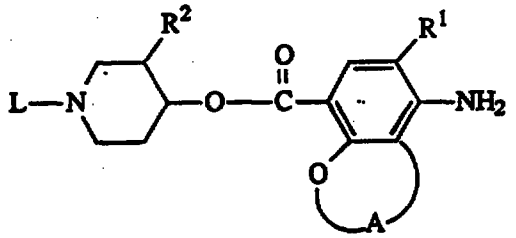
N-SUBSTITUTED PIPERIDINYL BICYCLIC BENZOATE DERIVATIVES

The present invention is concerned with novel benzoate derivatives, pharmaceutical compositions comprising said novel compounds, processes for preparing compounds and compositions, and the use thereof as a medicine, in particular in the treatment of conditions involving a decreased motility of the colon.

In our EP-0,389,037-A, published on September 26, 1990, *N*-(3-hydroxy-4-piperidinyl) (dihydrobenzofuran or dihydro-2*H*-benzopyran)carboxamide derivatives are disclosed as having gastrointestinal motility stimulating properties. In our EP-0,445,862-A, published on September 11, 1991, *N*-(4-piperidinyl) (dihydrobenzofuran or dihydro-2*H*-benzopyran)carboxamide derivatives are disclosed also having gastrointestinal motility stimulating properties. WO 93/03725 (SmithKline Beecham), published on March 4, 1993, generically discloses the use as $5HT_4$ receptor antagonists of esters of general formula X-CO-Y-Z, wherein X can be a substituted phenyl, Y can be oxygen, and Z can be a substituted piperidine moiety. WO 94/08995 (SmithKline Beecham), published on April 28, 1994 generically discloses, for instance, substituted 7-benzofuran carboxylates also having $5HT_4$ antagonistic activity. The latter two patent applications describe the use of the $5HT_4$ antagonistic compounds in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS.

Unexpectedly, we have discovered that the present novel compounds show intestinal prokinetic activity. Hence, the presently disclosed compounds show utility in treatment of conditions involving a decreased motility of the intestine, especially the colon.

The present invention is concerned with novel benzoate derivatives having the formula



(I),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein :

R^1 is halo or C_{1-6}alkylsulfonylamino;

A represents a bivalent radical of formula :

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$-CH_2-CH_2-$ (a),

$-CH_2-CH_2-CH_2-$ (b),

$-CH=CH-$ (c),

in the radicals (a), (b) and (c) one or two hydrogen atoms may be replaced by a C_{1-6}alkyl;

R^2 is hydrogen or C_{1-6}alkyloxy;

L is a radical of formula :

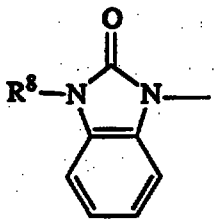
$-Alk-R^4$ (d),

$-Alk-O-R^5$ (e),

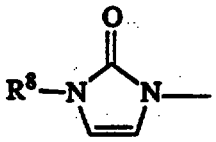
$-Alk-NR^6R^7$ (f);

Alk is C_{1-12}alkanediyl;

R^4 is hydrogen; cyano; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{3-7}cycloalkyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; tetrahydrofuran; dioxolane; dioxolane substituted with C_{1-6}alkyl; dioxane; dioxane substituted with C_{1-6}alkyl; pyridine; pyridine substituted with halo or C_{1-6}alkyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; or a radical of formula :


(g)

or


(h)

wherein R^8 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen; C_{1-6}alkyl; hydroxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; phenyl or phenyl substituted with up to three substituents selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy;

R^6 is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; pyrazine; pyrazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy.

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methylbutyl, pentyl, hexyl and the like; C_{3-7}cycloalkyl is generic to cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{1-12}alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 12 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl, 1,11-undecanediyl, 1,12-dodecanediyl and the branched isomers thereof.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methane-sulfonic, ethanesulfonic, benzenesulfonic, *p* toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids. The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like. Conversely the salt form can be converted by treatment with alkali into the free base form.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For instance, compounds of formula (I) wherein R^4 is 3- or 6-hydroxypyridazine, or a radical of formula (g) or (h) wherein R^8 is hydrogen may exist in their corresponding tautomeric form.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the

so-called *N*-oxide, particularly those *N*-oxides wherein the piperidine-nitrogen is *N*-oxidized.

R^1 is interestingly halo, preferably chloro;
R^2 is interestingly hydrogen or C_{1-4}alkyloxy, preferably hydrogen or methoxy,
A is interestingly a bivalent radical of formula (a) or (b),
when A is substituted, methyl substitution is preferred;
when A is a bivalent radical of formula (a) or (b), geminal dimethyl substitution is preferred, especially on the carbon atom adjacent to the oxygen atom;
when L is a radical of formula (d), R^4 is preferably hydrogen, cyano, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, C_{1-6}alkylsulfonyl, tetrahydrofuran, dioxolane substituted with C_{1-6}alkyl, pyridine, a radical of formula (g) wherein R^8 is C_{1-6}alkyl, pyridazine substituted with halo and hydroxy;
when L is a radical of formula (e), R^5 is preferably hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, or phenyl substituted with halo;
when L is a radical of formula (f), R^6 is preferably hydrogen and R^7 is preferably hydrogen, or pyridazine substituted with C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl.

Interesting compounds are those compounds of formula (I), wherein R^1 is chloro.

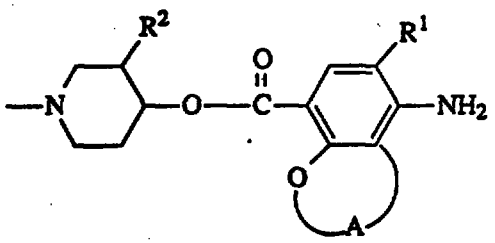
Further interesting compounds are those compounds of formula (I), wherein R^2 is hydrogen or methoxy.

More interesting compounds of formula (I) are those interesting compounds wherein A is a bivalent radical of formula (a) or (b).

Preferred compounds of formula (I) are :
1-[(tetrahydro-2-furanyl)methyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate;
1-[(tetrahydro-2-furanyl)methyl]-4-piperidinyl 5-amino-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-8-carboxylate;
1-(3-methoxypropyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate;
1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate;
1-[3-(1-methylethoxy)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate;
1-[2-(2-hydroxyethoxy)ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate;

1-[3-(3-chloro-6-oxo-1(6*H*)-pyridazinyl)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate;
1-(4-oxopentyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate;
ethyl 4-[[(4-amino-5-chloro-2,3-dihydro-7-benzofuranyl)carbonyl]oxy]-1-piperidinebutanoate; and
1-[2-(tetrahydro-2-furanyl)ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; the possible stereochemically isomeric forms thereof and the pharmaceutically acceptable acid addition salt thereof.

