

SUBSTITUTED BENZAMIDE

This invention relates to a substituted benzamide.

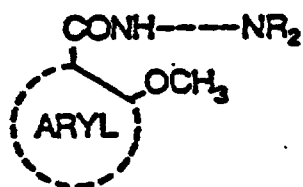
Emesis is a common and serious problem in patients receiving cancer chemotherapeutic agents. In a significant number of patients, nausea and vomiting is so severe that they discontinue their course of chemotherapeutic treatment prior to its completion. Although no known antiemetic agent is totally effective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

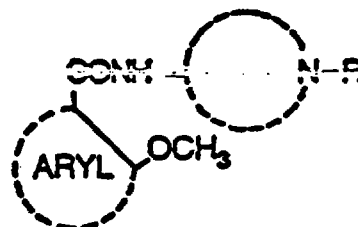
Although the complete mechanism of action of antiemetic agents is not known, the effective antiemetic agents are generally dopaminergic antagonists. Indeed, screening for potential antiemetic agents typically is conducted via tests designed to determine dopaminergic blockage, e.g. spiperone binding tests 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



and

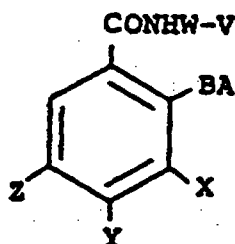


in which the aryl ring is most commonly the phenyl ring and where "a methoxy group ortho to the benzamide moiety is almost invariably present." It points out that the diverse actions of

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

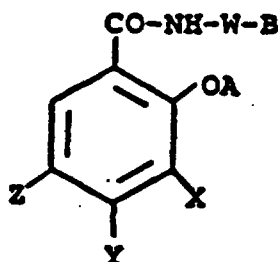


wherein V is $\begin{array}{c} \text{R}^1 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}^2 \end{array}$ or $\text{N} \begin{array}{c} \diagup \\ \text{L} \\ \diagdown \end{array}$

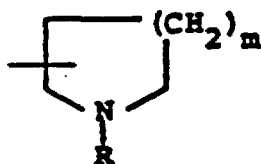
in which R^1 and R^2 are alkyl, L is oxygen, methylene or NR in which R is hydrogen, alkyl or alkylsulfamoyl; W is alkylene; A is alkyl; B is sulfur or oxygen; and X, Y and Z are hydrogen, halogen, alkoxy, nitro, amino, alkylamino, dialkylamino, (lower)acyl, (lower)acylamino, cyano, alkylmercapto, sulfamoyl, 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



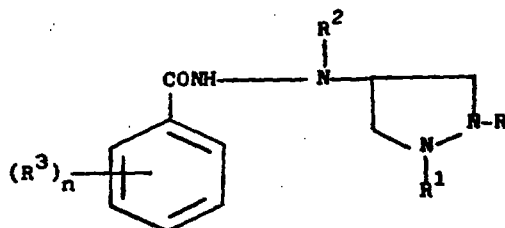
wherein A is hydrogen, C_{1-5} alkyl or C_{2-5} alkenyl; X is hydrogen, C_{1-5} alkoxy, C_{2-5} alkyl, C_{2-5} alkenyloxy or C_{2-5} alkenyl; Y is hydrogen, halogen, nitro, C_{1-5} alkyl, C_{1-5} alkoxy, amino or substituted amino; Z is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkylsulfonyl or a group 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.

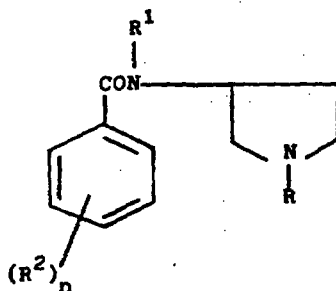
U.S. Patent 4,207,327, issued June 10, 1980 to C. D.

