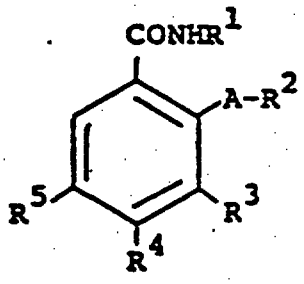
2205095

SUBSTITUTED BENZAMIDES

This invention relates to substituted benzamides of the formula



XXI

wherein R^1, R^2, R^3, R^4, R^5 and A are as defined below, which have useful gastro-intestinal properties and are useful in the treatment of emesis, particularly emesis resulting from standard cancer treatments such as chemotherapy-induced emesis, for example radiation treatment, cisplatin treatment of cancer patients, and/or in treatment of disorders related to impaired gastric motility, such as retarded gastric emptying, dyspepsia, flatulence, esophageal reflux and the like.

Background and Prior Art

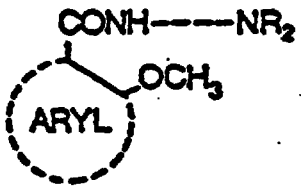
Emesis is a common and serious problem in patients receiving cancer chemotherapeutic agents. In a significant number of patients, nausea and vomiting is so severe that they discontinue their course of chemotherapeutic treatment prior to its completion. Although no known antiemetic agent is totally effective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

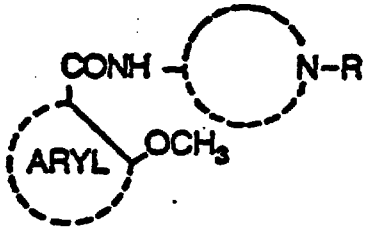
Although the complete mechanism of action of antiemetic agents is not known, the effective antiemetic agents are generally dopaminergic antagonists. Indeed, screening for potential antiemetic agents typically is conducted via tests designed to determine dopaminergic blockage, e.g. spiperone binding tests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

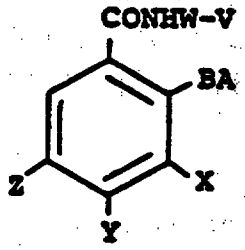


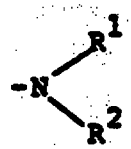
in which the aryl ring is most commonly the phenyl ring and where "a methoxy group ortho to the benzamide moiety is almost invariably present." It points out that the diverse actions of

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

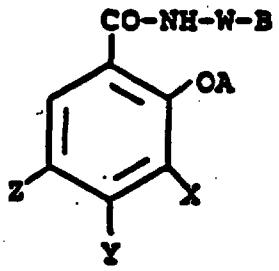


wherein V is  or 

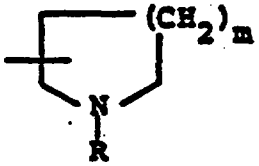
in which R^1 and R^2 are alkyl, L is oxygen, methylene or NR in which R is hydrogen, alkyl or alkylsulfamoyl; W is alkylene; A is alkyl; B is sulfur or oxygen; and X, Y and Z are hydrogen, halogen, alkoxy, nitro, amino, alkylamino, dialkylamino, (lower)acyl, (lower)acylamino, cyano, alkylmercapto, sulfamoyl,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



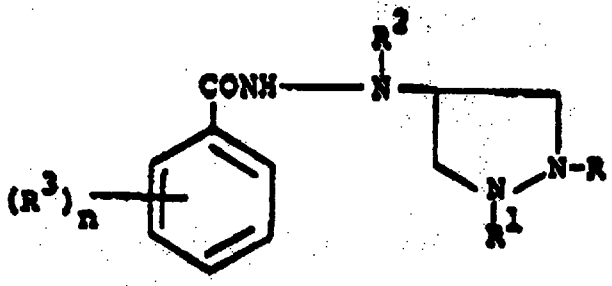
wherein A is hydrogen, C_{1-5} alkyl or C_{2-5} alkenyl; X is hydrogen, C_{1-5} alkoxy, C_{2-5} alkyl, C_{2-5} alkenyloxy or C_{2-5} alkenyl; Y is hydrogen, halogen, nitro, C_{1-5} alkyl, C_{1-5} alkoxy, amino or substituted amino; Z is hydrogen, halogen, C_{1-5} alkoxy, C_{1-5} alkylsulfonyl or a group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

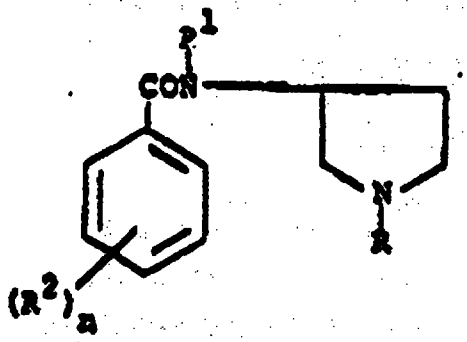
U.S. Patent 4,207,327, issued June 10, 1980 to C. D.

Lunsford et al., discloses compounds of the formula

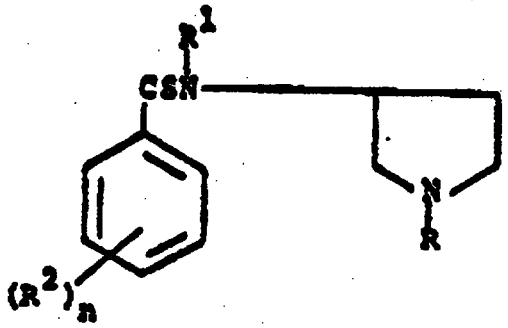


wherein R is alkyl, cycloalkyl or phenylalkyl; R^1 is alkyl, cycloalkyl or phenylalkyl; R^2 is hydrogen, alkyl or phenyl; and R^3 is hydroxy, cyano, nitro, amino, fluoro, chloro, bromo, trifluoromethyl, alkyl, alkoxy, sulfamoyl or acetamido, and each R^3 may be the same or different. The compounds are 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; R^1 is hydrogen, C_{1-8} alkyl or phenyl; R^2 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

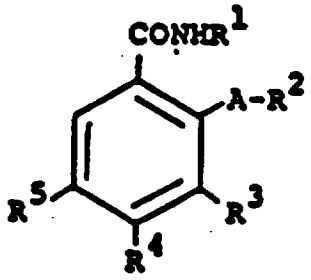


wherein R is cycloalkyl; R^1 is hydrogen, or C_{1-8} alkyl; R^2 is

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.