In order to simplify the structural representations of the compounds of formula (I) and certain starting materials and intermediates thereof, the radical



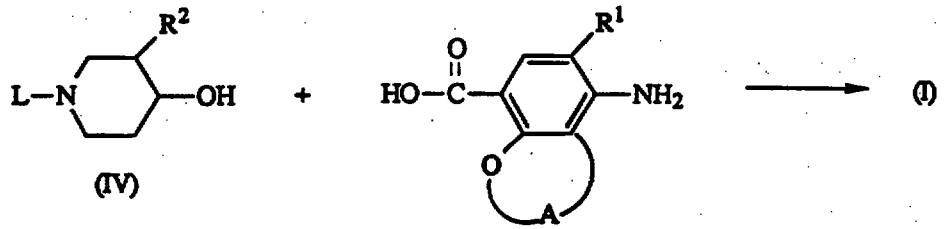
will hereafter be represented by the symbol D.

In the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, distillation, crystallization, trituration and chromatography.

The compounds of formula (I) may be prepared by *N*-alkylating a piperidine of formula (II) with an intermediate of formula (III), wherein W^1 is an appropriate leaving group such as, for example, halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methanesulfonyloxy, toluenesulfonyloxy and the like leaving groups. The *N*-alkylation reaction of (II) with (III) is conveniently conducted following art-known alkylation procedures.

$$\underset{\text{(III)}}{L\text{-}W^1} + \underset{\text{(II)}}{H\text{—}D} \xrightarrow{N\text{-alkylation}} \text{(I)}$$

The compounds of formula (I) may also be prepared by the ester formation of an alcohol of formula (IV) with a carboxylic acid of formula (V) or a functional derivative thereof, such as an acylhalide, a symmetrical or mixed anhydride or an ester, preferably an activated ester, following art-known procedures.

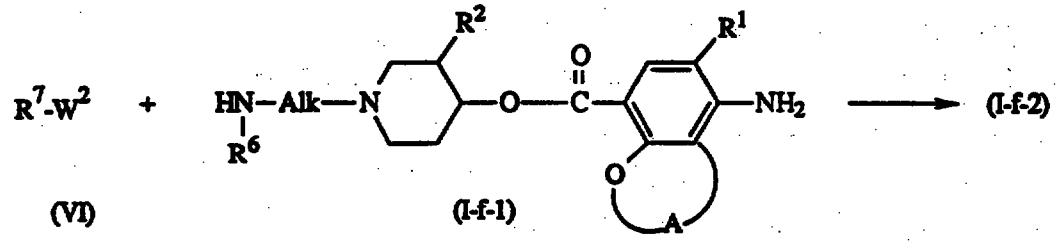


(IV) (V) (I)

It may be expedient to protect amino or hydroxy groups, i.e. other than the reacting hydroxy groups, during the course of the reaction to avoid undesired side reactions. Said amino or hydroxy protecting group is removed after completion of the ester formation. Suitable protecting groups comprise readily removable groups such as C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, phenylmethyl and the like protective groups.

The compounds of formula (I) may also be prepared by converting compounds of formula (I) into each other.

Compounds of formula (I), wherein L is a radical of formula (f), wherein R^7 is other than hydrogen, said compounds being represented by formula (I-f-2), may be prepared by reacting a compound of formula (I), wherein R^7 is hydrogen, said compounds being represented by formula (I-f-1) with a reagent of formula (VI), wherein W^2 is an appropriate leaving group such as, for example, halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methanesulfonyloxy, toluenesulfonyloxy and the like leaving groups, following art-known reaction procedures.



(VI) (I-f-1) (I-f-2)

Compounds of formula (I), wherein L is a radical of formula (d), Alk is 1,2-ethanediyl and R^4 is cyano may be prepared by reacting an intermediate of formula (II) with acrylonitrile, following art-known procedures.

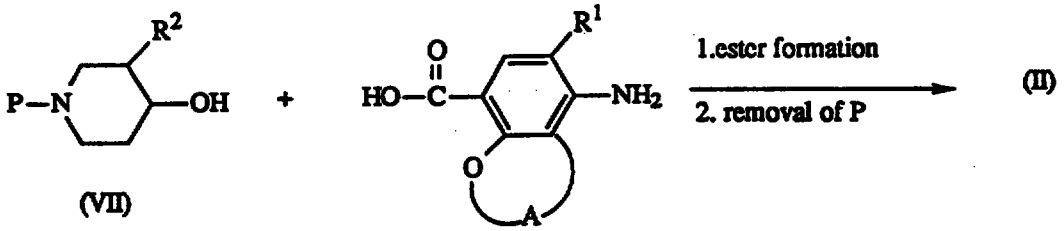
Compounds of formula (I), wherein L is a radical of formula (e), Alk is 1,2-ethanediyl and R^5 is hydrogen may be prepared by reacting an intermediate of formula (II) with oxirane following art-known reaction procedures.

The compounds of formula (I), wherein L is a radical of formula (f), wherein Alk is

1,3-propanediyl and wherein R^6 and R^7 is hydrogen may be prepared by hydrogenation of compounds of formula (I), wherein L is a radical of formula (d), Alk is 1,2-ethanediyl and R^4 is cyano.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. methylbenzene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

The intermediates of formula (II) may be derived from an appropriately substituted piperidine of formula (VII) with an intermediate acid of formula (V) or a functional derivative thereof, following art-known ester formation procedures, and subsequently removing the protective group P, following art-known procedures. P represents a readily removable protective group such as C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, phenylmethyl and the like protective groups.



The preparation of intermediate acids of formula (V) is disclosed in EP-0,389,037-A.

The intermediates of formula (VII'), wherein P^1 represents P as well as hydrogen, may be prepared by reduction of an intermediate of formula (VIII) following art-known methods.

The intermediates of formula (VII'), wherein R^2 is C_{1-6}alkyloxy, said intermediates being represented by formula (VII'-a), and wherein R^2 and the 4-hydroxyl group have a

cis-configuration may be prepared by reduction of an intermediate of formula (VIII-a) using a reductive agent such as substituted borohydrides, e.g. lithium tris-*sec*-butylborohydride, potassium tris-*sec*-butylborohydride, substituted aluminiumhydrides, lithium-tri-*tert*-butoxyaluminohydride and the like. Using stereochemically pure reagents said reduction may be performed in a stereospecific manner.



(VIII) (VII')

(VIII-a) : R^2 is C_{1-6}alkyloxy (VII'-a) : R^2 is C_{1-6}alkyloxy

The *cis* and *trans* diastereomeric racemates of the compounds of formula (I), or any of the other intermediates may also be resolved into their optical isomers, *cis*(+), *cis*(-), *trans*(+) and *trans*(-) by the application of art-known methodologies. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with enantiomerically pure acids or their enantiomerically pure derivatives.