Lunsford et al., discloses compounds of the formula

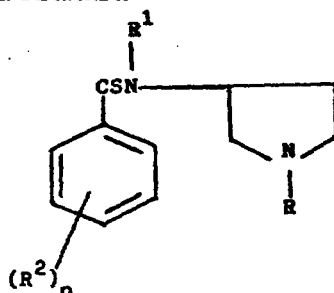


wherein R is alkyl, cycloalkyl or phenylalkyl; R¹ is alkyl, cycloalkyl or phenylalkyl; R² is hydrogen, alkyl or phenyl; and R³ is hydroxy, cyano, nitro, amino, fluoro, chloro, bromo, trifluoromethyl, alkyl, alkoxy, sulfamoyl or acetamido, and each R³ may be the same or different. The compounds are stated 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 compound of this invention is 4-acetamido-5-chloro-N-[2-diethylamino)ethyl]-2-[(2-acetoxy-but-3-yl]oxybenzamide. Also included are the erythro and threoisomers of this compound and the non-toxic pharmaceutically acceptable salts, hydrates, solvates and quaternary ammonium salt of this compound and the erythro and threoisomers thereof.

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 compound of this invention is an effective antiemetic agent but is not a dopaminergic antagonist, 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 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 it is not a dopaminergic antagonist, the compound of this invention does not have the above-mentioned side-effect liabilities of the commercially available substituted benzamides such as metoclopramide or clebopride.

The compound 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 compound is preferably 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 compound of the invention depends on the purpose for which it is 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 compound of the invention is 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 compound of the invention is 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 compound of the invention is 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 the invention may be used. In the case of aqueous solutions, either oral or parenteral, it is often preferred to utilize a salt of the compound 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 the compound of the 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 the compound of the invention, or a salt, hydrate or solvate thereof, and a pharmaceutically acceptable carrier.

The invention also relates to an effective antiemetic amount of the 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 the 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 the compound of the present invention relates to its 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, that the 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 the compound of the present invention in combination with the selected cancer chemotherapeutic agent and a pharmaceutical carrier. It is envisaged that the compound 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 Preparations and Example illustrate the compound of the invention and its preparation.

Preparation 1

4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(2-propanon-1-yl)-oxybenzamide

To a stirred suspension of 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide hydrochloride (5.0 g, 16 mmol) and potassium carbonate (10.62 g, 77 mmol) in DMF (25 ml) was added chloroacetone (2.32 g of 90%, 22 mmol) and the mixture stirred vigorously for 5 hours, followed by pouring into water (130 ml) and filtration to give, after drying, 4.57 g of crude product. This was dissolved in methylene chloride and filtered over a short alumina column, followed by concentration and recrystallization of the residue from toluene to give 4.16 g (78%) of the title compound as white solid, mp 105-106.5°. The NMR (90 MHz) in CDCl_3 gave the following resonances: δ 8.44 (s, 1H); 8.24 (s, 1H); 6.16 (s, 1H); 4.72 (s, 2H); 4.4 (s, 2H); 3.6 (m, 2H); 2.68 (m, 6H); 2.28 (s, 3H); 1.08 (t, 6H).

Anal. Calc'd. for $\text{C}_{16}\text{H}_{24}\text{ClN}_3\text{O}_3$: C, 56.21; H, 7.08; N, 12.29
Cl, 10.37

Found: C, 56.14; H, 6.97; N, 12.29
Cl, 10.29

Preparation 2A) 4-Amino-2-(butan-2-on-3-yl)oxy-5-chloro-N-[2-(diethylamino)-ethyl]benzamide

To a stirred suspension of sodium hydride (40 mg of 60%, 1 mmole, washed with n-pentane) in DMF (2 ml) was added 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(2-propanon-1-yl)-oxybenzamide, prepared in Preparation 1, (0.349 g, 1 mmole) under nitrogen. The mixture was stirred until evolution of hydrogen subsided, when iodomethane (0.07 ml, 160 mg, 1.1 mmol) was added and stirring continued for 1 hour. The mixture was partitioned between water and methylene chloride, and the organic phase washed with water, dried, concentrated and the residue chromatographed on deactivated silica using methylene chloride (100), methanol (4.5), ammonia (0.5) solvent system. The appropriate fractions were combined to give 160 mg of the title compound as a heavy oil. The NMR spectrum (90 MHz) in CDCl_3 gave the following resonances: δ 8.24 (s, superimposed over broad singlet, 2H); 6.08 (s, 1H); 4.70 (q, $J=5.4$ Hz, 1H); 4.44 (s, 2H); 3.56 (m, 2H); 2.62 (m, 6H); 2.2 (s, 3H); 1.6 (d, $J=5.4$ Hz, 3H); 1.04 (t, 6H).