Complete Disclosure

This invention relates to compounds of the formula



XXI

wherein

R^3 is hydrogen or, when R^4 and R^5 are each hydrogen, R^3 may be (lower)alkoxy;

R^4 is hydrogen, amino or (lower)alkoxy;

R^5 is hydrogen, chloro, bromo, fluoro, trifluoromethyl, (lower)alkylthio, (lower)alkanesulfinyl, (lower)alkanesulfonyl, sulfamyl or $R^6\text{-}\overset{O}{\overset{\|}{C}}\text{-}$, or R^4 and R^5, taken together, may be -HN-N=N- ;

R^6 is (lower)alkyl, (lower)alkenyl or (lower)alkynyl;

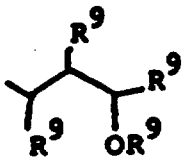
R^1 is



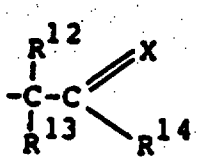
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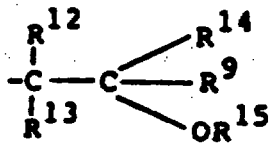
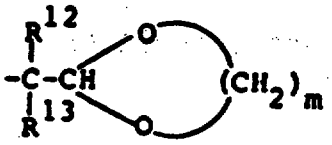
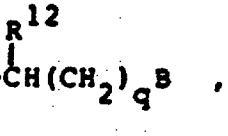
A is oxygen or $-S(O)_p-$;

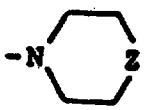
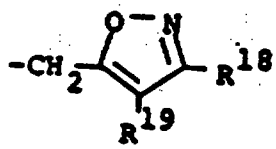
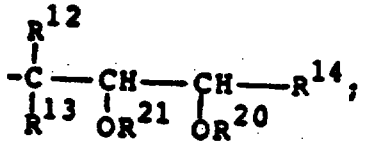
R^2 is alkenyl, alkynyl,


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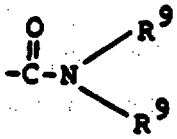
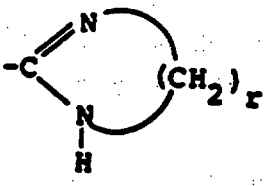

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or

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wherein

X is oxygen, sulfur or $=NOR^{16}$;

Z is $-(CH_2)_p-$, O, N or $-S(O)_p-$;

B is $-NHCR^9$, $-S(O)_pR^9$,
, 
, 
,

pyridyl or oxazolidinyl;

m is 2 or 3;

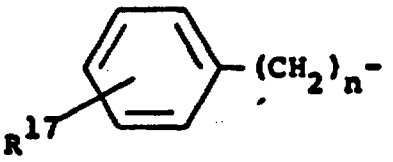
p is 0, 1 or 2;

q is an integer of from 0 to 4, inclusive;

r is 2 or 3;

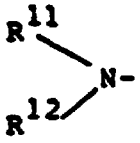
R^9 is hydrogen or (lower)alkyl;

R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are the same or different, and are hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkoxy(lower)alkyl, cycloalkyl containing from 5 to 7 carbon atoms, inclusive, or

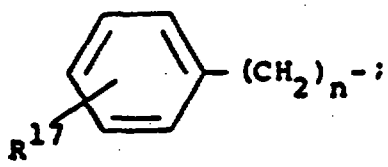


where n is an integer of from 1 to 4 inclusive and R^{17} is hydrogen, halogen, hydroxy, (lower) alkyl or (lower) alkoxy; provided that, when R^{11}, R^{15} or R^{16} is (lower) alkenyl or (lower) alkynyl, the unsaturated carbon atom may not be directly attached to an oxygen or nitrogen atom;

R^{14} is hydrogen, halogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cycloalkyl containing from 5 to 7 carbon atoms, inclusive, hydroxy, (lower)alkoxy, (lower)alkenyloxy, (lower)alkoxycarbonyl(lower)alkenyl, hydrazino, acetylhydrazino, thienyl, phenyl,

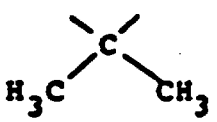


or

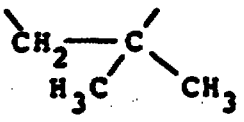


R^{18} and R^{19} are the same or different and are hydrogen or (lower)alkyl;

R^{20} and R^{21} are each hydrogen or, taken together, represent



or



or R^{12} and R^{13}, taken together with the carbon atom to which they are attached, may form a saturated ring of from 5 to 7 atoms, inclusive, optionally containing at least one heteroatom selected from oxygen, sulfur and nitrogen;

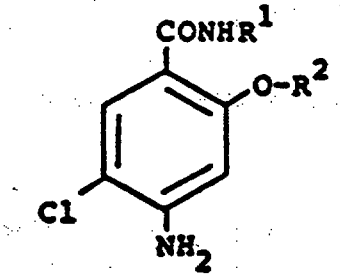
or R^{12} and R^{14}, taken together with the carbon atoms to which they are attached, may form a saturated or unsaturated ring of from 5 to 7 atoms, inclusive, optionally containing at least one heteroatom selected from oxygen, sulfur and nitrogen;

or R^{14} and R^{15}, taken together with the carbon and oxygen atoms to which they are attached, may form a 3 to 7 membered saturated oxygen-containing ring.

As used herein and in the claims, the term "(lower)-alkyl" means a straight or branched alkyl chain containing from 1 to 6 carbon atoms. Similarly, the terms "(lower)-alkenyl" and "(lower)alkynyl" refer to alkenyl or alkynyl chains containing from 2 to 6 carbon atoms. All temperatures given herein are in degrees Centigrade.

Also included in the invention are salts, hydrates or solvates of such compounds which may be pharmaceutically accepted acid addition salts, hydrates and/or solvates thereof.

