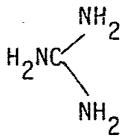
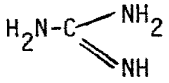
c) Salts of the formula I wherein A is  are prepared by treating omeprazole with the strong base  dissolved in a solvent, for example an alcohol.

d) A salt of formula I may be converted to another salt of the same formula by exchanging the cation. When both the starting material and the salt obtained as final product are sufficiently soluble, such an exchange may be performed by using a cation-exchange resin saturated with the cation desired in the product. The exchange may also be performed by utilizing the low solubility of a desired salt. By this principle, for example, Na^+ as a counter ion may be exchanged for Ca^{2+} or Mg^{2+}.

e) The reaction between the compounds (i) and (ii) may also be carried out by ion-pair extraction.For example, tetrabutylammonium salts of the invention may be prepared by dissolving the Na^+-salt in water containing tetrabutylammonium sulfate followed by extraction of the tetrabutylammonium salt I into a methylene chloride phase, and subsequent isolation of the tetrabutylammonium salt I. In this manner also other tetraalkylammonium salts I may be prepared.

Illustrative examples of the radical R are CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, i-C_4H_9, sec.-C_4H_9 and tert.-C_4H_9.

The invention also relates to pharmaceutical compositions containing a novel salt of omeprazole as active ingredient; to the use of the novel omeprazolesalts for providing gastrointestinal cytoprotective effects in mammals and man; to the use of the novel omeprazole salts in the prevention and treatment of gastrointestinal inflammatory diseases in mammals and man; to the use of the novel omeprazole salts for inhibiting gastric acid secretion in mammals and man; to a method for inhibiting gastric acid secretion in mammals and man by administering a compound of the formula I; to a method for the treatment of gastrointesti-

nal inflammatory diseases in mammals and man by administering a compound of the formula I; and to a method for providing gastrointestinal cytoprotective effects in mammals and man by administering a compound of the formula I.

For clinical use the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, e.g. lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with lubricating agents e.g. magnesium stearate, calcium stearate, sodium steryl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets. Since the compounds of the invention are susceptible to degradation in acid to neutral media, the above-mentioned granules or tablets are preferably coated with an enteric coating which protects the active compound from acid degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To this coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules are preferably enteric coated as described above. Hard gelatine capsules may contain enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier e.g. lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine; the hard gelatine capsules are preferably enteric coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose and thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilising agents and/or buffering agents and may be manufactured in unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

Sodium salts of the invention are preferably used in the preparation of parenteral formulations.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the manner of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 400 mg per day of active substance.

The following examples will further illustrate the invention.

Example 1. Preparation of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2--pyridinyl)-methyl]sulfinyl]-1H-benzimidazole sodium salt (omeprazole sodium salt).

Omeprazole (1000g, 2.90 mol) was added to a solution of NaOH (116g, 2.90 mol) in deionized water (25l). After stirring for 5 min methylene chloride (5l) was added and stirring was continued for 10 min. The two phases were separated. The aqueous phase was washed with methylene chloride (5l), filtered clear (Celite) and concentrated by evaporation under reduced pressure to about 2 l total volume. Absolute ethanol (6l) was added and the evaporation was continued until dryness. Ethyl acetate (7l) was added, the mixture was stirred under reflux for 30 min. After cooling and standing over night the resulting slurry was stirred with an additional amount (2l) of ethyl acetate and filtered. The filter cake was washed with diethyl ether and dried under reduced pressure at 40°C over night giving omeprazole sodium salt (975g, 92%), mp 208-210°C, NMR: $\delta(D_2O)$: 1.85(s,3H), 2.1(s,3H), 3.5(s,3H), 3.85(s,3H), 4.75(s,2H), 6.85 (dd,1H), 7.2(d,1H), 7.55(d,1H), 8.15(d,1H).

Example 2. Preparation of omeprazole sodium salt.
Omeprazole (1300g, 3.77 mol) was added under vigorous mechanic stirring to a mixture of tetrahydrofuran (13l) and 50% aqueous NaOH (296g, 3.7 mol) and stirring was then continued for 45 min. Trichloroethylene (5.7l) was added and stirring was continued over night at room temperature. The mixture was cooled to +5°C and then stirred for 3h. The precipitate was filtered off and the filter cake was washed with trichloroethylene (5l) and dried under reduced pressure at 50°C giving omeprazole

sodium salt (1314g, 95%), mp 208-210°C.

Example 3. Preparation of omeprazole potassium salt.
Omeprazole (10.0g, 0.0290 mol) was added to a solution of KOH (1.60g. 0.0285 mol) in deionized water and then methylene chloride (50ml) was added. The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous phase was washed with methylene chloride (50ml) and filtered clear (Celite). Evaporation to dryness gave a crystalline residue. Recrystallisation from ethyl acetate yielded omeprazole patassium salt, mp. 148-150°C (soluble in water).

Example 4. Preparation of di-omeprazole calcium salt dihydrate.
Anhydrous $CaCl_2$ (17.9g, 0.161 mol) dissolved in deionized water (200 ml) was added dropwise under viogorous stirring to a solution of omeprazole sodium salt (125g, 0.340 mol) in deionized water (1250 ml) and then stirring was continued for 1h at room temperature. The precipitate was centrifugated down and washed with deionized water until no Cl^- was detectable ($AgNO_3$). After drying in the air and grinding, the crystals were dried in vacuum at 40° for 20h yielding omeprazole calcium salt dihydrate (104g, 80%), mp 182-184°C, NMR: δ(CDCl$_3$+1 drop of DMSO-d$_6$) 2.0(s,3H), 2.15(s,3H), 3.6(s,3H), 3.7(s,3H), 4.5(s,2H), 6.7(dd,1H), 7.1(d,1H), 7.6(d,1H, 8.15(s,1H).

Example 5. Preparation of di-omeprazole magnesium salt dihydrate.
Anhydrous $MgCl_2$ (16.2g, 0.17 mol) dissolved in deionized water (625 ml) was added dropwise under vigorous stirring to a solution of omeprazole sodium salt (125g, 0.340 mol) in deionized water(1560ml) and then the stirring was continued for 1h at room temperature. The precipitate was centrifugated down and then washed with deionized water until no Cl^- was detectable ($AgNO_3$). Drying in the air, grinding and drying in vacuum at 40° for 24h yielded omeprazole magnesium salt dihydrate (111g, 87%) mp 177-178°C.

Example 6. Preparation of di-omeprazole magnesium salt.
Magnesium (0.35g, 0.0145 mol) was reacted with absolute methanol (10ml) (in the presence of one drop of CCl_4) to give a solution of $Mg(OCH_3)_2$ in methanol solution. More methanol (10ml) was added and the solution

was added dropwise to a solution of omeprazole (10 g, 0.029 m) in methanol (200 ml) and the mixture was then stirred for 30 min at room temperature. Evaporation gave a crystalline solid of the di-omeprazole magnesium salt, mp. 178-180°.

Example 7. Preparation of omeprazole tetrabutylammonium salt. Omeprazole sodium salt (3.8g, 0.010 mol) was added to a mixture of tetrabutylammonium hydrogensulphate (3.5g, 0.010 mol) and NaOH (0.42 g, 0.0105 mol) in deionized water (15ml). Methylene chloride (10ml) was added and the mixture was shaken in a separatory funnel. After separation of the phases the organic phase was dried and the solvent evaporated off giving omeprazole tetrabutylammonium salt (3.5g, 60%), NMR: $\delta(CDCl_3)$: 0.8-1.15(m,12H), 1.15-1.6(m,16H), 2.25(s,3H), 2.3(s,3H), 2.75-3.15(m,8H), 3.75(s,3H), 3.9(s,3H), 4.7(d,1H), 5.05(d,1H), 6.8 (dd,1H), 7.3(d,1H), 7.7(d,1H), 8.35(s,1H).

Example 8. Preparation of omeprazole guanidinium $[C^+(NH_2)_3]$ salt. A solution of guanidine (0.0029 mol)[prepared from guanidinium nitrate and KOH] in ethanol (50ml) was added to a solution of omeprazole (1.0g, 0.0029 mol) and the resulting solution was stirred for 15 min. The solvent was evaporated giving omeprazole guanidinium salt, mp 110-112°C (soluble in water).

Example 9. Preparation of tetra-omeprazole titanium salt. Titanium tetraisopropylate (1.03g, 0.0036 mol) was added to a solution of omeprazole in dry isopropanol (250ml) and the mixture was stirred under N_2 at room temperature for 4h. (A white precipitate was formed). Evaporation of the solvent followed by washing 3 times with light petroleum and drying in vacuum gave a white crystalline powder of tetra-omeprazole titanium salt, mp >260°C.