The compounds of formula (I) and the intermediates of formula (II), the *N*-oxide forms, the pharmaceutically acceptable salts and stereoisomeric forms thereof possess favourable intestinal motility stimulating properties. In particular the present compounds show significant motility enhancing effects on the small and large intestine. The latter properties are evidenced by the results obtained in the "Guinea Pig Ileum Coaxial Stimulation" test and the "Colon motility in conscious dog" test. Both said tests are described hereinafter. Some of the compounds also show activity in the "Lidamidine test in dogs".

In view of their useful intestinal motility enhancing properties the subject compounds may be formulated into various forms for administration purposes.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual

pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) or (II) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In view of their capability to stimulate the motility of the intestinal system and in particular their capacity to enhance the motility of the colon, the subject compounds are useful to normalize or to improve the intestinal transit in subjects suffering from symptoms related to disturbed motility, e.g. a decreased peristalsis of the small and large intestine alone or in combination with delayed gastric emptying.

In view of the utility of the compounds of the present invention, there is provided a method of treating warm-blooded animals suffering from motility disorders of the

intestinal system such as, for example, constipation, pseudo-obstruction, intestinal atony, post-operative intestinal atony, irritable bowel syndrome (IBS), drug-induced delayed transit, and in particular impaired colonic transit. Said method comprises the systemic administration of an effective intestinal stimulating amount of a compound of formula (I), a *N*-oxide, a pharmaceutically acceptable acid addition salt or a possible stereoisomeric form thereof, to warm-blooded animals. Hence, the use of a compound of formula (I) as medicine is provided, and in particular the use of a compound of formula (I) for the manufacture of a medicine for treating conditions involving a decreased motility of the colon.

In general it is contemplated that a therapeutically effective amount would be from about 0.001 mg/kg to about 10 mg/kg body weight, preferably from about 0.02 mg/kg to about 5 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Hereinafter "THF" means tetrahydrofuran and "DIPE" means diisopropylether.

Experimental part

A. Preparation of the intermediates

Example 1

a) A solution of 3-methoxy-1-(phenylmethyl)-4-piperidinone (4.4 g) in THF was cooled to -75°C. Lithium tris-*sec*-butylborohydride was added dropwise action and the reaction mixture was stirred for 2 hours at -70°C. Acetic acid 10% (100 ml) was added dropwise at room temperature. The organic solvent was evaporated. The aqueous residue was alkalized with NH_4OH, then extracted twice with DIPE. The separated organic layer was washed with water, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by short column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 95/5 upgrading to 98/2), yielding 1.3 g (29.4%) of *cis*-3-methoxy-1-(phenylmethyl)-4-piperidinol (intermediate 1)

b) A mixture of intermediate (1) (11.5 g) and methanol (150 ml) was hydrogenated at normal pressure and at room temperature with 2 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column-chromatography over silica gel (eluent : $CHCl_3/(CH_3OH/NH_3)$ 85/15). The pure fractions were collected and the eluent was evaporated, yielding 3.6 g (53%) of *cis*-3-methoxy-4-piperidinol as an oily residue (intermediate 2).

c) A solution of bis(1,1'-dimethylethyl)dicarbonate (65.5 g) in $CHCl_3$ (100 ml) was added dropwise to a solution of intermediate (2) (34 g) in $CHCl_3$ (350 ml) and the reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was washed with water and ammonia, then with water. The separated organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue (79 g) was purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 97/3, upgrading to 95/5). The pure fractions were collected and the solvent was evaporated, yielding 58 g of (±)-1,1-dimethylethyl *cis*-4-hydroxy-3-methoxy-1-piperidinecarboxylate (96.4% crude residue) (intermediate 3).

d) Sodium hydride (6.2 g) was added to a solution of intermediate (3) (30 g) in THF (1000 ml). The mixture was stirred and refluxed under nitrogen flow for 3 hours, then cooled (solution I). 1,1'-carbonylbis-1*H*-imidazole (21 g) was added to a solution of 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylic acid (31.4 g) in acetonitrile (1000 ml) and this mixture was stirred for 2 hours at room temperature. The solvent was evaporated. The residue was dissolved in THF (1000 ml), giving solution II. At room temperature, solution (II) was poured out into solution (I) and the reaction mixture was stirred for 2 hours at room temperature. The solvent was evaporated. The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The separated organic layer was dried $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the solvent was evaporated, yielding 50 g of (±)-1,1-dimethylethyl *cis*-4-[[(4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofuranyl)-carbonyl]oxy]-3-methoxy-1-piperidinecarboxylate (85%) (intermediate 4).

e) A mixture of intermediate (4) (50 g) in THF (600 ml) and hydrochloric acid (60 ml) was stirred and refluxed for 30 minutes. The reaction mixture was cooled and alkalized with NH_4OH. The separated aqueous layer was extracted with THF. The extract layer was evaporated and the residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 93/7). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE. The mixture was cooled and the resulting precipitate was filtered off, dissolved in 2-propanol and converted into the ethanedioic acid salt (1:1) with ethanedioic acid (0.6 g). The mixture was boiled, cooled and the resulting precipitate was filtered off and dried, yielding 16 g of (±)-*cis*-3-methoxy-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofuran-carboxylate ethanedioate(1:1) (33%); mp. 193.2°C (intermediate 5).

In a similar manner were also prepared :

4-piperidinyl 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylate;

mp. 161.0°C (intermediate 6).
(±)-*cis*-3-methoxy-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylate; (intermediate 7)
4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; mp. 161.0°C (intermediate 8)

B. Preparation of the final compounds

Example 2

A mixture of 1-[3-(1-methylethoxy)propyl]-4-piperidinol (2.5 g) and *N,N*-dimethyl-4-pyridinamine (2 g) in dichloromethane (100 ml) was stirred at room temperature. 4-(acetylamino)-5-chloro-2,3-dihydro-7-benzofurancarbonyl chloride (2.7 g) was added and the reaction mixture was stirred for 72 hours at room temperature. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue (3.2 g) was dissolved in THF (100 ml) and treated with hydrochloric acid (10 ml). The reaction mixture was stirred and refluxed for 2 hours. The mixture was cooled and alkalized with NH_4OH. The organic solvent was evaporated and the aqueous residue was extracted twice with CH_2Cl_2. The separated organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by short column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 97/3). The desired fractions were collected and the solvent was evaporated. The residue (2.9 g) was purified by high-performance liquid chromatoraphy (eluent: $CH_2Cl_2/(CH_3OH/NH_3)/CH_3OH$ 97/1/2). The pure fractions were collected and the solvent was evaporated. The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:1) with HCl/2-propanol. The mixture was boiled, then cooled. The precipitate was filtered off and dried (vacuum; 80 °C), yielding 0.50 g of 1-[3-(1-methylethoxy)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate monohydrochloride (12%); mp. 208.6°C (compound 4).