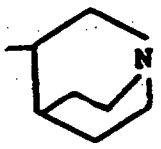
Preferred are compounds of the formula



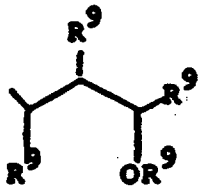
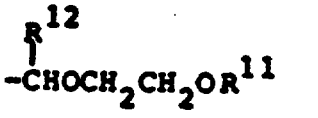
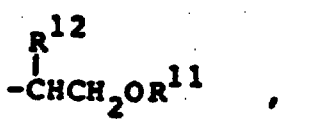
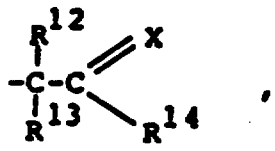
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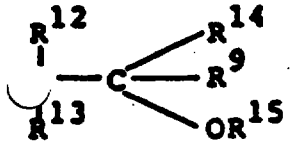
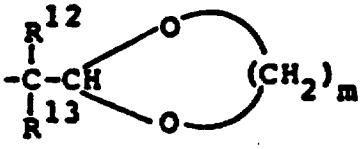
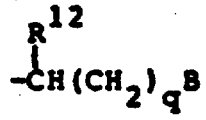
or their non-toxic pharmaceutically acceptable salts, hydrates, solvates or quaternary ammonium salts thereof wherein

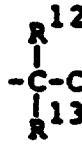
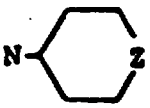
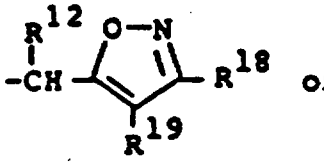
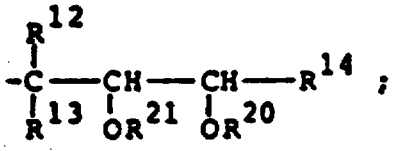
R^1 is



R^2 is alkenyl, alkynyl,

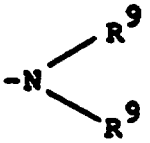
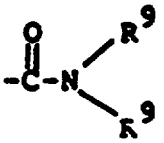
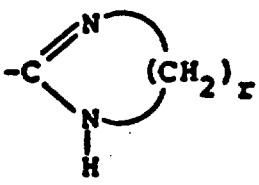

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or

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wherein
X is oxygen, sulfur or $=NOR^{16}$;

Z is $-(CH_2)_p-$, O, N or ;

B is $-NHCR^9$, , , , ,

pyridyl or oxazolidinyl;

m is 2 or 3;

p is 0, 1 or 2;

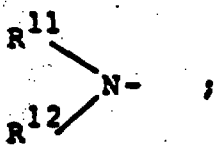
q is an integer of from 0 to 4;

r is 2 or 3;

R^9 is hydrogen or (lower)alkyl;

R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are the same or different, and are hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkoxy(lower)alkyl or cycloalkyl containing from 5 to 7 carbon atoms, inclusive, provided that, when R^{11}, R^{15} or R^{16} is (lower)alkenyl or (lower)alkynyl, the unsaturated carbon atom may not be directly attached to an oxygen or nitrogen atom;

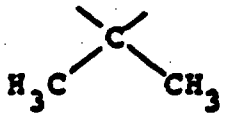
R^{14} is hydrogen, halogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cycloalkyl containing from 5 to 7 carbon atoms, inclusive, (lower)alkoxy, hydroxy, (lower)alkenyloxy, hydrazino, (lower)alkoxycarbonyl(lower)alkenyl, acetylhydrazino, thienyl, phenyl or



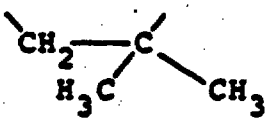
;

R^{18} and R^{19} are the same or different and are hydrogen or (lower)alkyl;

R^{20} and R^{21} are each hydrogen or, taken together, represent



or

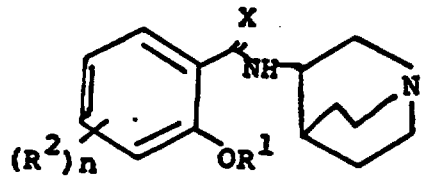


or R^{12} and R^{14}, taken together with the carbon atoms to which they are attached, may form a saturated or unsaturated ring of from 5 to 7 atoms, inclusive, optionally containing at least one heteroatom selected from oxygen, sulfur and nitrogen;

or R^{14} and R^{15}, taken together with the carbon and oxygen atoms to which they are attached, may form a 3 to 7 membered saturated oxygen-containing ring.

The group R^2 includes alkenyl and alkynyl and preferred compounds of this subclass comprise N-(1-azabicyclo [2.2.2]-oct-3-yl) benzamides wherein R^2 is allyl and propargyl.

Concerning these compounds of formula XXI wherein R^1 is a (1-azabicyclo [2.2.2]-oct-3-yl) moiety, attention is called to European Patent Application 158,532 of Munson and Boswell which was published October 16, 1985. This application discloses 2-alkoxy-N-(1-azabicyclo[2.2.2]-oct-3-yl)benzamides and thiobenzamides having the formula

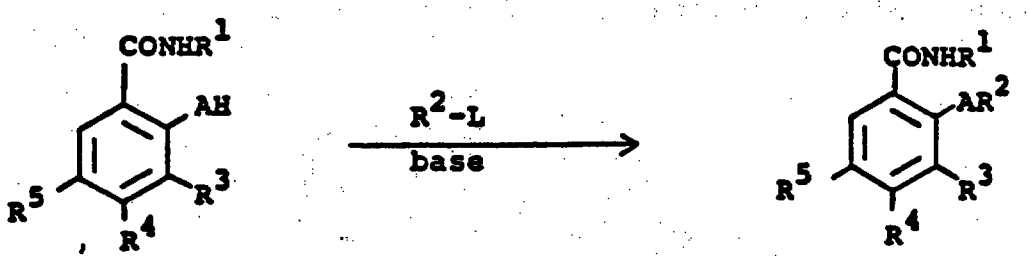


in which X is oxygen or sulfur; R^1 is lower alkyl; R^2 is hydrogen, halogen, 4,5-benzo, alkoxy or Am wherein Am is amino, methylamino or dimethylamino, and n is 1 or 2. These compounds may be distinguished from the compounds of this invention of formula XXI as substructure A-R^2 of XXI (which compares to substructure OR^1 of the European application) has a variety of definitions but never includes lower alkoxy, the only definition given for the prior art compounds.

Also included within the scope of this invention are all possible optical and geometric isomers of the compounds of Formula XXI, and tautomeric forms thereof, where applicable. In another aspect, this invention relates to processes for the preparation of the compounds of Formula XXI and to antiemetic and/or gastrokinetic compositions containing at least one compound of Formula XXI as an active ingredient.

The compounds of Formula XXI may be prepared via several procedures, e.g. by methods described in the chemical literature. In the preferred process, shown in Reaction Scheme 1, below, a compound of Formula II is reacted with a compound of Formula R^2-L (where L is a conventional leaving group) in the presence of a base as an acid scavenger, to produce the compound of Formula XXI.