Example 10. Preparation of omeprazole litium salt. Omeprazole (3.0 g, 0.0087 mol) was added to a solution of LiOH (0.207 g, 0.00865 mol) in deionized water and then methylene chloride (25 ml) was added. The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous phase was washed with methylene chloride (25 ml) and filtered clear (Celite). Evaporation to dryness gave a crystalline omeprazole litium salt, mp. 198-200°C (soluble in water).

NMR: δ ($CDCl_3$) 1.65 (s,3H), 1.8 (s,3H), 3.45 (s,3H), 3.4 (s,3H), 4.2 (s,2H), 6.6 (dd,1H), 6.95 (d,1H), 7.45 (d,1H), 7.75 (s,1H).

The NMR data given in the examples are measured at 90 MHz.

Incorporation of the novel omeprazole salts of the present invention in pharmaceutical preparations is exemplified in the following examples.

Example 11. Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

I	Omeprazole sodium salt	1.0 g
	Sugar, powder	30.0 g
II	Saccharine	0.6 g
	Glycerol	5.0 g
	Flavouring agent	0.05g
	Ethanol	5.0 g
	Sorbic acid	0.5 g
	Sodium dihydrogen phosphate q.s. to pH=	9.0 g
	Distilled water q.s. to a final volume of	100 ml

I Powdered omeprazole sodium salt was carefully dry mixed with powdered sugar, dried in a vacuum oven over-night and dispensed into bottles each containing 31.0 gram of the powder mixture.

II A solution of saccharine, glycerol, flavouring agent, ethanol, sodium dihydrogen phosphate, sorbic acid and water was prepared, and dispensed into vials. When mixed with the powder mixture of omeprazole sodium salt and sugar the final volume was 100 ml.

Solvent vial II is to be added to powder mixture vial I just prior to use. The formed suspension is stable for ten days when stored at refrigerator temperature.

The salt given above may be replaced with another salt of the invention.

Example 12. Enteric-coated tablets

An enteric-coated tablet containing 20 mg of active compound was prepared from the following ingredients:

I	Omeprazole magnesium salt	200 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Omeprazole magnesium salt, powder, was mixed with lactose, and granulated with a water solution of methyl cellulose. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 20 mg of active substance, in a tabletting machine using 6 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota®, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Example 13. Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

I	Omeprazole sodium salt	4.26 g
	Sterile water	200 ml
II	Polyethylene glycol 400 for injection	400 g
	Sodium dihydrogen phosphate	1.5 g
	Sterile water to a final volume of	1000 ml

I Omeprazole sodium salt 4.26 g, corresponding to 4.0 g of omeprazole, was dissolved in sterile water to a final volume of 200 ml. The solution was filtered through a 0.22 μ filter and dispensed into sterile vials, each vial containing 2.0 ml. The vials were placed in a freeze drier with a shelf temperature of -40°C. When the solution in the vials had frozen, the solution was freeze dried. After drying the vials were stoppered.

II A solution of polyethylene glycol and sodium dihydrogen phosphate in sterile water was prepared, filtered through a 0.22 μ filter, dispensed into sterile vials and the vials closed with a rubber stopper. The vials were sterilised in an autoclave at +120°C for twenty minutes. Immediately before use 10.0 ml of solvent II is added to vial I. The clear solution contains 4 mg of omeprazole per millilitre.

Test of the stability of omeprazole salts of the invention

The stability of omeprazole sodium salt, of the invention, obtained according to Example 1, was compared with the stability of the neutral form of omeprazole. Both test compounds were stored for six months at + 37°C and at a relative humidity of 80%. Thereafter, the amount of degradation products which had formed was measured. The result is given in Table 1 below.

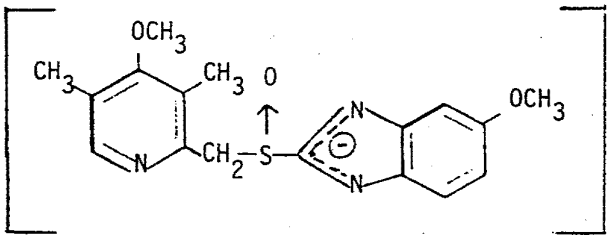
Table 1. Stability of neutral omeprazole and of omeprazole sodium salt after six months storage at + 37°C and 80% relative humidity

Test compound	Amount of degradation products formed (per cent calculated on original amount of omeprazole)
neutral omeprazole	6
omeprazole sodium salt	0.4

As is seen in Table 1 the omeprazole sodium salt of the invention gave rise to substantially lower amounts of degradation products than the neutral form of omeprazol. This shows the improved stability of the novel omeprazole salts of the invention.

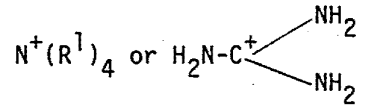
What we claim is:

1. A compound of the formula



A^{n+} I

wherein n is 1, 2, or 4; and A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or



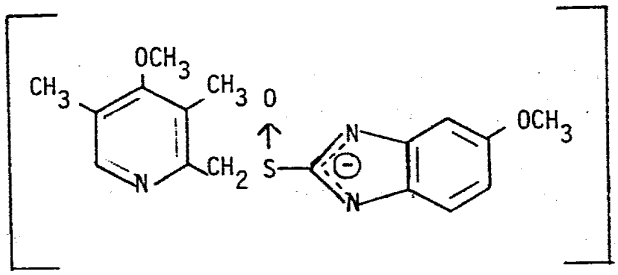
wherein R^1 is an alkyl group containing 1-4 carbon atoms.

2. A compound according to claim 1 wherein A^{n+} is Na^+, K^+, Mg^{2+} or Ca^{2+}.

3. A compound according to claim 1 wherein A^{n+} is Na^+.

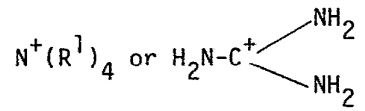
4. A compound according to claim 1 wherein A^{n+} is Mg^{2+}.

5. A process for the preparation of a compound of the formula

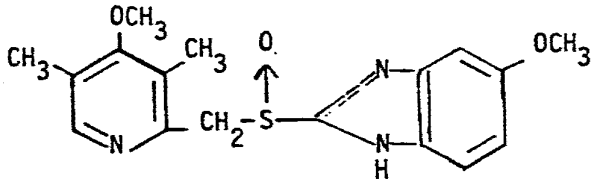


A^{n+} I

wherein n is 1, 2, or 4; and A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or



wherein R^1 is an alkyl group containing 1-4 carbon atoms characterized by reacting omeprazole of the formula



(i)

with a base capable of releasing the cation

$$A^{n+} \qquad \text{(ii)}$$

to give a salt of the formula I, which salt is thereafter isolated.

6. A process according to claim 5 wherein the base releasing the cation A^{n+} is NaOH, $NaNH_2$, or $NaNR_2$ wherein R is an alkyl group containing 1-4 carbon atoms.

7. A process according to claim 5 wherein the base releasing the cation A^{n+} is $Mg(OR)_2$ wherein R is an alkyl group containing 1-4 carbon atoms.

8. A pharmaceutical composition containing as active ingredient a compound according to any of claims 1-4.

9. A compound as defined in any of claims 1-4, for use in inhibiting gastric acid secretion in mammals and man.

10. A compound as defined in any of claims 1-4, for use as gastrointestinal cytoprotecting agent in mammals and man.

11. A compound as defined in any of claims 1-4, for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

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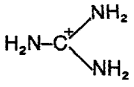
(54) **Omeprazole salts.**

(57) Novel salts of omeprazole with Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or



as cation; processes for their preparation thereof, pharmaceutical compositions containing such salts and their use in medicine.

EP 0 124 495 A3

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
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TECHNICAL FIELDS SEARCHED (Int. Cl. 3)

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☒ par substitution ☐ par adjonction et/ou ☐ par suppression ou
☐ de la manière suivante :
(le cas échéant, indiquer la marche à suivre .....)

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(12) EUROPÄISCHE PATENTANMELDUNG

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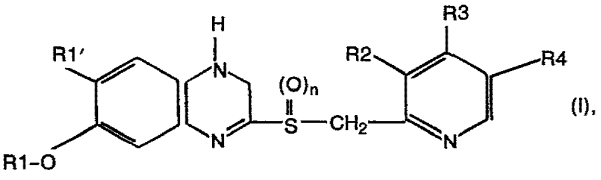
(43) Veröffentlichungstag der Anmeldung: **02.01.86**
Patentblatt 86/1

(84) Benannte Vertragsstaaten: **AT BE CH DE FR GB IT LI LU NL SE**

(54) Dialoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel.