Example 3

A mixture of intermediate (8) (3 g), 2-(3-chloropropyl)-2-methyl-1,3-dioxolane (2.5 g), sodium carbonate (2.1 g) and potassium iodide (catalytic quantity) in 4-methyl-2-pentanone (150 ml) was stirred and refluxed overnight. The mixture was cooled, washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2, upgrading to $CH_2Cl_2/(CH_3OH/NH_3)$ 97/3). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE, cooled, stirred,

filtered and recrystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding 1.00 g of 1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate (24%); mp. 128.1°C (compound 6).

Example 4

A mixture of intermediate (5) (10 g) and 2-propenenitrile (2 ml) in 2-propanol (150 ml) was stirred and refluxed overnight. More 2-propenenitrile (1 ml) was added and the reaction mixture was stirred and refluxed for 20 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/-(CH_3OH/NH_3) 97/3). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE, cooled, stirred and the resulting precipitate was filtered off and dried (vacuum; 80 °C), yielding 10.7 g of (±)-*cis*-1-(2-cyanoethyl)-3-methoxy-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylate (94%); mp. 180.3°C (compound 27).

Example 5

At room temperature, oxirane (gas) was allowed to bubble through a solution of intermediate (6) (3.3 g) in methanol (80 ml) for 3 hours keeping the temperature below 30 °C. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 93/7). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE, cooled to room temperature and the precipitate was filtered off and dried (vacuum; 80 °C), yielding 1.66 g of 1-(2-hydroxyethyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylate (45%); mp. 166.3°C (compound 21).

Example 6

A mixture of compound (6) (2 g) in THF (50 ml) and hydrochloric acid (5 ml) was stirred and refluxed for 30 minutes. The reaction mixture was cooled and alkalized with NH_4OH. The separated aqueous layer was extracted with THF. The combined organic layers were evaporated and the residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 97/3). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE. The precipitate was filtered off and dried and further purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 90/10). The pure fractions were collected and the solvent was evaporated, yielding 0.90 g of 1-(4-oxopentyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate (47%); mp. 104.8°C (compound 8).

Example 7

A mixture of compound (9) (8.5 g) in THF (500 ml) was hydrogenated with Raney nickel catalyst (catalytic quantity) as a catalyst. After uptake of H_2 (2 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE, then cooled and the resulting precipitate was filtered off and dried, yielding 5.2 g of (±)-*cis*-1-(2-aminoethyl)-3-methoxy-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate (61%); mp. 133.9°C (compound 11).

Example 8

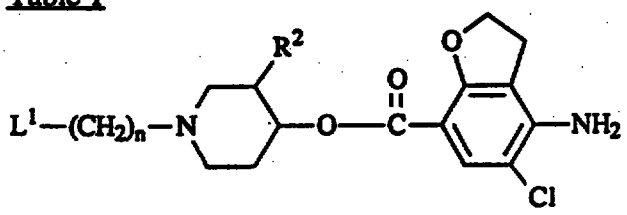
A mixture of compound (11) (4 g), 2-chloro-3-methylpyrazine (2.8 g) and *N,N*-diethylethanamine (2.8 ml) was stirred for 24 hours at 120 °C. The mixture was cooled and dissolved in CH_2Cl_2. The organic solution was purified twice by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5). The pure fractions were collected and the solvent was evaporated. The residue was stirred in boiling DIPE, cooled and the resulting precipitate was filtered off and dried, yielding 0.53 g of (±)-*cis*-3-methoxy-1-[2-[(3-methyl-2-pyrazinyl)amino]ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate (11.5%); mp. 124.1°C (compound 12).

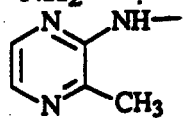
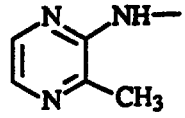
Example 9

A mixture of compound (38) (4.5 g), 2-chloro-3-methylpyrazine (3.3 g) and *N,N*-diethylethanamine (2.1 ml) was stirred for 20 hours at 120 °C. The reaction mixture was cooled and purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 95/5). The desired fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 90/10). The pure fractions were collected and the solvent was evaporated. The residue was solidified in DIPE. The precipitate was filtered off and dried, yielding 2.10 g of 1-[2-[(3-methyl-2-pyrazinyl)amino]ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate (38%); mp. 108.6°C (compound 39).

Tables 1 through 3 list compounds that were prepared in a similar way as in one of the hereinabove mentioned examples.