Reaction Scheme 1



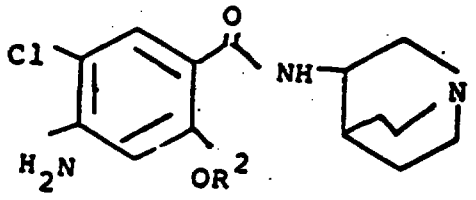
II XXI

Suitable leaving groups L are well-known to those skilled in the art and include, for example, chloro, bromo, iodo, methanesulfonyl, toluenesulfonyl and the like. The base may be a mild one such as K_2CO_3, Na_2CO_3, $MgSO_4$ or a quaternary ammonium hydroxide such as tetrabutylammonium hydroxide or benzyltriethylammonium hydroxide, or a mixture thereof. The reaction is conducted in an inert organic solvent such as acetone, acetonitrile, methylene chloride, dimethylformamide, dimethylacetamide, methanol, ethanol, isopropanol, diglyme, or the like. It is also possible to utilize sodium hydride or potassium hydride as the base, in an anhydrous, non-protonic organic solvent, or to use a strong base such as NaOH or KOH as a highly concentrated solution in a phase transfer solvent system such as CH_2Cl_2/H_2O, with the addition of a quaternary ammonium halide, sulfate or hydroxide as a phase transfer catalyst, e.g. tetrabutylammonium chloride, cetyltrimethylammonium bromide, benzyltriethylammonium chloride, or the like.

It will be apparent to those skilled in the art that Reaction Scheme 1 also may be varied to the extent that substituent groups R^3, R^4 and/or R^5 may be inserted into the compound of Formula XXI (or converted from a precursor group) as the final step, rather than being present in the compound of Formula II. Thus, for example, Compound I, where R^5 is hydrogen, may be chlorinated to produce Compound I in which R^5 is chloro. Similarly, R^4 of Compound I may be, for example, $-NO_2$, -NHCOR or $-N=CHN(R)_2$ where R may be (lower)alkyl. The $-NO_2$ group may then be reduced to an amino group, or the -NHCOR or $-N=CHN(R)_2$ groups may be hydrolyzed to an amino group.

We prefer to use an organic solvent-soluble tetrasubstituted ammonium salt as illustrated below for one of the preferred compounds of Formula XXI.

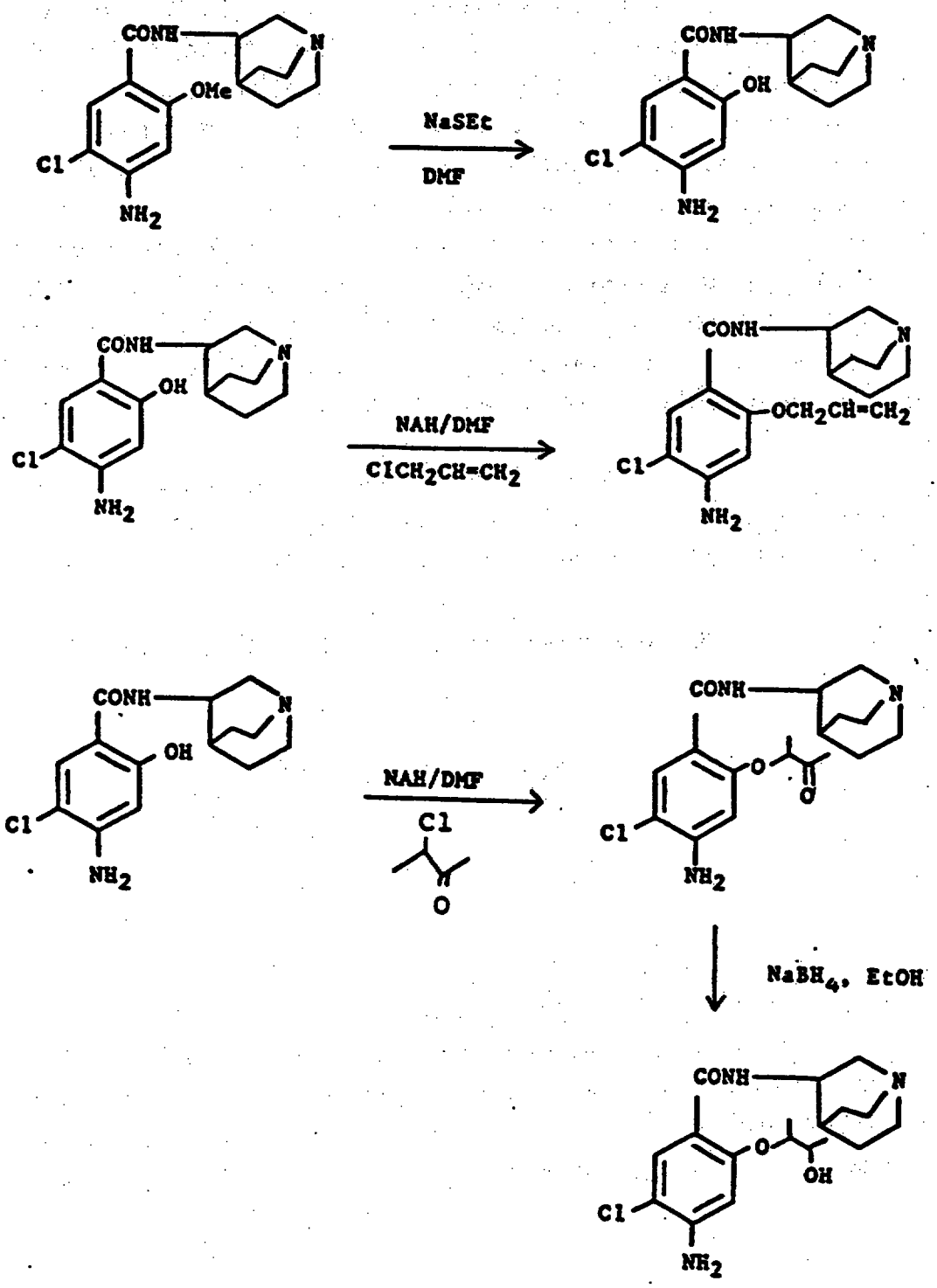
The preferred compounds of Formula XXI having structure