(57) Dialkoxypyridine der allgemeinen Formel I



(I),

sowie deren Salze sind neue Verbindungen mit interessanten pharmakologischen Eigenschaften.

worin
R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chloridfluormethylrest und
R1′ Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder
R1 und R1′ gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,
R3 einen 1-3C-Alkoxyrest,
einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und
n die Zahlen 0 oder 1 darstellt,

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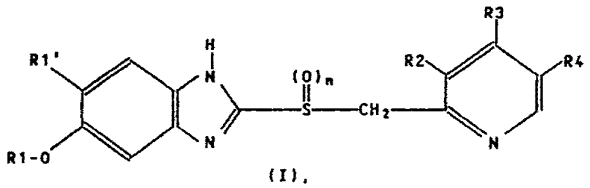
(54) Dialkoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel.

(57) Dialkoxypyridine der allgemeinen Formel I



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R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chloridfluormethylrest und
R1′ Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder
R1 und R1′ gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,
R3 einen 1-3C-Alkoxyrest,
einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und
n die Zahlen 0 oder 1 darstellt,

sowie deren Salze sind neue Verbindungen mit interessanten pharmakologischen Eigenschaften.

Dialkoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel

Anwendungsgebiet der Erfindung

Die Erfindung betrifft neue Dialkoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel. Die erfindungsgemäßen Verbindungen werden in der pharmazeutischen Industrie als Zwischenprodukte und zur Herstellung von Medikamenten verwendet.

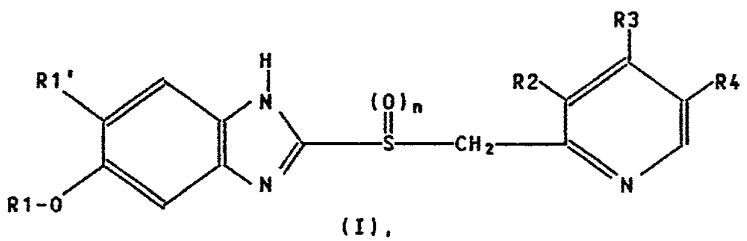
Stand der Technik

In der europäischen Patentanmeldung 0 005 129 werden substituierte Pyridylsulfinylbenzimidazole beschrieben, die magensäuresekretionshemmende Eigenschaften besitzen sollen. - In der europäischen Patentanmeldung 0 074 341 wird die Verwendung einer Reihe von Benzimidazolderivaten zur Magensäuresekretionshemmung beschrieben. In der britischen Patentanmeldung GB 2 082 580 werden tricyclische Imidazolderivate beschrieben, die die Magensäuresekretion hemmen und die Entstehung von Ulcera verhindern sollen.

Es wurde nun überraschenderweise gefunden, daß die unten näher beschriebenen Dialkoxypyridine interessante und unerwartete Eigenschaften aufweisen, durch die sie sich in vorteilhafter Weise von den bekannten Verbindungen unterscheiden.

Beschreibung der Erfindung

Gegenstand der Erfindung sind neue Dialkoxypyridine der allgemeinen Formel I



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worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest und

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest, oder

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindungen.

Als ganz oder überwiegend durch Fluor substituierte 1-3C-Alkylreste seien beispielsweise der 1,1,2-Trifluorethylrest, der Perfluorpropylrest, der Perfluorethylrest und insbesondere der 1,1,2,2-Tetrafluorethylrest, der Trifluormethylrest, der 2,2,2-Trifluorethylrest und der Difluormethylrest genannt.

Halogen im Sinne der vorliegenden Erfindung ist Brom, Chlor und insbesondere Fluor.

1-3C-Alkylreste sind der Propyl-, Isopropyl-, Ethyl- und insbesondere der Methylrest.

1-3C-Alkoxyreste enthalten neben dem Sauerstoffatom die vorstehend genannten 1-3C-Alkylreste. Bevorzugt ist der Methoxyrest.

Ganz oder überwiegend durch Fluor substituierte 1-3C-Alkoxyreste enthalten neben dem Sauerstoffatom die vorstehend aufgeführten ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylreste. Beispielsweise seien der

1,1,2,2-Tetrafluorethoxy-, der Trifluormethoxy-, der 2,2,2-Trifluorethoxy- und der Difluormethoxyrest genannt.

Als gegebenenfalls ganz oder teilweise durch Fluor substituierte 1-2C-Alkylendioxyreste seien beispielsweise der 1,1-Difluorethylendioxyrest ($-O-CF_2-CH_2-O-$), der 1,1,2,2-Tetrafluorethylendioxyrest ($-O-CF_2-CF_2-O-$), der 1,1,2-Trifluorethylendioxyrest ($-O-CF_2-CHF-O-$) und insbesondere der Difluormethylendioxyrest ($-O-CF_2-O-$) als substituierte, und der Ethylendioxyrest und der Methylendioxyrest als unsubstituierte Reste genannt.

Als Salze kommen für Verbindungen der Formel I, in denen n die Zahl 0 bedeutet (Sulfide), bevorzugt alle Säureadditionssalze in Betracht. Besonders erwähnt seien die pharmakologisch verträglichen Salze der in der Galenik üblicherweise verwendeten anorganischen und organischen Säuren. Pharmakologisch unverträgliche Salze, die beispielsweise bei der Herstellung der erfindungsgemäßen Verbindungen im industriellen Maßstab als Verfahrensprodukte zunächst anfallen können, werden durch dem Fachmann bekannte Verfahren in pharmakologisch verträgliche Salze übergeführt. Als solche eignen sich beispielsweise wasserlösliche und wasserunlösliche Säureadditionssalze, wie das Hydrochlorid, Hydrobromid, Hydroiodid, Phosphat, Nitrat, Sulfat, Acetat, Citrat, Gluconat, Benzoat, Hibenzat, Fendizoat, Butyrat, Sulfosalicylat, Maleat, Laurat, Malat, Fumarat, Succinat, Oxalat, Tartrat, Amsonat, Embonat, Metembonat, Stearat, Tosilat, 2-Hydroxy-3-naphthoat, 3-Hydroxy-2-naphthoat oder Mesilat.

Für Verbindungen der Formel I, in denen n die Zahl 1 bedeutet (Sulfoxide), kommen als Salze bevorzugt basische Salze in Betracht, insbesondere pharmakologisch verträgliche Salze mit in der Galenik üblicherweise verwendeten anorganischen und organischen Basen. Als Beispiele für basische Salze seien Natrium-, Kalium-, Calcium- oder Aluminiumsalze erwähnt.

Eine Ausgestaltung (Ausgestaltung a) der Erfindung sind Verbindungen der Formel I, worin R1' Wasserstoff darstellt und R1, R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung b) der Erfindung sind Verbin-

dungen der Formel I, worin R1' Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest darstellt und R1, R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung c) der Erfindung sind Verbindungen der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen 1-2C-Alkylendioxyrest darstellen und R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung d) der Erfindung sind Verbindungen der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest darstellen und R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung e) der Erfindung sind Verbindungen der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Chlortrifluorethylendioxyrest darstellen und R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Bevorzugte Verbindungen der Ausgestaltung a sind solche der Formel I, worin R1 1,1,2,2-Tetrafluorethyl, Trifluormethyl, 2,2,2-Trifluorethyl, Difluormethyl oder Chlordifluormethyl, R1' Wasserstoff, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung b sind solche der Formel I, worin R1 Difluormethyl, R1' Difluormethoxy oder Methoxy, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung c sind solche der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das

R1 gebunden ist, einen Methylen- oder Ethylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung d sind solche der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Difluormethylendioxyrest oder einen 1,1,2-Trifluorethylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung e sind solche der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Chlortrifluorethylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Als erfindungsgemäße Verbindungen seien beispielsweise genannt:
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,

5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
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5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,

5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,

2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,

2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,

2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,

2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,

2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,

2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,

5-Difluormethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,

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5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazol,

2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,

2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,

2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,

2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-

benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
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5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
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5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
2,2-Difluor-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
2,2-Difluor-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
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6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-3-methyl-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-3-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylthio]-2,2-difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-2,2-difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,

6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,

6-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,

6-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,

6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

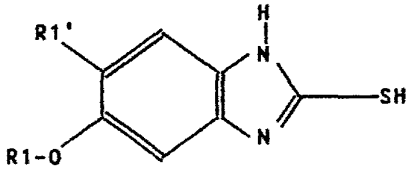
6,7-Dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,7-Dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,7-Dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino-[2,3-f]benzimidazol,
6,7-Dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino-[2,3-f]benzimidazol
und die Salze dieser Verbindungen.