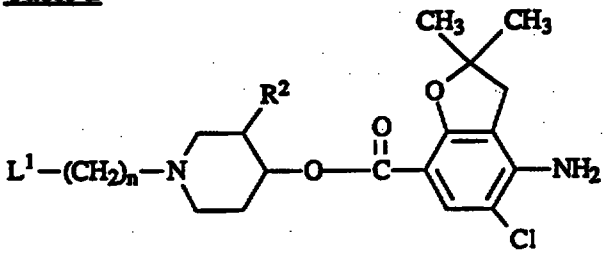
Table 1



Co. no.	Ex. no.	R^2	n	L^1	physical data
1	3	H	2	3-ethyl-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl	mp. 191.7°C
2	2	H	3	3-ethyl-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl	mp. 150.2°C
3	2	H	1	tetrahydro-2-furanyl	mp. 147.0°C / (±)
4	2	H	3	-O-CH(CH$_3$)2	mp. 208.6°C / HCl
5	2	H	3	3-(1-methylethyl)-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl	mp. 165.2°C
6	3	H	3	2-methyl-1,3-dioxolan-2-yl	mp. 128.1°C
7	3	H	3	3-chloro-6-oxo-1(6*H*)pyridazinyl	mp. 134.0°C
8	6	H	3	-C(=O)-CH$_3$	mp. 104.8°C
9	3	OCH$_3$	1	-CN	mp. 178.4°C / (±) *cis*
10	3	OCH$_3$	2	-H	mp. 138.2°C / (±) *cis*
11	7	OCH$_3$	2	-NH$_2$	mp. 133.9°C / (±) *cis*
12	8	OCH$_3$	2		mp. 124.1°C / (±) *cis*
13	3	OCH$_3$	1	2-pyridinyl	mp. 153.3°C / (±) *cis*
14	3	H	2	-O-(CH$_2$)$_2$-OH	mp. 171.6°C
15	3	H	3	-O-CH$_3$	mp. 117.4°C
33	3	H	3	-C(=O)-O-CH$_2$-CH$_3$	mp. 115.2°C
34	3	H	1	cyclopropyl	mp. 183.2°C
35	3	H	3	tetrahydro-2-furanyl	mp. 122.4°C / (±)
36	3	H	2	tetrahydro-2-furanyl	mp. 123.7°C / (±)
37	3	H	1	-CN	mp. 169.3°C
38	7	H	2	-NH$_2$	mp. 139.8°C
39	9	H	2		mp. 108.6°C
40	2	OCH$_3$	1	tetrahydro-2-furanyl	mp. 189.9°C / (±) *cis* / (COOH)$_2$
41	3	OCH$_3$	3	-O-CH$_3$	mp. 92.6°C / (±) *cis*
42	3	OCH$_3$	3	3-(1-methylethyl)-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl	mp. 177.3°C / (±) *cis*
43	8	OCH$_3$	2	-O-(CH$_2$)$_2$-OH	mp. 145.1°C / (±) *cis*
44	3	OCH$_3$	1	cyclopropyl	mp. 133.0°C / (±) *cis*
45	3	OCH$_3$	2	tetrahydro-2-furanyl	mp. 119.4°C / (±) *cis*
46	3	OCH$_3$	3	2-methyl-1,3-dioxolan-2-yl	mp. 121.9°C / (±) *cis*
47	3	OCH$_3$	3	-O-CH(CH$_3$)$_2$	mp. 76.4°C / (±) *cis*

Co. no.	Ex. no.	R^2	n	L^1	physical data
48	6	OCH_3	3	-C(=O)-CH_3	mp. 115.8°C / (±) *cis*
49	3	OCH_3	3	tetrahydro-2-furanyl	mp. 94.3°C / (±) *cis*
50	3	OCH_3	3	3-chloro-6-oxo-1(6*H*)pyridazinyl	mp. 138.3°C / (±) *cis*
51	3	OCH_3	3	-C(=O)-O-CH_2-CH_3	mp. 170.9°C / (±) *cis* / $(COOH)_2$

Table 2



Co. no.	Ex. no.	R^2	n	L^1	physical data
16	3	H	2	-H	mp. 186.1°C
17	3	H	3	-CN	mp. 127.1°C
18	3	H	3	-S(O)$_2$-CH_3	mp. 140.8°C
19	3	H	1	tetrahydro-2-furanyl	mp. 142.9°C / (±)
20	3	H	4	-NH-C(=O)-O-CH_2-CH_3	mp. 116.2°C
21	5	H	2	-OH	mp. 166.3°C
22	3	OCH_3	1	tetrahydro-2-furanyl	mp. 152.7°C / (±)-*cis*
23	3	OCH_3	3	-CN	mp. 134.9°C / (±)-*cis*
24	5	OCH_3	2	-OH	mp. 126.6°C / (±)-*cis*
25	3	OCH_3	4	-NH-C(=O)-O-CH_2-CH_3	mp. 135.4°C / (±)-*cis*
26	3	OCH_3	2	-H	mp. 139.6°C / (±)-*cis*
27	4	OCH_3	2	-CN	mp. 180.3°C / (±)-*cis*
28	7	OCH_3	3	-NH_2	mp. 111.2°C / (±)-*cis*
29	3	OCH_3	3	-S(O)$_2$-CH_3	mp. 145.7°C / (±)-*cis*
52	8	H	2	-O-$(CH_2)_2$-OH	mp. 152.2°C
53	3	H	3	2-methyl-1,3-dioxolan-2-yl	mp. 104.7°C
54	3	H	3	-O-CH_3	mp. 113.1°C
55	3	H	3	-C(=O)-O-CH_2-CH_3	mp. 79.2°C
56	3	H	3	-O-CH$(CH_3)_2$	mp. 84.7°C
57	3	H	3	3-(1-methylethyl)-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl	mp. 226.4°C

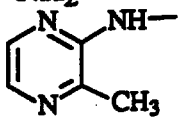
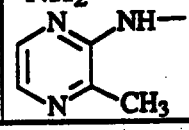
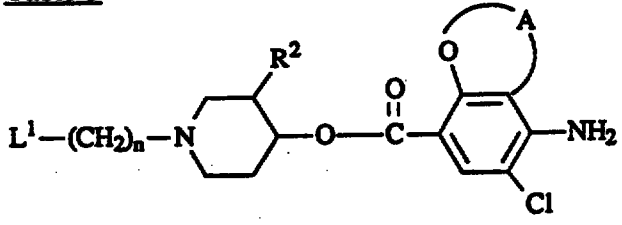
Co. no.	Ex. no.	R^2	n	L^1	physical data
58	3	H	1	cyclopropyl	mp. 161.5°C
59	3	H	3	3-chloro-6-oxo-1(6*H*)pyridazinyl	mp. 172.4°C
60	3	H	3	tetrahydro-2-furanyl	mp. 88.2°C / $(COOH)_2$ / (±)
61	3	H	2	tetrahydro-2-furanyl	mp. 118°C / $(COOH)_2$ / (±)
62	3	H	1	-CN	mp. 196.6°C
63	7	H	2	$-NH_2$	mp. 135.8°C
64	9	H	2		mp. 134.7°C
65	3	OCH_3	2	tetrahydro-2-furanyl	mp. 126.8°C / (±) *cis*
66	3	OCH_3	3	3-(1-methylethyl)-2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl	mp. 239.9°C / (±) *cis*
67	3	OCH_3	1	cyclopropyl	mp. 143.3°C / (±) *cis*
68	3	OCH_3	3	$-O-CH_3$	mp. 128.0°C / (±) *cis*
69	8	OCH_3	2	$-O-(CH_2)_2-OH$	mp. 107.8°C / (±) *cis*
70	3	OCH_3	3	$-O-CH(CH_3)_2$	mp. 89.2°C / (±) *cis* / $(COOH)_2$
71	3	OCH_3	3	3-chloro-6-oxo-1(6*H*)pyridazinyl	mp. 167.5°C / (±) *cis*
72	3	OCH_3	3	$-C(=O)-O-CH_2-CH_3$	mp. 105.1°C / (±) *cis* / $(COOH)_2$
73	3	OCH_3	3	tetrahydro-2-furanyl	mp. 185.4°C / (±) *cis* / $(COOH)_2$
74	3	OCH_3	3	2-methyl-1,3-dioxolan-2-yl	mp. 180.8°C / (±) *cis* / $(COOH)_2$
75	3	OCH_3	1	-CN	mp. 144.2°C / (±) *cis*
76	6	OCH_3	3	$-C(=O)-CH_3$	mp. 153.0°C / (±) *cis*
77	7	OCH_3	2	$-NH_2$	mp. 142.8°C / (±) *cis*
78	9	OCH_3	2		mp. 149.7°C / (±) *cis*