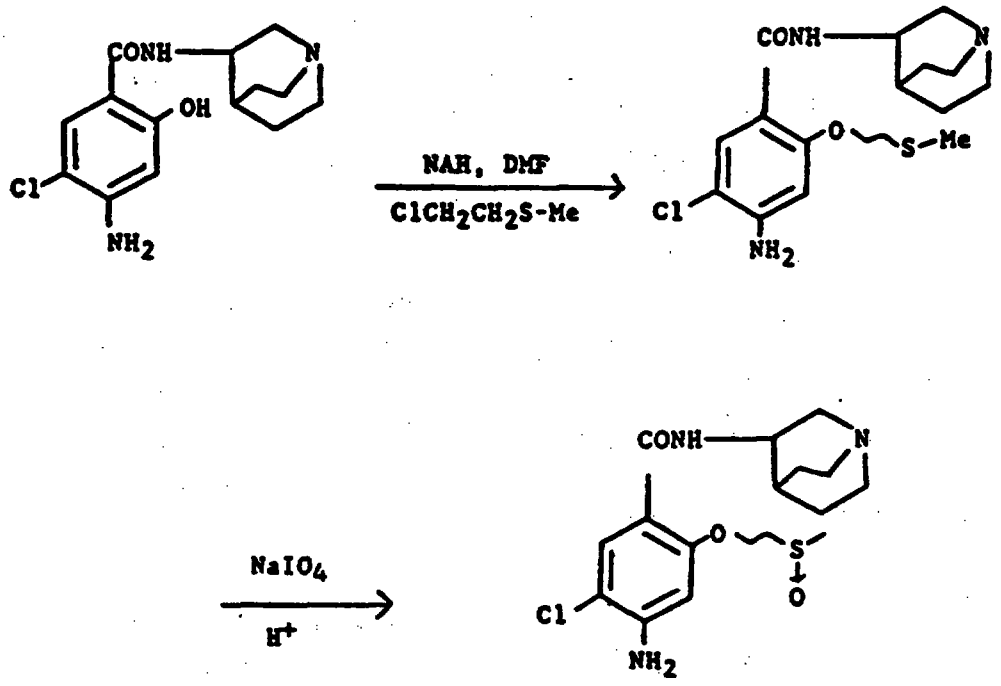


II'

wherein R^2 is as defined previously

may also be prepared by methods such as those outlined below. Additional synthesis processes as well as modifications of the synthetic methods described hereinbelow would be obvious to one skilled in the pertinent art.


CONH
N
OMe
Cl
NH2
NaSEt
DMF
OH
OCH2CH=CH2
NAH/DMF
ClCH2CH=CH2
O
NaBH4, EtOH



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 <u>in vitro</u>, 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 Formula XXI of the present invention are effective antiemetic agents but are not dopaminergic antagonists, as shown by both <u>in vitro</u> tests (spiperone binding) and <u>in vivo</u> tests (apomorphine emesis in the dog). Thus, the compounds of Formula XXI 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. Some of the compounds of Formula I have been shown to have activity similar to metoclopramide in the field-stimulated guinea pig ileum test (Table 2), which is one standard screening test for gastrokinetic activity. Again, because they are not dopaminergic antagonists, the compounds of Formula I do not have the above-mentioned side-effect liabilities of the commercially available substituted benzamides such as metoclopramide or clebopride.

The compounds of Formula XXI 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 Formula XXI 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 Formula XXI 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 bed-time.

For the prevention of nausea and vomiting associated with emetogenic cancer chemotherapeutic agents, the compounds of Formula XXI 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, tabletting 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 Formula XXI 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 XXI 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 Formula XXI, 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 Formula XXI, 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 Formula I, or a salt, hydrate or solvate thereof, and a pharmaceutically acceptable carrier.

This invention also relates to an effective antiemetic amount of at least one compound of Formula XXI, or a salt, hydrate or solvate thereof, in a pharmaceutically acceptable carrier for use through its administration to a warm-blooded mammal in alleviating nausea and vomiting in said mammal.

This invention also relates to an effective gastric motility facilitating amount of at least one compound of Formula XXI, or a salt, hydrate or solvate thereof, in a pharmaceutically acceptable carrier for use through its administration to a warm-blooded mammal in treating disorders related to impaired gastric motility in said mammal.

The invention also relates to an effective antiemetic amount of at least one compound of formula XXI 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 the instant series 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 present compounds 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.

Preferred compounds of formula XXI are those with R^2 being alkenyl or alkynyl. More preferred compounds of the present invention are those wherein R^3 is hydrogen, R^4 is amino, and R^5 is chloro.

PREPARATION 1

A. 4-Amino-N-(1-azabicyclo[2.2.2.]oct-3-yl)-5-chloro-2-hydroxybenzamide.

A suspension of sodium hydride (0.25 g of a 60% oil emulsion, washed with pentane) in DMF (10 mL) was cooled to 0°C and a solution of ethanethiol (0.376 g) in DMF (10 mL) was slowly added. After the evolution of hydrogen had subsided, 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide[1] (1.3 g) was added and the solution was heated to 95°C for 1 hour. The reaction mixture was concentrated in vacuo and the residue dissolved in water (25 mL). This aqueous solution was washed with methylene chloride, and then saturated with carbon dioxide. The product was isolated by filtration to yield 1.21 g (98%), m.p. 311-314°C.

Lit. ref. 1. European Patent Application 99,789, Delalande S. A., Feb. 1, 1984.

B. 4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-hydroxybenzamide hydrochloride dihydrate.

To an aqueous solution of the free base of the title compound, obtained above was added an equimolar amount of 37% (conc.) hydrochloric acid. The solution was concentrated in vacuo and chromatographed on silica gel eluting with methylene chloride, methanol and ammonium hydroxide in the ratio of 70:30:0.5 to afford the hydrochloride, dihydrate, m.p.>170°C decomp.

Anal. Calcd for $C_{14}H_{18}ClN_3O_2 \cdot 0.75HCl \cdot 2H_2O$:
C,46.82; H, 6.38; N,11.70; Cl, 17.28..
Found: C,46.58; H,6.03; N,11.96; Cl,16.37.

The following Examples illustrate the invention.

EXAMPLE 1

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-(2-propanon-1-yl)oxybenzamide

When the starting benzamide intermediate from Preparation 1 is first reacted with one equivalent of sodium hydride in DMF and then to this is added on equivalent of chloroacetone and the mixture stirred for 5h followed by heating to 50°C for 30 min and workup, the title compound is isolated.

