-1-ol-2-yl)oxy-N-[2-(diethylamino)ethyl]-benzamide [NMR (CDCl₃) δ 8.7 (s, 1H); 8.07 (s, 1H); 6.27 (s, 1H); 4.30 (br s, 2H); 4.21 (br d, 1H); 4.01 (m, 1H); 3.78 (br m, 1H); 3.31 (br m, 1H); 2.72 (br m, 6H); 1.9-1.27 (br m, 9H); 1.03 (t, 6H)] as gummy foams.

Preparation No. 14-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamideA) 4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide Hydrochloride

To a cooled (<10°) stirred suspension of sodium hydride (57.44 g of 60%, 1.436 moles) in DMF (1275 ml) was added dropwise a cold solution of ethanethiol (89.22 g, 1.436 moles) in DMF (250 ml). After hydrogen evolution had ceased 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide (287.0 g, 0.957 moles) (prepared according to U.S. Patent 3,357,978 [1965]) was added and the mixture was heated in an oil bath at 100-105° for 90 minutes. The solvent was removed in vacuo and the residue partitioned between methylene chloride (800 ml) and water (400 ml). The aqueous layer was washed with another portion of methylene chloride and the combined organic extracts were back-washed with water (150 ml). The combined aqueous phase was cooled in an ice bath and treated with concentrated hydrochloric acid (200 ml). After 20 minutes the precipitate was collected by filtration, sucked briefly on the filter, slurried with methanol (500 ml) and again filtered. The product was dried in vacuo to give 302.3 g (98%) of the title compound as a light beige solid, mp 235-237°.

Anal. Calc'd. for $C_{13}H_{20}ClN_3O_2 \cdot HCl$: C, 48.46; H, 6.57;
N, 13.04; Cl, 22.00

Found: C, 47.67; H, 6.73;
N, 12.84; Cl, 21.43

B) 4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide

To stirred concentrated ammonium hydroxide (6 ml) was added 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide hydrochloride (3.0 grams, 0.0093 mole) and the mixture stirred an additional five minutes followed by the addition of

three to four ml of water and another five minute stirring. After filtration the solid was washed two times with three ml of water each time to give, after drying, 2.37 g of the title compound, mp 134-136°C. NMR spectrum (90 MHz) in CDCl_3 gave the following resonances δ : 7.26 (s, 1H); 6.90 (s, 1H); 6.14 (s, 1H); 4.39 (s, 2H); 3.40 (s, 2H); 2.60 (multiplet, 6H); 1.06 (t, 6H).

Example 24-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(3-methoxybut-1-yl)oxybenzamide

A stirred solution of 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide (1.715 g, 6 μ moles; prepared according to Preparation 1B), triphenylphosphine (1.58 g, 6 μ moles), 3-methoxy-1-butanol (0.62 g, 6 μ moles) in dry tetrahydrofuran (50 ml) was treated dropwise with diethyl azodicarboxylate (1.1 g of 95% purity material, 6 μ moles). The solution was left to stir overnight. After evaporation of the solvent the residue was dissolved in methylene chloride. The solution was washed with 0.4N NaOH, water, dried and the solvent evaporated. The residue was chromatographed over deactivated silica using methylene chloride (100), methanol (2.5), ammonium hydroxide (0.5) solvent system. The appropriate fractions were combined and the solvent evaporated. The residue (1.7 g) was crystallized from toluene to yield 1.17 g (52%) of the title compound, m.p. 76-78°C.

Anal. Calc'd. for $C_{18}H_{20}ClN_3O_3$: C, 58.13; H, 8.13; N, 11.30; Cl, 9.53

Found: C, 58.43; H, 8.35; N, 11.33; Cl, 9.70

Example 34-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(3-hydroxybut-1-yl)oxy-benzamide -

A stirred solution of 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide (2.86 g, 10 μ moles; prepared according to Preparation 1 B), triphenylphosphine (2.62 g, 10 μ moles), ($\pm$) 1,3 butandiol (0.90 g, 10 μ moles) in dry tetrahydrofuran (50 ml) was treated dropwise with diethyl azodicarboxylate (1.75 g of 95% purity material, 10 μ moles). The solution was left to stir overnight. After evaporation of the solvent the residue was taken up in methylene chloride. The solution was washed with 0.4N NaOH, water, dried and the solvent evaporated. The residue was chromatographed over deactivated silica using methylene chloride (100), methanol (3), ammonium hydroxide (0.5) solvent system. The appropriate fractions were combined and the solvent evaporated. The residue was crystallized from methylene chloride-pentane to yield 1.05 g (29%) of the title compound. m.p. 136.5-137.5°C. An additional amount of 0.56 g of material was obtained from the mother liquor after crystallization from toluene, followed by recrystallization from methylene chloride-pentane, and from a dilute solution of ethyl acetate, m.p. 135-137°C.

Anal. Calc'd. for $C_{17}H_{28}ClN_3O_3$: C, 57.05; H, 7.89; N, 11.74; Cl, 9.91

Found: C, 56.90; H, 8.12; N, 11.62; Cl, 9.99

**CLAIMS:**

1. 4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(3-hydroxybut-1-yl)oxybenzamide.
2. 4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(3-methoxybut-1-yl)oxybenzamide.
3. 4-Amino-5-chloro-2-(cyclohexane-1-ol-2-yl)oxy-N-[(2-diethylamino)ethyl]oxybenzamide.
4. The compound of claim 3 in the form of its cis isomer.
5. The compound of claim 3 in the form of its trans isomer.
6. A non-toxic pharmaceutically acceptable salt, hydrate, solvate or quaternary ammonium salt of one of the compounds claimed in any one of claims 1 to 5.
7. A pharmaceutical composition for the alleviation of nausea and vomiting, which comprises an effective antiemetic amount of at least one compound, salt, hydrate or solvate thereof according to any one of claims 1 to 6, plus a pharmaceutically acceptable carrier.
8. A pharmaceutical composition for the treatment of disorders related to impaired gastric motility, which comprises an effective gastric motility facilitating amount of at least one compound, salt, hydrate or solvate thereof according to any one of claims 1 to 6, and a pharmaceutically acceptable carrier.
9. An antiemetic amount of at least one compound, salt, hydrate or solvate thereof according to any one of claims 1 to 6, in a pharmaceutically acceptable carrier for use through its systemic administration to a warm-blooded mammal in alleviating nausea and vomiting in said mammal.



10. A gastric motility facilitating amount of at least one compound salt, hydrate or solvate thereof according to any one of claims 1 to 6, in a pharmaceutically acceptable carrier for use through its systemic administration to a warm-blooded mammal in treating disorders related to impaired gastric motility in said mammal.

11. A process for preparing a compound or a salt, hydrate or solvate thereof as defined in any one of claims 1 to 5 substantially as hereinbefore described with reference to the Examples.

12. A compound as defined in any one of claims 1 to 5 prepared by a process as claimed in claim 11.

13. A pharmaceutical composition comprising a compound as claimed in claim 12 and a pharmaceutically acceptable carrier.