Table 3



Co. no.	Ex. no.	R^2	n	-O-A	L^1	physical data
30	2	OCH_3	3	$-O-C(CH_3)=CH-$	2,3-dihydro-3-(1-methyl ethyl)-2-oxo-1*H*-benzimidazol-1-yl	mp. 221.8°C / (±)-*cis*
31	2	OCH_3	3	$-O-C(CH_3)=CH-$	2,3-dihydro-3-ethyl-2-oxo-1*H*-benzimidazol-1-yl	mp. 192.5°C / (±)-*cis*
32	2	H	1	$-O-C(CH_3)_2-(CH_2)_2-$	tetrahydro-2-furanyl	mp. 146.7°C / (±) / $(COOH)_2$

C. Pharmacological examples

Example 10 : Guinea Pig Ileum Coaxial Stimulation.

Dunkin Hartley guinea-pigs of both sexes (body weight ± 500 g) were killed by decapitation. The ileum was removed and cleansed with warmed and oxygenated Krebs-Henseleit solution. Non-terminal, intact ileum segments, 4.5 cm long, of the guinea pig were vertically suspended with a preload of 1 g in 100 ml Krebs-Henseleit solution (37.5°C), gassed with a mixture of 95% O_2 and 5% CO_2. Transmural excitation was applied over the whole length of the ileum segment by means of two platinum electrodes, the anode threaded through the lumen of the ileum, the cathode in the bathing solution. The preparation was excited with single rectangular stimili [1 msec; 0.1 Hz; submaximal response (current leading to 80% of maximal reponse)] from a progammable stimulator. Contractions were measured isometrically. During the stabilization period of 30 min, the strips were repeatedly stretched to a tension of 2g, in order to obtain a steady state tension of 1g. Before starting the electrical stimulation, a cumulative dose response curve of acetylcholine was given. The electrical stimulation was started at supramaximal current to determine the maximal amplitude of the twitch responses. When these responses were stable, a submaximal stimulation to obtain 80% of the maximal responses was given until the twitch responses were constant for at least 15 min, whereafter a single dose of the test compound was added to the bath fluid. The amplitude of the twitch response five minutes after the administration of the test compound is compared with the amplitude before the administration of the test compound. The compounds with number 1, 4, 6-8, 14-16, 32-36, 39, 46 and 50 showed an increase of the amplitude of the twitch response of more than 5 % at a concentration of 3.10^{-9} M.

Example 11 : Motility of the colon in the conscious dog.

Female beagle dogs, weighing 7-17 kg, were implanted with isometric force transducers, under general anaesthesia and aseptic precautions. To study the colonic motility, transducers were sutured on the colon at 8, 16, 24 and 32 cm distance from the ileo-caecal-

valve. Dogs were allowed a recovery period of at least two weeks. Experiments were started after a fasting period of ± 20 hours, during which water was available *ad libitum*. During the experiments, dogs were free to move in their cages, thanks to the telemetric (wireless) system. The cages were built in a special room, provided with glass pervious to light in one direction, i.e. the observator can see the dogs while the dogs can not see the observator. Via this system it was possible to observe the dogs for behavioral changes and to determine defecation events. The information from the transduceres was transmitted in digitized form by a small, specially built transmitter box. This box was placed in a jacket worn by the dog. The signals were received via a microphone above each cage and were transmitted to a central computer system.
One of the parameters in this test is the defecation of the dogs. During the first three hours after administration of the test compound, the dogs were observed to determine whether and when defecation occurred. Compounds of the present invention induced defecation in the test animals during those first three hours.

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 12 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example 13 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each

comprising 20 mg of the A.I..

Example 14 : Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example 15 : Injectable solution

1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg/ml of A.I. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

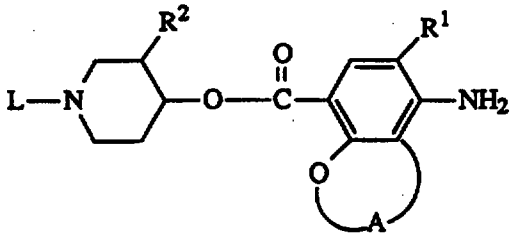
Example 16 : Suppositories

3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxy-butanedioic acid in 25 ml polyethylene glycol 400. 12 G surfactant and triglycerides q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37~38°C to form 100 suppositories each containing 30 mg of the active ingredient.

THIS SHEET HAS BEEN REPLACED

Claims

1. A compound having the formula



(I),

a *N*-oxide form, a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

R^1 is halo or C_{1-6}alkylsulfonylamino;

A represents a bivalent radical of formula :

$-CH_2-CH_2-$ (a),

$-CH_2-CH_2-CH_2-$ (b),

$-CH=CH-$ (c),

in the radicals (a), (b) and (c) one or two hydrogen atoms may be replaced by a C_{1-6}alkyl;

R^2 is hydrogen or C_{1-6}alkyloxy;

L is a radical of formula :

$-Alk-R^4$ (d),

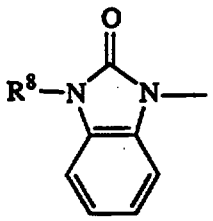
$-Alk-O-R^5$ (e),

$-Alk-NR^6R^7$ (f),

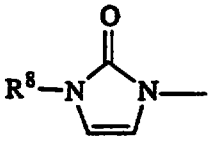
Alk is C_{1-12}alkanediyl;

R^4 is hydrogen; cyano; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{3-7}cycloalkyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; tetrahydrofuran; dioxolane; dioxolane substituted with C_{1-6}alkyl; dioxane; dioxane substituted with C_{1-6}alkyl; pyridine; pyridine substituted with halo or C_{1-6}alkyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; or a radical of formula :

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(g) or



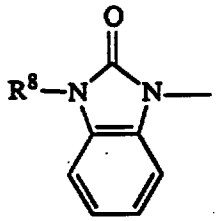
(h)

wherein R^8 is hydrogen or C_{1-6}alkyl;

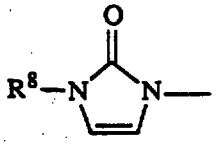
R^5 is hydrogen; C_{1-6}alkyl; hydroxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; phenyl or phenyl

substituted with up to three substituents selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy; R^6 is hydrogen or C_{1-6}alkyl;
R^7 is hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; pyrazine; pyrazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy.