EXAMPLE 2

4-Amino-N-(1-azabicyclo[2.2.2.]oct-3-yl)-2-(butan-2-on-3-yl)oxy-5-chlorobenzamide

To a stirred solution of 4-amino-N-(1-azabicyclo[2.2.2] oct-3-yl)-5-chloro-2-hydroxybenzamide (400 mg) in 8 mL DMF was added anhydrous potassium carbonate (700 mg), sodium iodide (10 mg) and 3-chloro-2-butanone (235 mg). The mixture was heated at 45-46°C for 2 hours. The solvent was removed in vacuo and the product was dissolved in dichloromethane and chromatographed on silica gel eluting with dichloromethane, methanol, ammonium hydroxide in the ratio of 94:6:1. Appropriate fractions were combined and concentrated in vacuo to give 327 mg of the title compound as a light beige solid, m.p.> 200°C.

In another preparation, the product was isolated as a 1.25 malate monohydrate by crystallization from methanol-acetone-acetonitrile, to give a white solid, m.p. 183-4°C.

Anal. Calcd for $C_{18}H_{24}ClN_2O_3 \cdot 1.25C_4H_4O_4 \cdot H_2O$: C,52.22, H.5.90, N,7.94, Cl,6.70.

Found: C,52.06; H,5.54; N,7.76; Cl,6.63

EXAMPLE 3

2-Allyloxy-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-benzamide

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-hydroxybenzamide (444 mg) was added to a suspension of sodium hydride (66 mg of a 60% oil emulsion, washed with pentane) in DMF (10 mL). When the evolution of hydrogen ceased, the solution was treated with allyl bromide (195 mg) for 1 hour. The solution was diluted with ethyl acetate and the volume of solvent mixture consisting of acetonitrile, methanol and ammonium hydroxide in the ratio of 100:15:0.5, and flash chromatagraphed over silica gel eluting with the same solvent system. The appropriate fractions were combined and concentrated. The solid obtained was collected by filtration and dried under vacuum to yield 0.230 g (46%) of the title compound, m.p. 220°C.

Anal. Calcd for $C_{17}H_{22}ClN_3O_2$: C,60.80; H,6.60; N,12,57; Cl,10.56.
Found: C,60.67; H,6.65; N,12,86; Cl,10.09.

EXAMPLE 4

4-Amino-N-(1-azabicyclo [2.2.2]oct-3-yl)-5-chloro-2-propargyl-oxybenzamide

A mixture of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-hydroxybenzamide (590 mg), potassium carbonate (2.8g), propargyl bromide (9.3 g of an 80% solution of propargyl bromide in toluene) in DMF (10 mL) was stirred at room temperature for 1 hour. The solid was filtered off,

and the filtrate diluted with ether. The resulting precipitate was collected and washed with ether. This solid was dissolved in a small amount of a mixture of acetonitrile, methanol and ammonium hydroxide in the ratio of 100:15:0.5, and flash chromatographed over silica gel eluting with the same solvent system. The appropriate fractions were combined and concentrated. The resulting solid was dried under vacuum to yield the title compound (0.115 g; 17%), m.p.>170°C decomp.

Anal. Calcd for $C_{17}H_{20}Cl_3O_2.H_2O$: C,58.17; H,6.27; N,11.97; Cl, 10.10; H_2O,5.13.
Found: C,57.81; H,6.16; N,11.75;Cl,9.77; H_2O,4.67.

EXAMPLE 5

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-(2-hydroxyethoxy)benzamide

The general procedure of Example 1 is repeated except that chloroacetone utilized therein is replaced by 2-chloro ethanol to give the title compound.

EXAMPLE 6

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-(cyclohexanon-2-yl)oxybenzamide

The general procedure of Example 1 is repeated except that chloroacetone utilized therein is replaced by 2-chloro-cyclohexanone to give the title compound.

EXAMPLE 7

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-[2-(methylsulfinyl)ethoxy]benzamide.

A. 4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-[2-hydroxybenzamide (590 mg) was added to a stirred suspension of sodium hydride (88 mg of a 60% oil emulsion, washed with pentane). After the evolution of hydrogen ceased, 2-chloroethyl methyl sulfide (221 mg) and potassium iodide (133 mg) was added and the reaction mixture was heated to 70°C for 2.5 hours. The solvent was then evaporated and the residue chromatographed on deactivated silica gel eluting with acetonitrile, methanol, ammonium hydroxide in the ratio of 100:10:0.5. Chromatography yielded 210 mg (28%) of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-[2-(methylthio)ethoxy]benzamide.

B. The product described in A (576 mg,) was dissolved in aqueous methanol (26 mL) and treated with hydrochloric acid (3.6 mL of a 2N solution) and then sodium metaperiodate (331 mg) for 2 hours. The mixture was then concentrated at 5 mm pressure and ambient temperature, and the residue basified (cold, 4N sodium hydroxide), extracted (CH_2Cl_2), dried, and concentrated. The resulting residue was chromatographed on deactivated silica gel eluting with acetonitrile, methanol, and ammonium hydroxide in the ratio of 100:10:0.5 to yield the title compound as a foam (282 mg, 47%).

Anal. Calcd for $C_{17}H_{24}ClN_2O_3S$: C,52.91; H,6.27; N,10.89; Cl,9.19; S,8.31

Found: (corrected for 2.27% of H_2O): C,51.18; H,6.32; N,10.70; Cl,9.54; S,7.90.

EXAMPLE 8

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-(2-hydroxypropan-1-yl)oxybenzamide

The product from Example 1 is treated with sodum borohydride in absolute ethanol at reflux to give the title compound.

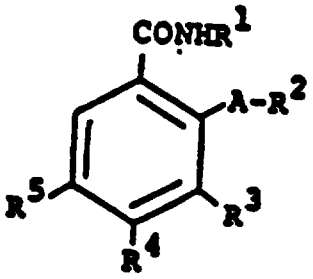
EXAMPLE 9

4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-(2-hydroxy-but-3-yl)oxybenzamide (mixture of threo and erythro isomers)

The product from Example 2 is treated with sodium borohydride in absolute ethanol at reflux to give the title product.