Bedingt durch die Tautomerie im Imidazolring ist die 5-Substitution im Benzimidazol mit der 6-Substitution identisch. Entsprechend ist bei den Verbindungen, in denen R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen substituierten Ethylendioxyrest darstellen, die 6-Position im [1,4]-Dioxino[2,3-f]benzimidazolteil mit der 7-Position identisch.

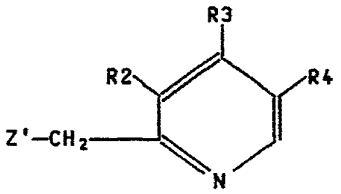
Ein weiterer Gegenstand der Erfindung ist ein Verfahren zur Herstellung der Dialkoxypyridine der Formel I, worin R1, R1', R2, R3. R4 und n die oben angegebenen Bedeutungen haben, und ihrer Salze.

Das Verfahren ist dadurch gekennzeichnet, daß man

a) Mercaptobenzimidazole der Formel II mit Picolinderivaten III,



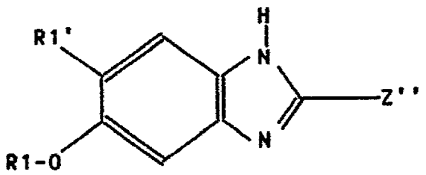
(II)



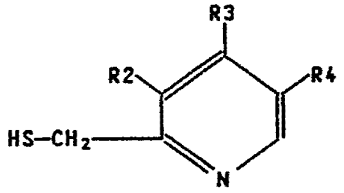
(III),

oder

b) Benzimidazole der Formel IV mit Mercaptopicolinen V,



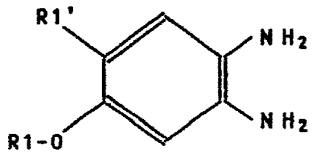
(IV)



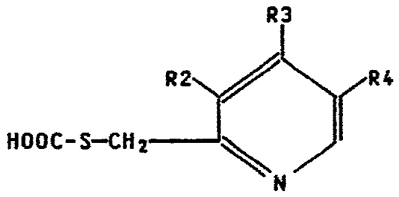
(V),

oder

c) o-Phenylendiamine der Formel VI mit Ameisensäurederivaten VII

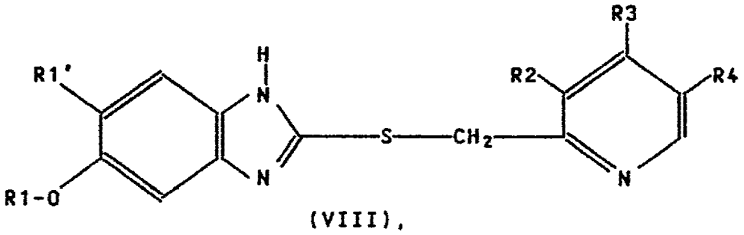


(VI)



(VII),

umsetzt und gegebenenfalls anschließend die nach a), b) oder c) erhaltenen 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII

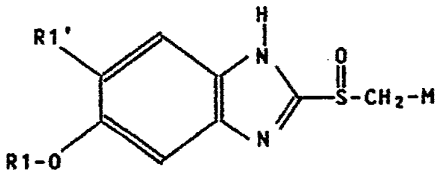


(VIII),

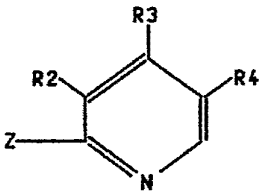
oxidiert und/oder in die Salze überführt,

oder daß man

d) Benzimidazole der Formel IX mit Pyridinderivaten X



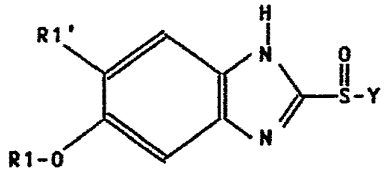
(IX)



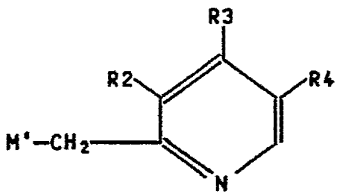
(X),

oder

e) Sulfinylderivate der Formel XI mit 2-Picolinderivaten XII



(XI)



(XII),

umsetzt und gegebenenfalls anschließend in die Salze überführt, wobei Y, Z, Z' und Z'' geeignete Abgangsgruppen darstellen, M für ein Alkalimetallatom (Li, Na oder K) steht, M' für das Äquivalent eines Metallatoms steht und R1, R1', R2, R3, R4 und n die oben angegebenen Bedeutungen haben.

Bei den vorstehend aufgeführten Umsetzungen können die Verbindungen II-XII als solche oder gegebenenfalls in Form ihrer Salze eingesetzt werden.

Die Herstellungsverfahren a), b) und c) führen zu den erfindungsgemäßen Sulfiden, die Oxidation der Verbindungen VIII und die Verfahren d) und e) liefern die erfindungsgemäßen Sulfoxide.

Welche Abgangsgruppen Y, Z, Z' bzw. Z'' geeignet sind, ist dem Fachmann

aufgrund seines Fachwissens geläufig. Eine geeignete Abgangsgruppe Y ist beispielsweise eine Gruppe, die zusammen mit der Sulfinylgruppe, an die sie gebunden ist, ein reaktives Sulfinsäurederivat bildet. Als geeignete Abgangsgruppen Y seien beispielsweise Alkoxy-, Dialkylamino- oder Alkylmercaptogruppen genannt. Als geeignete Abgangsgruppen Z, Z' bzw. Z'' seien beispielsweise Halogenatome, insbesondere Chloratome, oder durch Veresterung (z.B. mit p-Toluolsulfonsäure) aktivierte Hydroxylgruppen genannt. Das Äquivalent eines Metallatoms M' ist beispielsweise ein Alkalimetall- (Li, Na oder K), oder ein Erdalkalimetallatom (z.B. Mg), das durch ein Halogenatom (z.B. Br, Grignard-Reagenz) substituiert ist, oder irgendein anderes, gegebenenfalls substituiertes Metallatom, von dem bekannt ist, daß es bei Substitutionsreaktionen metallorganischer Verbindungen wie die obenerwähnten Metalle reagiert.

Die Umsetzung von II mit III erfolgt in an sich bekannter Weise in geeigneten, vorzugsweise polaren protischen oder aprotischen Lösungsmitteln (wie Methanol, Isopropanol, Dimethylsulfoxid, Aceton, Dimethylformamid oder Acetonitril) unter Zusatz oder unter Ausschluß von Wasser. Sie wird beispielsweise in Gegenwart eines Protonenakzeptors durchgeführt. Als solche eignen sich Alkalimetallhydroxide, wie Natriumhydroxid, Alkalimetallcarbonate, wie Kaliumcarbonat, oder tertiäre Amine, wie Pyridin, Triethylamin oder Ethyldiisopropylamin. Alternativ kann die Umsetzung auch ohne Protonenakzeptor durchgeführt werden, wobei - je nach Art der Ausgangsverbindungen - gegebenenfalls zunächst die Säureadditionssalze in besonders reiner Form abgetrennt werden können. Die Reaktionstemperatur kann zwischen 0^0 und 150^0C liegen, wobei in Gegenwart von Protonenakzeptoren Temperaturen zwischen 20^0 und 80^0C und ohne Protonenakzeptoren zwischen 60^0 und 120^0C - insbesondere die Siedetemperatur der verwendeten Lösungsmittel - bevorzugt sind. Die Reaktionszeiten liegen zwischen 0,5 und 24 Stunden.

Bei der Umsetzung von IV mit V, die in an sich bekannter Weise erfolgt, kommen ähnliche Reaktionsbedingungen wie bei der Umsetzung von II mit III zur Anwendung.

Die Reaktion von VI mit VII wird bevorzugt in polaren, gegebenenfalls was-

serHaltigen Lösungsmitteln in Gegenwart einer starken Säure, z.B. Salzsäure, insbesondere bei der Siedetemperatur des verwendeten Lösungsmittels durchgeführt.