B) 4-Amino-2-(butan-2-on-3-yl)oxy-5-chloro-N-[2-(diethylamino)-ethyl]benzamide hydrochloride

To a stirred suspension of 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide hydrochloride (1.94 g, 6 mmols) and potassium carbonate (4.16 g, 30 mmols) in DMF (10 ml) was added 3-chloro-2-butanone (0.95 g, 8.9 mmols) and the mixture stirred for 3 hours, followed by pouring into water and extraction with methylene chloride. The extract was washed well with water, dried and concentrated in vacuo. The residue was dissolved in 1-propanol and treated with 2N HCl followed by concentration to give an oily residue. This was crystallized from acetone and the product recrystallized from 2-propanol to give 1.4 g of the title compound mp 98°C as the hemihydrate.

Anal. Calc'd. for $C_{17}H_{26}ClN_3O_3 \cdot HCl \cdot 0.5H_2O$: C, 51.00; H, 6.80; N, 10.50; Cl, 17.71
 Found: C, 51.26; H, 6.86; N, 10.51; Cl, 17.38

C) 4-Amino-2-(butan-2-on-3-yl)oxy-5-chloro-N-[2-(diethylamino)-ethyl]benzamide Hydrochloride

To a stirred suspension of 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-hydroxybenzamide hydrochloride (19.4 g, 60 mmols), potassium carbonate (41.6 g, 0.3 moles) and sodium iodide (10 g) in DMF (100 ml) was added 3-chloro-2-butanone (9.5 g, 89 mmols) and the mixture vigorously stirred and heated to 70-80° for 2 hours followed by cooling and partition between water and methylene chloride. The organic phase was washed with water, dried and concentrated. The residue was treated with 2N HCl and azeotroped with n-propanol, and crystallized from acetone to give 19.0 g (81%) of the title compound mp 177-179°.

EXAMPLE

erythro-4-Acetamido-5-chloro-N-[2-(diethylamino)ethyl]-2-[(2-acetoxy)-but-3-yl]oxybenzamide and threo-4-acetamido-5-chloro-N-[2-(diethylamino)ethyl]-2-[(2-acetoxy)-but-3-yl]oxybenzamide.

4-Amino-2-(butan-2-one-3-yl)oxy-5-chloro-N-[2-(diethylamino)ethyl]-benzamide hydrochloride (prepared in Preparation 2) (30.0 g; .0765 mole) was added to 300 ml of abs. ethanol and the mixture was warmed to ca. 50°C. The heat source was removed and sodium borohydride (3.18 g; .084 mole) was added slowly, in small portions, with good stirring. When the addition was complete the mixture was stirred at reflux for one hour. The reaction mixture was filtered, the ethanol removed in vacuo and the residue was treated with 100 ml of water followed by 40 ml of 3N HCl. The acid solution was extracted twice with ether (discarded), cooled in an ice bath and made strongly basic with 40% NaOH. The separated oil was then extracted with several portions of CH₂Cl₂, dried over Na₂SO₄ and the solvent evaporated to leave 25.88 g of sticky gum. An nmr (CDCl₃) showed ca. 7:3 mixture of threo to erythro diastereoisomers. Some enrichment of the erythro isomer was effected by crystallizing from the mixture the threo isomer (6.60 g) using solvent systems of ethyl acetate/skelly B, nitromethane and toluene/ether.

The mother liquors from the collected crystals were evaporated to dryness and the residual oil (ca. 20 g of the intermediate alcohol; .0559 mole) was dissolved in 200 ml of pyridine. 31.6 ml of acetic anhydride (34.23 g; .0335 mole) was added and the solution was heated in an oil bath at 72-75°C (oil bath temperature) for one hour and at 100-105°C for 2.5 hrs. The reaction solution was concentrated at reduced pressure and the residue was partitioned between water and CH₂Cl₂. 40% NaOH was added to make the aqueous layer strongly basic and then extracted with several portions of CH₂Cl₂. The combined extracts were dried and the solvent evaporated to give a mixture of the diacylated products as a dark oil.