CLAIMS

1. A compound or a salt, hydrate or solvate thereof, said compound having the formula



XXI

wherein

R^3 is hydrogen or, when R^4 and R^5 are each hydrogen, R^3 may be (lower)alkoxy;

R^4 is hydrogen, amino or (lower)alkoxy;

R^5 is hydrogen, chloro, bromo, fluoro, trifluoromethyl, (lower)alkylthio, (lower)alkanesulfinyl, (lower)alkanesulfonyl, sulfamyl or $R^6\text{-}\overset{O}{\overset{\|}{C}}\text{-}$, or R^4 and R^5, taken together, may be -HN-N=N- ;

R^6 is (lower)alkyl, (lower)alkenyl or (lower)alkynyl;

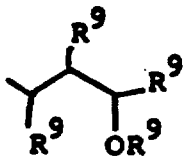
R^1 is



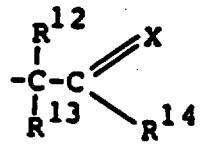
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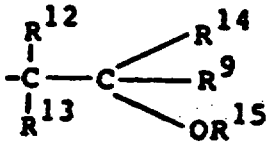
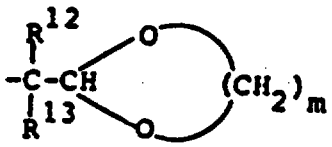
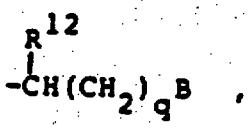
A is oxygen or $-S(O)_p-$;

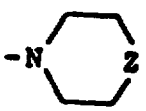
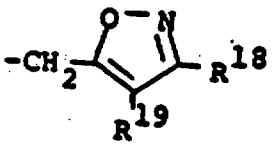
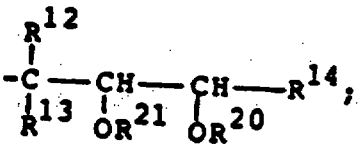
R^2 is alkenyl, alkynyl,


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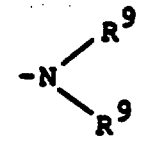
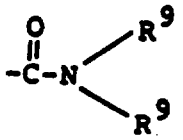
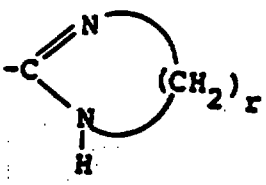

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,

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or

,

wherein

X is oxygen, sulfur or $=NOR^{16}$;

Z is $-(CH_2)_p-$, O, N or $-S(O)_p-$;

B is $-NHCR^9$, $-S(O)_p-R^9$, 
, 
, 
,

pyridyl or oxazolidinyl;

m is 2 or 3;

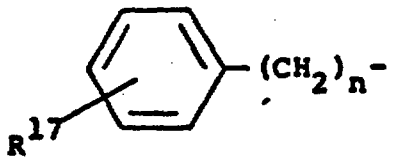
p is 0, 1 or 2;

q is an integer of from 0 to 4, inclusive;

r is 2 or 3;

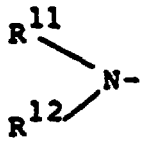
R^9 is hydrogen or (lower)alkyl;

R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are the same or different, and are hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkoxy(lower)alkyl, cycloalkyl containing from 5 to 7 carbon atoms, inclusive, or

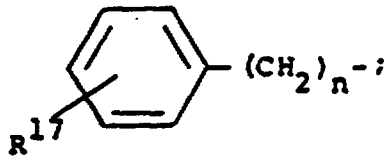


where n is an integer of from 1 to 4 inclusive and R^{17} is hydrogen, halogen, hydroxy, (lower) alkyl or (lower) alkoxy; provided that, when R^{11}, R^{15} or R^{16} is (lower) alkenyl or (lower) alkynyl, the unsaturated carbon atom may not be directly attached to an oxygen or nitrogen atom;

R^{14} is hydrogen, halogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cycloalkyl containing from 5 to 7 carbon atoms, inclusive, hydroxy, (lower)alkoxy, (lower)alkenyloxy, (lower)alkoxycarbonyl(lower)alkenyl, hydrazino, acetylhydrazino, thienyl, phenyl,

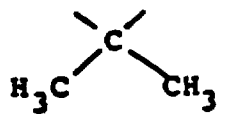


or

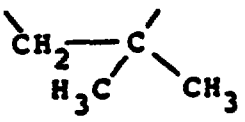


R^{18} and R^{19} are the same or different and are hydrogen or (lower)alkyl;

R^{20} and R^{21} are each hydrogen or, taken together, represent



or

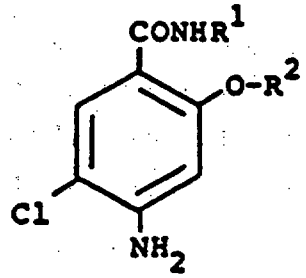


or R^{12} and R^{13}, taken together with the carbon atom to which they are attached, may form a saturated ring of from 5 to 7 atoms, inclusive, optionally containing at least one heteroatom selected from oxygen, sulfur and nitrogen;

or R^{12} and R^{14}, taken together with the carbon atoms to which they are attached, may form a saturated or unsaturated ring of from 5 to 7 atoms, inclusive, optionally containing at least one heteroatom selected from oxygen, sulfur and nitrogen;

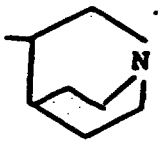
or R^{14} and R^{15}, taken together with the carbon and oxygen atoms to which they are attached, may form a 3 to 7 membered saturated oxygen-containing ring.

2. A compound, or a non-toxic pharmaceutically acceptable salt, hydrate, solvate or quaternary ammonium salt thereof wherein said compound has the formula

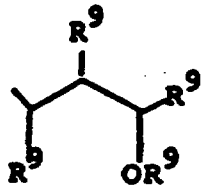
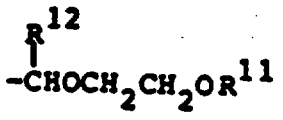
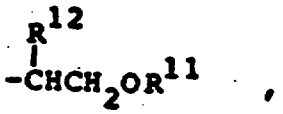
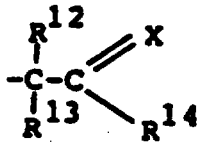


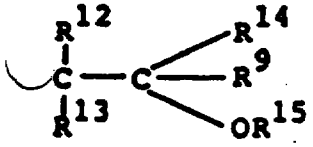
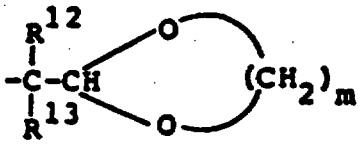
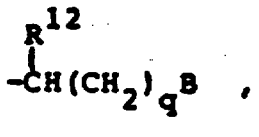
XXI

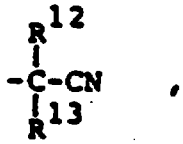
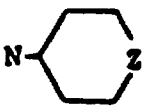
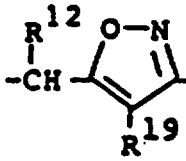
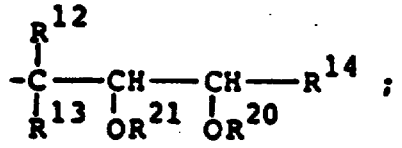
wherein
R^1 is