Die Oxidation der Sulfide VIII erfolgt in an sich bekannter Weise und unter den Bedingungen, wie sie dem Fachmann für die Oxidation von Sulfiden zu Sulfoxiden geläufig sind [siehe hierzu z.B. J. Drabowicz und M. Mikolajczyk, Organic preparations and procedures int. 14(1-2), 45-89(1982) oder E. Block in S. Patai, The Chemistry of Functional Groups, Supplement E. Part 1, S. 539-608, John Wiley and Sons (Interscience Publication), 1980]. Als Oxidationsmittel kommen alle für die Oxidation von Sulfiden zu Sulfoxiden üblicherweise verwendeten Reagenzien in Frage, z.B. Hypohalogenite, insbesondere Peroxysäuren, wie z.B. Peroxyessigsäure, Trifluorperoxyessigsäure, 3,5-Dinitroperoxybenzoesäure, Peroxymaleinsäure oder bevorzugt m-Chlorperoxybenzoesäure.

Die Reaktionstemperatur liegt (je nach Reaktivität des Oxidationsmittels und Verdünnungsgrad) zwischen -70°C und der Siedetemperatur des verwendeten Lösungsmittels, bevorzugt jedoch zwischen -50° und +20°C. Die Oxidation wird zweckmäßigerweise in inerten Lösungsmitteln, z. B. aromatischen oder chlorierten Kohlenwasserstoffen, wie Benzol, Toluol, Dichlormethan oder Chloroform, oder in Estern, wie Essigsäureethylester oder Essigsäureisopropylester, oder in Ethern, wie Dioxan, mit Zusatz von Wasser oder ohne Wasser durchgeführt.

Die Umsetzung von IX mit X erfolgt bevorzugt in inerten Lösungsmitteln, wie sie auch für die Reaktion von Enolationen mit Alkylierungsmitteln üblicherweise verwendet werden. Beispielsweise seien aromatische Lösungsmittel wie Benzol oder Toluol genannt. Die Reaktionstemperatur liegt (je nach Art des Alkalimetallatoms M und der Abgangsgruppe Z) in der Regel zwischen 0° und 120°C, wobei die Siedetemperatur des verwendeten Lösungsmittels bevorzugt ist. Beispielsweise [wenn M Li(Lithium) und Z Cl(Chlor) darstellt und die Umsetzung in Benzol durchgeführt wird] ist die Siedetemperatur von Benzol (80°C) bevorzugt.

Die Verbindungen XI werden mit den Verbindungen XII in an sich bekannter

Weise umgesetzt, wie sie dem Fachmann für die Reaktion metallorganischer Verbindungen geläufig ist.

Je nach Art der Ausgangsverbindungen, die gegebenenfalls auch in Form ihrer Salze eingesetzt werden können, und in Abhängigkeit von den Reaktionsbedingungen werden die erfindungsgemäßen Verbindungen zunächst entweder als solche oder in Form ihrer Salze gewonnen.

Im übrigen erhält man die Salze durch Auflösen der freien Verbindungen in einem geeigneten Lösungsmittel, z.B. in einem chlorierten Kohlenwasserstoff, wie Methylenchlorid oder Chloroform, einem niedermolekularen aliphatischen Alkohol (Ethanol, Isopropanol), einem Ether (Diisopropylether), Keton (Aceton) oder Wasser, das die gewünschte Säure bzw. Base enthält, oder dem die gewünschte Säure bzw. Base - gegebenenfalls in der genau berechneten stöchiometrischen Menge anschließend zugegeben wird.

Die Salze werden durch Filtrieren, Umfällen, Ausfällen oder durch Verdampfen des Lösungsmittels gewonnen.

Erhaltene Salze können durch Alkalisieren bzw. Ansäuern, z.B. mit wäßrigem Natriumhydrogencarbonat bzw. mit verdünnter Salzsäure, in die freien Verbindungen umgewandelt werden, welche wiederum in die Salze übergeführt werden können. Auf diese Weise lassen sich die Verbindungen reinigen, oder es lassen sich pharmakologisch nicht verträgliche Salze in pharmakologisch verträgliche Salze umwandeln.

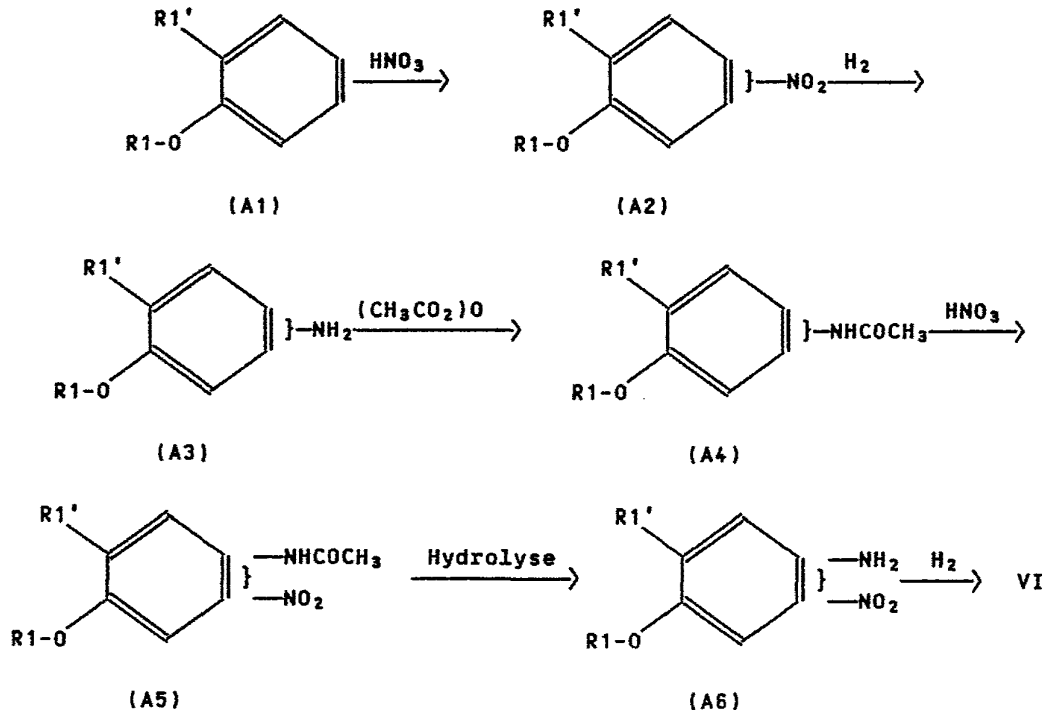
Die erfindungsgemäßen Sulfoxide sind optisch aktive Verbindungen. Die Erfindung umfaßt daher sowohl die Enantiomeren als auch ihre Mischungen und Racemate. Die Enantiomeren können in an sich bekannter Weise (beispielsweise durch Herstellung und Trennung entsprechender diastereoisomerer Verbindungen) separiert werden. Die Enantiomeren können aber auch durch asymmetrische Synthese, beispielsweise durch Reaktion optisch aktiver reiner Verbindungen XI oder diastereoisomer reiner Verbindungen XI mit Verbindungen XII hergestellt werden [siehe hierzu K.K. Andersen, Tetrahedron Lett., 93 (1962)].

Die erfindungsgemäßen Verbindungen werden bevorzugt durch Umsetzung von II mit III und gegebenenfalls anschließende Oxidation des entstandenen Sulfids VIII synthetisiert.

Die Verbindungen der Formel II sind teils bekannt (DE-OS 31 32 613), oder sie können nach bekannten Vorschriften analog hergestellt werden. Verbindungen II erhält man beispielsweise durch Umsetzen von Verbindungen VI mit Kohlendisulfid in Gegenwart von Alkalihydroxiden oder mit Alkali-O-ethyldithiocarbonaten.

Die Verbindungen VI können nach der im folgenden Reaktionsschema A angegebenen allgemeinen Herstellungsmethode synthetisiert werden:

Reaktionsschema A:



Die Ausgangsverbindungen A1 - A3 können nach bekannten Methoden oder analog zu diesen [z.B. J.Org.Chem. 44, 2907-2910 (1979); J.Org.Chem. 29, 1-11 (1964); DE-OS 20 29 556; DE-OS 28 48 531; J.Fluorine Chem. 18, 281-91 (1981); Synthesis 1980, 727-8] hergestellt werden, wobei bei ungleichen Substituenten R1' und R1-O- auch Isomerengemische entstehen können.

Die Verbindungen IV, IX und XI können beispielsweise aus den Verbindungen II in für den Fachmann bekannter Weise hergestellt werden.

Die Verbindungen IX werden beispielsweise aus den Verbindungen II durch Methylierung, Oxydation und anschließende Deprotonierung - z.B. mit Alkalimetallhydriden oder -alkoholaten oder üblichen metallorganischen Verbindungen erhalten. Die Verbindungen X werden in Anlehnung an Z. Talik, Roczniki Chem. 35, 475 (1961) hergestellt.