The crude mixture was purified by flash chromatography on 400 g of silica gel (32-63 μ m) using 98 CH_2Cl_2 :2 CH_3OH :0.3% NH_4OH as the eluant. 34 x 400 ml fractions were collected and combined into four lots as follows:

Fractions 9, 10, 11 ----- 6.62 g (92:8 threo:erythro)

Fractions 12-17 ----- 5.62 g (86:14 threo:erythro)

Fractions 18-25 ----- 10.28 g (57:43 threo:erythro)

Fractions 26-33 ----- 4.46 g (14:86 threo:erythro)

Determination of the isomer ratio was done by analytical HPLC using a 10 μ Alltech silica 600 column and a mobile phase of 800 CH_2Cl_2 :8 IPA: 4 NH_4OH ; UV detector at 280 nm.

Separation of the two diastereoisomers was effected by chromatographing the four lots (in six runs) on a Waters Prep 500 HPLC System.

Column: new silical gel column (1)

Detector: refractive index

Mobile Phase: CH_2Cl_2 + 2-5% IPA + 0.5% NH_4OH

Each of the collected fractions was assayed on the analytical HPLC and the appropriate ones were combined to yield 4.44 g of amber oil that was 96.8% pure erythro isomer. Also isolated was 6.74 g of the threo isomer (97.4% pure), 2.12 g threo isomer (94% pure) and 1.14 g of erythro isomer (94.8% pure).

Anal. (erythro isomer) Calcd. for $\text{C}_{21}\text{H}_{32}\text{ClN}_3\text{O}_5$: C, 57.07; H, 7.30; N, 9.51

Found: C, 56.67; H, 7.25;

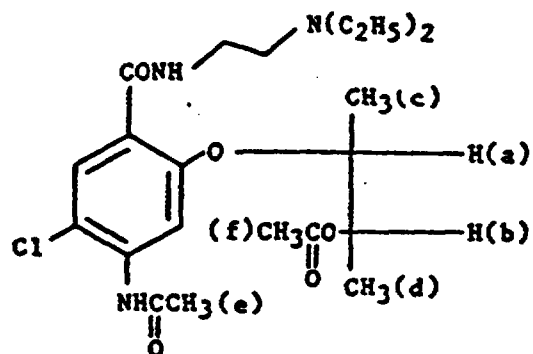
N, 9.56

Anal. (threo isomer) Calcd. for $\text{C}_{21}\text{H}_{32}\text{ClN}_3\text{O}_5$: C, 57.07; H, 7.30; N, 9.51

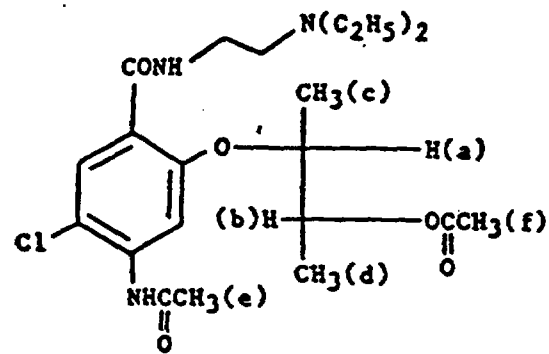
Found: C, 56.68; H, 7.26;

N, 9.25

¹H-NMR DATA - All spectra were run in CDCl₃



erythro isomer



threo isomer

Proton	Shape	Assignment (ppm)		erythro	threo
		erythro	threo		
C-6	s	8.30	8.30	$J(a-b) = 6.4 \text{ Hz}$	4.4 Hz
C-3	s	8.20	8.18	$J(a-c) = 6.4 \text{ Hz}$	6.4 Hz
a	m	5.15	5.13	$J(b-d) = 6.4 \text{ Hz}$	6.4 Hz
b	m	4.56	4.60		
c	d	1.34	1.38		
d	d	1.27	1.31		
e	s	2.24	2.24		
f	s	1.99	2.03		



CLAIMS:

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

9. A process for preparing the compounds defined in claims 1, 2 or 3 substantially as hereinbefore described with reference to the Example.

10. A compound as defined in claims 1, 2 or 3 prepared by the process as claimed in claim 9.

11. A pharmaceutical composition comprising a compound as claimed in claim 10 and a pharmaceutically acceptable carrier.