2. A compound as claimed in claim 1 wherein R^4 is hydrogen; cyano; C_{1-6}alkylcarbonyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; tetrahydrofuran; dioxolane; dioxolane substituted with C_{1-6}alkyl; dioxane; dioxane substituted with C_{1-6}alkyl; pyridine; pyridine substituted with halo or C_{1-6}alkyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; or a radical of formula :


(g)

or


(h)

wherein R^8 is hydrogen or C_{1-6}alkyl.

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3. A compound as claimed in claim 1 wherein R^1 is chloro.

4. A compound as claimed in claim 1 wherein R^2 is hydrogen or methoxy.

5. A compound as claimed in claim 1 wherein the compound is selected from 1-[(tetrahydro-2-furanyl)methyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[(tetrahydro-2-furanyl)methyl]-4-piperidinyl 5-amino-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-8-carboxylate; 1-(3-methoxypropyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[3-(1-methylethoxy)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[2-(2-hydroxyethoxy)ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[3-(3-chloro-6-oxo-1(6*H*)-pyridazinyl)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-(4-oxopentyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; ethyl 4-[[(4-amino-5-chloro-2,3-dihydro-7-benzofuranyl)carbonyl]oxy]-1-piperidinebutanoate; and 1-[2-(tetrahydro-2-furanyl)ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofuran-

carboxylate; a stereochemically isomeric form thereof or a pharmaceutically acceptable acid addition salt thereof.

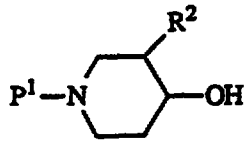
6. A pharmaceutical composition comprising a therapeuticaly effective amount of a compound as claimed in claim 1 and a pharmaceutically acceptable carrier.

7. A process for preparing a pharmaceutical composition as claimed in claim 6 wherein the compound as claimed in claim 1 is intimately mixed with a pharmaceutically acceptable carrier.

8. A compound as claimed in claim 1 for use as a medicine.

9. Use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of intestinal disorders involving a decreased motility of the colon.

10. An intermediate of formula (VII'-a), wherein R^2 is C_{1-6}alkyloxy, P^1 is hydrogen or a readily removable protective group such as C_{1-4}alkylcarbonyl, C_{1-4}alkyloxy-carbonyl, phenylmethyl, and the like protective groups and wherein R^2 and the hydroxyl group have the *cis* configuration, or an enantiomer thereof.



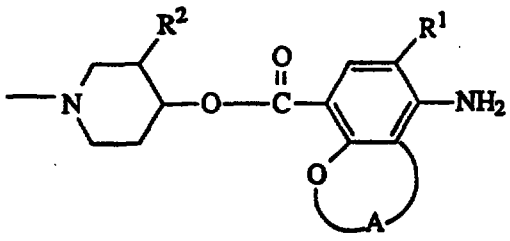
(VII'-a) : R^2 is C_{1-6}alkyloxy

12. A process for preparing a compound as claimed in claim 1 wherein
a) a piperidine of formula (II) is *N*-alkylated with an intermediate of formula (III),



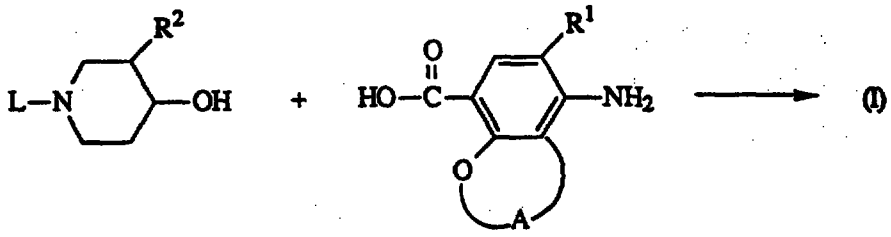
(III) (II) (I)

wherein L is as defined in claim 1, W^1 is an appropriate leaving group and D is a radical of formula



wherein R^1, R^2 and A are defined as in claim 1;

b) an alcohol of formula (IV) is reacted with a carboxylic acid of formula (V) or a functional derivative thereof, such as an acylhalide, a symmetrical or mixed anhydride or an ester;



(IV) (V) (I)

wherein R^1, R^2, L and A are defined as in claim 1;

and optionally converting the compounds of formula (I) into each other by a functional group transformation reaction; and, if desired, converting a compound of formula (I) into a therapeutically active non-toxic acid addition salt, or conversely, converting an acid addition salt into a free base form with alkali; and/ or preparing stereochemically isomeric forms thereof.

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$-CH_2-CH_2-$ (a),
$-CH_2-CH_2-CH_2-$ (b),
$-CH=CH-$ (c),

in the radicals (a), (b) and (c) one or two hydrogen atoms may be replaced by a C_{1-6}alkyl;

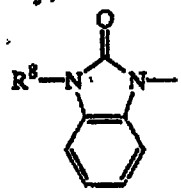
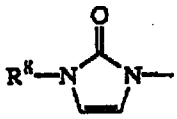
R^2 is hydrogen or C_{1-6}alkyloxy;

L is a radical of formula :

$-Alk-R^4$ (d),
$-Alk-O-R^5$ (e),
$-Alk-NR^6R^7$ (f);

Alk is C_{1-12}alkanediyl;

R^4 is hydrogen; cyano; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{3-7}cycloalkyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; tetrahydrofuran; dioxolane; dioxolane substituted with C_{1-6}alkyl; dioxane; dioxane substituted with C_{1-6}alkyl; pyridine; pyridine substituted with halo or C_{1-6}alkyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; or a radical of formula :

 (g) or  (h)

wherein R^8 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen; C_{1-6}alkyl; hydroxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; phenyl or phenyl substituted with up to three substituents selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy;

R^6 is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; pyrazine; pyrazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; provided that when A is a bivalent radical of formula (c) and L is a radical of formula (d) then R^4 is not hydrogen, cyano, C_{1-6}alkylcarbonyl, phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; or when A is a bivalent radical of formula (c) and L is a radical of formula (e) then R^5 is not hydrogen, C_{1-6}alkyl or phenyl; or when A is a bivalent radical of formula (c) and L is a radical of formula (f) then R^7 is not C_{1-6}alkylcarbonyl.