Die Verbindungen III können - je nach Substitutionsmuster - auf verschiedene Weise hergestellt werden:

1. Verbindungen III mit R2 und R3 = 1-3C-Alkoxy und R4 = Wasserstoff oder 1-3C-Alkyl.

   Diese Verbindungen werden z.B. ausgehend von bekannten oder auf bekanntem Wege herstellbaren 3-Hydroxy- bzw. 3-Hydroxy-5-alkyl-pyridinen durch Benzylierung der Hydroxygruppe (z.B. mit Kaliumhydroxid und Benzylchlorid in Dimethylsulfoxid), N-Oxidation (z.B. mit 30 %-igem Wasserstoffperoxid), Nitrierung in 4-Position (z.B. mit Nitriersäure), Austausch der Nitrogruppe gegen die 1-3C-Alkoxygruppe (z.B. durch Umsetzung mit Alkali-alkoxid), reduktive Debenzylierung und gleichzeitige N-Deoxygenierung (z.B. mit Wasserstoff an Palladium/Kohle in saurem Medium), Einführung der Hydroxymethylgruppe in o-Position zum Pyridinstickstoff (z.B. durch Umsetzung mit alkalischer Formalinlösung), Umwandlung der 3-Hydroxy- in eine 1-3C-Alkoxygruppe (z.B. durch Alkylierung mit 1-3C-Alkyliodid in basischem Medium) und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt. In einer bevorzugten Alternative werden die Verbindungen ausgehend von bekannten oder auf bekanntem Wege herstellbaren

3-Hydroxy-2-alkyl- bzw. 3-Hydroxy-2,5-dialkyl-pyridinen durch Alkylierung der Hydroxygruppe (z.B. mit Kaliumhydroxid und Methyliodid in Dimethylsulfoxid), N-Oxidation (z.B. mit 30%igem Wasserstoffperoxid), Nitrierung in 4-Position (z.B. mit Salpetersäure), Austausch der Nitrogruppe gegen die 1-3C-Alkoxygruppe (z.B. durch Umsetzung mit Alkalialkoxid), Umwandlung in das 2-Acetoxymethylpyridin (z.B. mit heißem Essigsäureanhydrid), Verseifung (z.B. mit verdünnter Natronlauge) zur Hydroxymethylgruppe und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt.

2. Verbindungen III mit R3 und R4 = 1-3C-Alkoxy und R2 = Wasserstoff.

Diese Verbindungen werden z.B. ausgehend vom bekannten 5-Hydroxy-2-methylpyridinen durch Alkylierung der Hydroxygruppe (z.B. mit 1-3C-Alkyliodid und Kaliumhydroxid in Dimethylsulfoxid), N-Oxidation (z.B. mit 30 %-igem Wasserstoffperoxid), Nitrierung in 4-Position (z.B. mit Nitriersäure), Austausch der Nitrogruppe gegen die 1-3C-Alkoxygruppe (z.B. durch Umsetzung mit Alkali-alkoxid), Umwandlung in das 2-Acetoxymethylpyridin (z.B. mit heißem Essigsäureanhydrid), Verseifung (z.B. mit verdünnter Natronlauge) zur 2-Hydroxymethylgruppe und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt.

3. Verbindungen III mit R3 und R4 = 1-3C-Alkoxy und R2 = 1-3C-Alkyl.

Diese Verbindungen werden z.B. ausgehend von bekannten oder auf bekanntem Weg herstellbaren 2-Methyl-3-alkyl-4-alkoxypyridinen (siehe z.B. EP-A 0 080 602) durch N-Oxidation (z.B. mit 30 %-igem Wasserstoffperoxid), gezielte Acetoxylierung und anschließende Verseifung in 5-Postition (z.B. mit Essigsäureanhydrid und anschließend Natronlauge), Alkylierung der 5-Hydroxygruppe (z.B. mit 1-3C-Alkyliodid und Natronlauge in Dimethylsulfoxid), N-Oxidation (z.B. mit m-Chlorperoxibenzoesäure), Umwandlung in das 2-Acetoxymethylpyridin (z.B. mit heißem Essigsäureanhydrid), Verseifung (z.B. mit verdünnter Natronlauge) zur 2-Hydroxymethylgruppe und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt.

Welche Reaktionsbedingungen (Temperaturen, Reaktionszeiten, Lösungsmittel etc.) bei den oben skizzierten Synthesewegen für die Herstellung der Verbindungen III im einzelnen erforderlich sind, ist dem Fachmann aufgrund seines Fachwissens geläufig. Die genaue Herstellung einzelner Vertreter der Verbindungen III ist in den Beispielen angegeben. Die Herstellung weiterer Vertreter erfolgt in analoger Weise.

Verbindungen der Formel III, worin R3 einen 1-3C-Alkoxyrest darstellt, einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere einen 1-3C-Alklyrest darstellt sind neu und ebenfalls Gegenstand der Erfindung.

Die Verbindungen V, VII und XII werden beispielsweise ausgehend von den Verbindungen III auf für den Fachmann bekannten Wegen hergestellt.

Die folgenden Beispiele erläutern die Erfindung näher, ohne sie einzuschränken. Die in den Beispielen namentlich aufgeführten Verbindungen der Formel I sowie Salze dieser Verbindungen sind bevorzugter Gegenstand der Erfindung. In den Beispielen bedeutet F. Schmelzpunkt, Zers. steht für Zersetzung, Sdp. steht für Siedepunkt.

Beispiele

1. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol

Zu einer Lösung von 1,64 g 2-Mercapto-5-trifluormethoxy-1H-benzimidazol in 40 ml Ethanol und 20 ml 1n Natronlauge werden 1,57 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid zugegeben, 2 Stunden bei 20°C und anschließend noch 1 Stunde bei 40°C gerührt, Ethanol am Rotationsverdampfer (1 kPa/40°C) abdestilliert, der dabei ausfallende farblose Niederschlag über eine Nutsche filtriert, mit 1n Natronlauge und Wasser nachgewaschen und getrocknet. Man erhält 2,15 g (79 % d.Th.) der Titelverbindung vom F. 92-93°C.

Analog erhält man
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (Öl),
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (F. 159-160°C) und
5-Difluormethoxy-6-fluor-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol
durch Umsetzung von
5-Chlordifluormethoxy-2-mercapto-1H-benzimidazol,
5-Difluormethoxy-2-mercapto-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-mercapto-1H-benzimidazol,
5-Difluormethoxy-2-mercapto-6-methoxy-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2-mercapto-1H-benzimidazol
mit
2-Chlormethyl-4,5-dimethoxypyridiniumchlorid.

2. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol

Zu einer Lösung von 0,36 g 2-[4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol in 10 ml Methylenchlorid tropft man bei -50°C 5,5 ml einer 0,2m Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid zu und rührt weitere 30 Minuten bei der angegebenen Temperatur. Nach Zugabe von 0,3 ml Triethylamin wird die kalte Reaktionsmischung in 10 ml 5 %-ige Natriumthiosulfat- und 10 ml 5 %-ige Natriumcarbonatlösung eingerührt, nach Phasentrennung wird noch dreimal mit 10 ml Methylenchlorid extrahiert, die vereinigten organischen Phasen werden einmal mit 5 ml einer 5 %igen Natriumthiosulfatlösung gewaschen, getrocknet, vom Trockenmittel (Magnesiumsulfat) filtriert und eingeengt. Der Rückstand wird mit Diisopropylether zur Kristallisation gebracht und anschließend aus Methylenchlorid/Diisopropylether umgefällt. Man erhält 0,27 g (72 % d.Th.) der Titelverbindung als farblosen Feststoff vom F. 159-61°C (Zers.).

Analog erhält man
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol [F. 159°C (Zers.)],
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2,2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol
durch Oxidation der weiteren Sulfide des Beispiels 1 mit m-Chlorperoxibenzoesäure.

3. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 1,07 g 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit

0,90 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid in 15 ml Ethanol unter Zusatz von 17 ml 0,5 n Natronlauge 1,40 g der Titelverbindung als gelbes Öl. Umkristallisation aus Petrolether liefert das Produkt in Form farbloser Kristalle vom F. 125-127°C. Ausbeute: 1,20 g (72% d.Th).

4. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 2 angegebenen Arbeitsweise erhält man durch Oxidation von 0,76 g 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit 19 ml einer 0,1 m Lösung von m-Chlorperoxibenzoesäure in 30 ml Methylenchlorid bei -40°C nach Extraktion eine Lösung des Produktes in Methylenchlorid. Nach Trocknung über Magnesiumsulfat wird vom Trockenmittel filtriert, eingeengt und der Rückstand aus Methylenchlorid/Diisopropylether kristallisiert. Man erhält 0,64 g (82% d.Th.) der Titelverbindung in Form farbloser Kristalle vom F. 160-162°C (Zers.).

5. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol

1,0 g 2-Mercapto-5-(2,2,2-trifluorethoxy)-1H-benzimidazol werden in 15 ml Ethanol und 8,5 ml 1n Natronlauge gelöst, mit 0,90 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid versetzt und 20 Stunden gerührt. Nach Zugabe von 30 ml Wasser extrahiert man dreimal mit je 30 ml Methylenchlorid, wäscht die Methylenchloridphase einmal mit 5 ml 0,1 n Natronlauge, trocknet die vereinigten organischen Phasen über Magnesiumsulfat und engt nach Filtration des Trockenmittels vollständig ein. Man erhält 1,51 g (94% d.Th.) der Titelverbindung als amorphen, festen Rückstand vom F. 55-57°C.

6. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol

0,8 g 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol werden in 15 ml Dioxan und 2,5 ml 1 n Natronlauge gelöst. Innerhalb von 2 Stunden wird ein Gemisch von 3 ml 8-prozentiger Natriumhypochloritlösung und 3,5 ml 1n Natronlauge unter Kühlung auf 0-5°C zuge-

tropft. Nach Zugabe von 5 ml 5%iger Natriumthiosulfatlösung wird zur Trockene eingeengt, der Rückstand in Wasser aufgenommen und mit Phosphatpuffer auf pH7 gestellt. Man filtriert vom ausgefallenen Feststoff, trocknet und kristallisiert aus Essigester/Diisopropylether um. Man erhält 0,45 g (55% d.Th.) der Titelverbindung als farblose Kristalle vom F. 142-143°C (Zers.).

7. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 1,07 g 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit 0,96 g 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in 12 ml Ethanol unter Zusatz von 17 ml 0,5 n Natronlauge 1,46 g (83% d.Th.) der Titelverbindung vom F. 127-128°C (farbloses Pulver).

8. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 2 angegebenen Arbeitsweise erhält man durch Oxidation von 0,99 g 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit 12 ml einer 0,2 m Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid bei -40°C und einer Reaktionszeit von 1,5 Stunden 0,8 g eines blaßgelben Öls. Zweimalige Umkristallisation aus Methylenchlorid/Diisopropylether liefert 0,30 g (34% d.Th.) der Titelverbindung in Form farbloser Kristalle vom F. 125°C (Zers.).

9. 5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 0,38 g (2 mMol) 5-Difluormethoxy-2-mercapto-1H-benzimidazol mit 0,48 g (2 mMol) 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in 10 ml Ethanol unter Zusatz von 8,8 ml 1n Natronlauge nach zwei Stunden bei 50°C 0,64 g (84% d.Th.) der Titelverbindung vom F. 100-102°C (farbloses Kristallpulver).

10. 2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Zu einer Lösung von 0,46 g (1,7 mMol) 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol in 10 ml Ethanol, 10 ml Wasser und 1,8 ml 2n Natronlauge werden 0,38 g (1,7 mMol) 2-Chlormethyl-3,4-dimethoxy-pyridiniumchlorid zugegeben; nach einer Stunde Rühren bei 20°C werden erneut 10 ml Wasser zugetropft; anschließend wird bei 20°C nochmals vier Stunden gerührt. Man filtriert vom ausgefallenen Feststoff, wäscht mit 0,01 n Natronlauge und anschließend mit Wasser neutral und trocknet bis zur Gewichtskonstanz. Man erhält 0,63 g (90% d.Th.) der Titelverbindung als farbloses Kristallpulver vom F. 98-102°C.

Analog erhält man
5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (F. 104-108°C) und
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (F. 137-138°C) durch Umsetzung von
5-Difluormethoxy-2-mercapto-1H-benzimidazol und
5-Difluormethoxy-6-methoxy-2-mercapto-1H-benzimidazol mit
2-Chlormethyl-3,4-dimethoxypyriniumchlorid.

11. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 1,15 g 2-Mercapto-5-trifluormethoxy-1H-benzimidazol mit 1,20 g 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in 20 ml Isopropanol unter Zusatz von 20,5 ml 0,5n Natronlauge 1,40 g (70 % d.Th) der Titelverbindung. Umkristallisation aus Diisopropylether/Petrolether liefert ein Produkt vom F. 94-97°C.

Analog erhält man
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,

5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol
durch Umsetzung von
2-Mercapto-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Chlordifluormethoxy-2-mercapto-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-mercapto-1H-benzimidazol,
5-Difluormethoxy-2-mercapto-6-methoxy-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2-mercapto-1H-benzimidazol
mit
2-Chlormethyl-4,5-dimethoxy-3-methyl-pyridiniumchlorid.

12. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol

Nach der in Beispiel 2 angegebenen Arbeitsweise erhält man durch Oxidation von 0,24 g 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol mit 3,3 ml einer 0,2m Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid bei -50°C und Umfällung aus Methylenchlorid/Diisopropylether 0,19 g (76 % d.Th.) der Titelverbindung als farbloses Pulver; 158-159°C Zers.

Analog erhält man
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol [F. 133-135 (Zers.)],
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methyl-

sulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-fluor-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methyl-sulfinyl]-1H-benzimidazol
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol [F. 117-119°C (Zers.)] und
5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol [F. 136°C (Zers.)]
durch Oxidation der Sulfide der obigen Beispiele 9 bis 11 mit m-Chlorperoxibenzoesäure.

13. 2,2-Difluor-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Zu einer Lösung von 0,92g 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol in 10 ml Ethanol und 10 ml 1n Natronlauge werden 0,96 g 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid zugegeben. Man rührt die gelbe Reaktionsmischung 1 Stunde bei 20°C, setzt nochmals 10 ml Wasser zu, wobei ein farbloser Feststoff ausfällt, rührt weitere 5 Stunden, filtriert, wäscht mit 1n Natronlauge und Wasser nach und trocknet bis zur Gewichtskonstanz. Das amorphe Pulver wird aus Methylenchlorid/Diisopropylether umkristallisiert. Man erhält 1,5 g (93 % d.Th.) der Titelverbindung in Form farbloser Kristalle vom F. 160-61°C.

Analog erhält man
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol und
6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol
durch Umsetzung von
6,6,7-Trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol bzw.
6,7-Dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol mit
2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid.

14. 2,2-Difluor-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Zu einer auf -40°C gekühlten Suspension von 0,80 g 2,2-Difluor-6[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol in 10 ml Methylenchlorid tropft man innerhalb von 10 Minuten 21 ml einer 0,1n Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid zu. Man rührt weitere 20 Minuten und läßt die Temperatur dabei auf -20°C ansteigen, setzt 0,5 ml Triethylamin zu und gießt das Reaktionsgemisch in 40 ml einer jeweils 5 %-igen Natriumthiosulfat- und 5 %-igen Natriumcarbonatlösung ein. Nach Phasentrennung wird die Wasserphase noch zweimal mit je 20 ml Methylenchlorid extrahiert; die vereinigten organischen Phasen werden mit einem Gemisch aus jeweils 5 ml Natriumthiosulfat- und Natriumcarbonatlösung gewaschen, getrocknet und eingeengt. Der Rückstand wird aus Methylenchlorid/Diisopropylether umkristallisiert. Man erhält 0,62 g (75 % d.Th.) der Titelverbindung; Zers. 189-90°C.

Analog erhält man
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol und
6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol
durch Oxidation der unter Beispiel 13 genannten weiteren Sulfide mit m-Chlorperoxibenzoesäure.

15. 6-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol

Nach der in Beispiel 13 beschriebenen Arbeitsweise erhält man durch Umsetzung von 0,85 g 5H-[1,3]-dioxolo[4,5-f]-benzimidazol-6-thiol mit 0,98 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid in 10 ml Ethanol und 10 ml Wasser unter Zusatz von 8,5 ml 1n Natronlauge nach einer Reaktionszeit von 20 Stunden und nach Einengen des Lösungsmittels im Vakumm auf ein Volumen von 10 ml einen bräunlichen Feststoff. Man löst das Rohprodukt in 30 ml

Methylenchlorid, klärt mit Bleicherde (z. B. Tonsil®), engt ein, kristallisiert durch Zugabe von Diisopropylether und kocht den nun blaßgelben Feststoff in 5 ml Methanol aus. Man erhält 0,90 g (60% d.Th.) der Titelverbindung als farblosen Feststoff vom F. 198-200°C.