R^2 is alkenyl, alkynyl,


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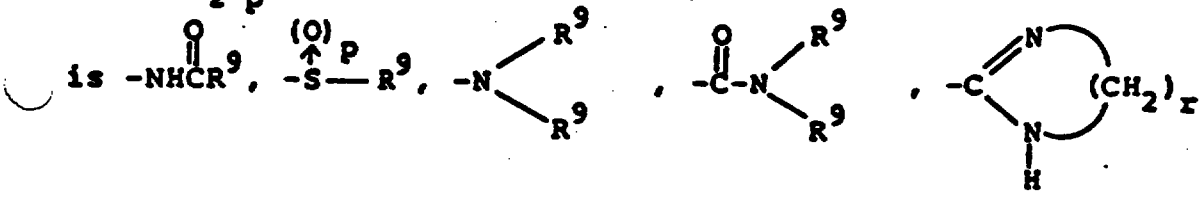

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or

;

wherein

X is oxygen, sulfur or $=NOR^{16}$;

Z is $-(CH_2)_p-$, O, N or ;



pyridyl or oxazolidinyl;

m is 2 or 3;

p is 0, 1 or 2;

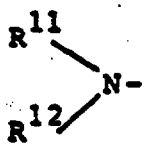
q is an integer of from 0 to 4;

r is 2 or 3;

R^9 is hydrogen or (lower)alkyl;

R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are the same or different, and are hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkoxy(lower)alkyl or cycloalkyl containing from 5 to 7 carbon atoms, inclusive, provided that, when R^{11}, R^{15} or R^{16} is (lower)alkenyl or (lower)alkynyl, the unsaturated carbon atom may not be directly attached to an oxygen or nitrogen atom;

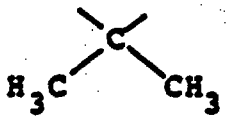
R^{14} is hydrogen, halogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cycloalkyl containing from 5 to 7 carbon atoms, inclusive, (lower)alkoxy, hydroxy, (lower)alkenyloxy, hydrazino, (lower)alkoxycarbonyl(lower)alkenyl, acetylhydrazino, thienyl, phenyl or



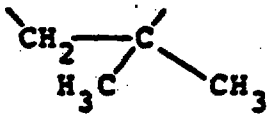
;

R^{18} and R^{19} are the same or different and are hydrogen or (lower)alkyl;

R^{20} and R^{21} are each hydrogen or, taken together, represent



or



or R^{12} and R^{14}, taken together with the carbon atoms to which they are attached, may form a saturated or unsaturated ring of from 5 to 7 atoms, inclusive, optionally containing at least one heteroatom selected from oxygen, sulfur and nitrogen;

or R^{14} and R^{15}, taken together with the carbon and oxygen atoms to which they are attached, may form a 3 to 7 membered saturated oxygen-containing ring.

* C L M S *

3. 4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-2-(butan-2-on-3-yl)oxy-5-chlorobenzamide.

4. 2-Allyloxy-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chlorobenzamide.

5. 4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-propargyloxy-benzamide.

6. 4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-[2-(methyl-sulfinyl)ethoxy]benzamide.

7. A non-toxic pharmaceutically acceptable salt, hydrate, solvate or quaternary ammonium salt of the compound claimed in any one of claims 3 to 6.

8. A compound, salt, hydrate, solvate or quaternary ammonium compound according to claim 2 wherein R^2 is alkenyl or alkynyl.

9. A compound, salt, hydrate, solvate or quaternary ammonium compound according to claim 2 wherein R^2 is butan-2-on-3-yl.

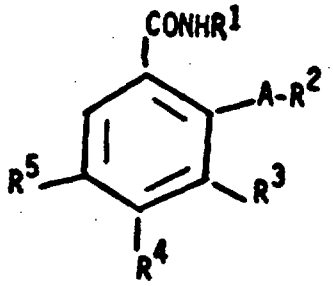
10. A pharmaceutical composition for the alleviation of nausea and vomiting, which comprises an effective antiemetic amount of at least one compound, salt, hydrate or solvate thereof according to any one of claims 1 to 9, plus a pharmaceutically acceptable carrier.

11. 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 9, and a pharmaceutically acceptable carrier.

12. An antiemetic amount of at least one compound, salt, hydrate or solvate thereof according to any one of claims 1 to 9, in a pharmaceutically acceptable carrier for use through its systemic administration to a warm-blooded mammal in alleviating nausea and vomiting in said mammal.

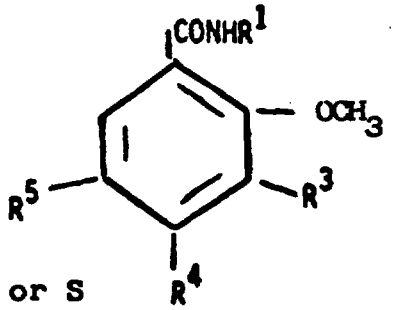
13. A gastric motility facilitating amount of at least one compound salt, hydrate or solvate thereof according to any one of claims 1 to 9, in a pharmaceutically acceptable carrier for use through its administration to a warm-blooded mammal in treating disorders related to impaired gastric motility in said mammal.

14. A process for preparing a compound of claim 1 of the formula



XXI

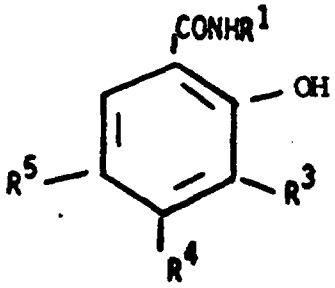
wherein R^1, R^2, R^3, R^4, R^5 and A are as defined in claim 1, which comprises hydrolysing a compound of the formula XXII



XXII

wherein X is O or S

to give a compound of the formula XXIII



XXIII

and then reacting a compound of the formula XXIII with R^2-L in the presence of a base, wherein L is a leaving group to give the compound of formula XXI.

15. A process for preparing a compound or a salt, hydrate or solvate thereof as defined in claim 1 substantially as hereinbefore described with reference to the Examples.

16. A compound of the formula XXI as defined in claim 1 prepared by a process as claimed in either of claims 14 and 15.

17. A pharmaceutical composition comprising a compound, or a salt, hydrate or solvate thereof as claimed in any of claims 1 to 11, or claim 16, and a pharmaceutically acceptable carrier.