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl

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and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methylbutyl, pentyl, hexyl and the like; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{1-12}alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 12 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl, 1,11-undecanediyl, 1,12-dodecanediyl and the branched isomers thereof.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methane-sulfonic, ethanesulfonic, benzenesulfonic, *p* toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids. The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like. Conversely the salt form can be converted by treatment with alkali into the free base form.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

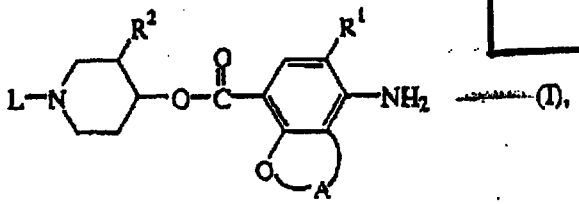
Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For instance, compounds of formula (I) wherein R^4 is 3- or 6-hydroxypyridazine, or a radical of formula (g) or (h) wherein R^8 is hydrogen may exist in their corresponding tautomeric form.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the

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Claims

1. A compound having the formula



(I),

a *N*-oxide form, a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

R^1 is halo or C_{1-6}alkylsulfonylamino;

A represents a bivalent radical of formula :

$-CH_2-CH_2-$ (a),

$-CH_2-CH_2-CH_2-$ (b),

$-CH=CH-$ (c),

in the radicals (a), (b) and (c) one or two hydrogen atoms may be replaced by a C_{1-6}alkyl;

R^2 is hydrogen or C_{1-6}alkyloxy;

L is a radical of formula :

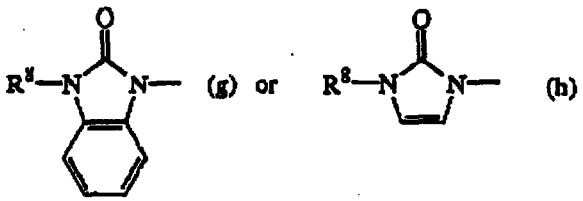
$-Alk-R^4$ (d),

$-Alk-O-R^5$ (e),

$-Alk-NR^6R^7$ (f),

Alk is C_{1-12}alkanediyl;

R^4 is hydrogen; cyano; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{3-7}cycloalkyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; tetrahydrofuran; dioxolane; dioxolane substituted with C_{1-6}alkyl; dioxane; dioxane substituted with C_{1-6}alkyl; pyridine; pyridine substituted with halo or C_{1-6}alkyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; or a radical of formula :



(g) or (h)

wherein R^8 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen; C_{1-6}alkyl; hydroxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; phenyl or phenyl substituted with up to three substituents selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy;

R^6 is hydrogen or C_{1-6}alkyl;

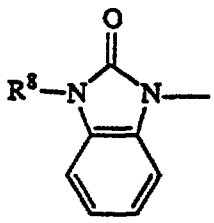
R^7 is hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; pyrazine; pyrazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy;

provided that when A is a bivalent radical of formula (c) and L is a radical of formula (d) then

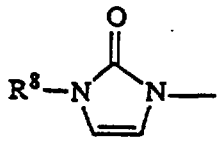
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R^4 is not hydrogen, cyano, C_{1-6}alkylcarbonyl, phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; or when A is a bivalent radical of formula (c) and L is a radical of formula (e) then R^5 is not hydrogen, C_{1-6}alkyl or phenyl; or when A is a bivalent radical of formula (c) and L is a radical of formula (f) then R^7 is not C_{1-6}alkylcarbonyl.

2. A compound as claimed in claim 1 wherein R^4 is hydrogen; cyano; C_{1-6}alkylcarbonyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; tetrahydrofuran; dioxolane; dioxolane substituted with C_{1-6}alkyl; dioxane; dioxane substituted with C_{1-6}alkyl; pyridine; pyridine substituted with halo or C_{1-6}alkyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; or a radical of formula :


(g)

or


(h)

wherein R^8 is hydrogen or C_{1-6}alkyl.

3. A compound as claimed in claim 1 wherein R^1 is chloro.

4. A compound as claimed in claim 1 wherein R^2 is hydrogen or methoxy.

5. A compound as claimed in claim 1 wherein the compound is selected from 1-[(tetrahydro-2-furanyl)methyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[(tetrahydro-2-furanyl)methyl]-4-piperidinyl 5-amino-6-chloro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-8-carboxylate; 1-(3-methoxypropyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[3-(1-methylethoxy)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[2-(2-hydroxyethoxy)ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-[3-(3-chloro-6-oxo-1(6*H*)-pyridazinyl)propyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; 1-(4-oxopentyl)-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; ethyl 4-[[(4-amino-5-chloro-2,3-dihydro-7-benzofuranyl)carbonyl]oxy]-1-piperidinebutanoate; and 1-[2-(tetrahydro-2-furanyl)ethyl]-4-piperidinyl 4-amino-5-chloro-2,3-dihydro-7-benzofuran-

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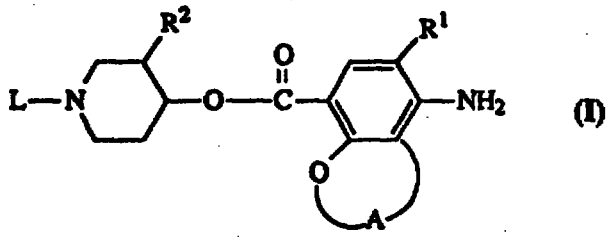
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(54) **Title:** N-SUBSTITUTED PIPERIDINYL BICYCLIC BENZOATE DERIVATIVES

(57) **Abstract**



(I)

The present invention is concerned with novel benzoate derivatives having formula (I), the *N*-oxide forms, the salts and the stereochemically isomeric forms thereof, wherein: R^1 is halo or C_{1-6}alkylsulfonylamino; A represents a bivalent radical of formula $-CH_2-CH_2-$ (a), $-CH_2-CH_2-CH_2-$ (b), -CH=CH- (c), in the radicals (a), (b) and (c) one or two hydrogen atoms may be replaced by a C_{1-6}alkyl; R^2 is hydrogen or C_{1-6}alkyloxy; L is a radical of formula: -Alk-R^4 (d), -Alk-O-R^5 (e), -Alk-NR^6R^7 (f), Alk is C_{1-12}alkanediyl; R^4 is hydrogen; cyano; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{3-7}cycloalkyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; phenyl or phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy; tetrahydrofuran; dioxolane; dioxolane substituted with C_{1-6}alkyl; dioxane; dioxane substituted with C_{1-6}alkyl; pyridine; pyridine substituted with halo or C_{1-6}alkyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy or an optionally substituted benzimidazolone or an optionally substituted imidazolone; R^5 is hydrogen; C_{1-6}alkyl; hydroxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; phenyl or phenyl substituted with up to three substituents selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy; R^6 is hydrogen or C_{1-6}alkyl; R^7 is hydrogen; C_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; pyridazine; pyridazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy; pyrazine; pyrazine substituted with one or two substituents selected from halo, C_{1-6}alkyl, hydroxy. Pharmaceutical compositions comprising said compounds, processes for preparing compounds and compositions as well as the use as a medicine, in particular for the treatment of gastrointestinal disorders involving a decreased colon motility are described.

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CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

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