16. 6-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol

Nach der in Beispiel 14 beschriebenen Arbeitsweise erhält man durch Oxidation von 0,7 g 6-[4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]-benzimidazol mit 23 ml einer 0,1 m Lösung von m-Chlorperoxibenzoesäure nach Umkristallisation aus Diethylether 0,27 g der Titelverbindung in Form farbloser Kristalle vom F. 199°C (Zers.).

17. 2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol

Nach der in Beispiel 13 angegebenen Arbeitsweise erhält man durch Umsetzung von 0,69 g (3 mMol) 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]-benzimidazol-6-thiol mit 0,67 g (3 mMol) 2-Chlormethyl-3,4-dimethoxypyridiniumchlorid in einem Gemisch von 10 ml Ethanol und 10 ml Wasser unter Zusatz von 3,3 ml 2n Natronlauge nach 10 Stunden Reaktionszeit 1,05 g (92% d.Th.) der Titelverbindung als feinkristallines, farbloses Pulver vom F. 185-187°C.

Analog erhält man
6-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol (F. 155-157°C)
durch Umsetzung von
5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol
mit
2-Chlormethyl-3,4-dimethoxypyridiniumchlorid.

18. 6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol

0,78 g (4 mMol) 5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol werden mit 0,95 g (4 mMol) 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in

30 ml Isopropanol 15 Stunden unter Rückfluß zum Sieden erhitzt. Man filtriert vom ausgefallenen Feststoff, rührt mit Isopropanol aus, filtriert erneut und trocknet bis zur Gewichtskonstanz. Man erhält 1,0 g (59% d.Th.) des Dihydrochlorids der Titelverbindung als farblosen Feststoff vom F. 206°C (Zers.).

19. 2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Zu einer auf 50°C erwärmten Lösung von 0,69 g 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol und 0,67 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid in 9 ml Ethanol und 4 ml Wasser tropft man innerhalb einer Minute 6,3 ml 1n Natronlauge zu. Beim Abkühlen der klaren Reaktionsmischung auf 20°C fällt nach kurzer Zeit ein farbloser Niederschlag aus. Man rührt weitere 5 Stunden bei 20°C, saugt über eine Nutsche ab, wäscht mit 1n Natronlauge und Wasser nach und trocknet bis zur Gewichtskonstanz. Der beige Feststoff wird in 10 ml Methylenchlorid gelöst, von unlöslichen Bestandteilen filtriert, das Filtrat eingeengt und durch Zugabe von Diisopropylether und nach Abkühlung zur Kristallisation gebracht. Man erhält 1,02 g (90 % d.Th.) der Titelverbindung vom F. 189-91°C.

Analog erhält man
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol und
6,7-Dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino-[2,3-f]benzimidazol
durch Umsetzung von
6,6,7-Trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol, bzw.
6,7-Dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol
mit
2-Chlormethyl-4,5-dimethoxy-pyridiniumchlorid.

20. 2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

0,76 g 2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol werden in 10 ml Dioxan und 2 ml 1n Natronlauge gelöst. Unter Eiskühlung tropft man zuerst eine äquimolare Menge einer titrierten wäßrigen Natriumhypochloritlösung, die mit 1 Mol pro Liter Natronlauge versetzt ist, zu, und setzt nach einer Stunde nochmals 1 Äquivalent und nach 3 Stunden die halbe äquimolare Menge Natriumhypochlorit zur Erreichung einer vollständigen Umsetzung zu. Nach 4 Stunden Reaktionszeit werden 5 ml 5 %-ige Natriumthiosulfatlösung und weitere 25 ml Dioxan zugegeben, die obere Dioxanphase abgetrennt, einmal mit 5 ml Natriumthiosulfatlösung gewaschen und am Rotationsverdampfer eingeengt. Der ölige Rückstand wird in 20 ml Wasser und 10 ml Essigsäureethylester gelöst und mit ca. 100 ml einer Pufferlösung vom pH 6,8 auf pH 7 gestellt. Der ausgefallene Feststoff wird über eine Nutsche abgesaugt, mit Wasser gewaschen, bei 0°C mit Aceton ausgerührt und getrocknet. Man erhält 0,7 g (87 % d.Th.) der Titelverbindung in Form farbloser Kristalle; Zers. bei 211-213°C.

Analog erhält man

2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]-benzimidazol [F. 177-178°C (Zers.)]

6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]-benzimidazol,

6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol [F. 170-171°C (Zers.)],

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol und

6,7-Dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol

durch Oxidation der in den Beispielen 17 bis 19 genannten weiteren Sulfide mit Natriumhypochloritlösung.

21. 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

a) 55 g 1-Nitro-4-(1,1,2,2-tetrafluorethoxy)benzol werden in 300 ml Ethanol an 0,5 g 10%iger Palladiumkohle in einer Umlaufhydrierungsapparatur unter Atmosphärendruck 1 h bei 20-45°C hydriert, der Katalysator abfiltriert und die Lösung bei 40°C im Vakuum eingeengt. Man verdünnt das 4-(1,1,2,2-tetrafluorethoxy)anilin mit 100 ml Eisessig und tropft 23 ml Essigsäureanhydrid bei Raumtemperatur zu, versetzt nach 30 Min. mit 2 ml Wasser, engt nach kurzer Zeit die Lösung bei 50°C im Vakuum ein und versetzt mit 500 ml Eiswasser. Man erhält 56 g (97%) N-[4-(1,1,2,2-tetrafluorethoxy)phenyl]-acetamid vom Schmp. 121-122°C.

b) Man löst 55 g der vorstehenden Verbindung in 380 ml Dichlormethan, tropft 55 ml 100%ige Salpetersäure in 10 Min. bei Raumtemperatur zu und rührt noch 6 h. Die organische Lösung wird dann mit wäßriger Natriumcarbonatlösung und Wasser gewaschen, mit Magnesiumsulfat getrocknet und eingeengt. Man erhält 65 g (100%) N-[2-Nitro-4-(1,1,2,2-tetrafluorethoxy)phenyl]-acetamid vom Schmp. 80-81°C (aus Cyclohexan).

c) Man löst 63 g vorstehender Verbindung in 450 ml Methanol, tropft bei Raumtemperatur 106 ml 6 m Natronlauge zu, kühlt im Eisbad und fällt durch Zutropfen von 900 ml Wasser 53 g (98%) 2-Nitro-4-(1,1,2,2-tetrafluorethoxy)-anilin (Schmp. 85-86°C).

d) 33 g vorstehender Verbindung werden in ca. 600 ml Isopropanol an 1 g 10%iger Palladiumkohle in einer Umlaufhydrierungsapparatur drucklos bei Raumtemperatur hydriert. Man saugt den Katalysator ab und fällt mit 4 m Chlorwasserstoff in Ether 34 g (89%) 4-(1,1,2,2-Tetrafluorethoxy)-1,2-phenylendiamin-dihydrochlorid vom Schmp. 275-276°C (Zersetzung).

e) 33 g vorstehender Verbindung werden mit 330 ml Ethanol, 60 ml Wasser, 8,9 g Natriumhydroxid und 23 g Kalium-O-ethyldithiocarbonat (umkristallisiert aus Isopropanol) versetzt und 15 h unter Rückfluß zum Sieden erhitzt. Man versetzt mit 1,2 l Eiswasser, stellt mit Natronlau-

ge auf pH 13-14, klärt mit Aktivkohle und fällt mit verdünnter Salzsäure bis pH 3,5. Man erhält 27 g (91%) der Titelverbindung vom Schmp. 316-319°C (aus Isopropanol).

22. 2-Mercapto-5-trifluormethoxy-1H-benzimidazol

Analog Beispiel 21e) erhält man durch Umsetzen von 4-Trifluormethoxy-1,2-phenylendiamin-dihydrochlorid (vgl. C.A. 55, 23408d, 1961) mit Kalium-O-ethyldithiocarbonat und Natronlauge in Ethanol in 75 % Ausbeute die Titelverbindung vom Schmp. 305-307°C (Zersetzung, aus Toluol).

23. 2-Mercapto-5-(2,2,2-trifluorethoxy)-1H-benzimidazol

a) 50 g 1-(2,2,2-Trifluorethoxy)-4-nitrobenzol (Synthesis 1980, Seite 727) werden analog Beispiel 21a) hydriert und acetyliert. Man erhält 50 g (95 %) N-[4-(2,2,2-Trifluorethoxy)phenyl]acetamid (Schmp. 140-141°C).

b) Man rührt 42 g voranstehender Verbindung mit 9,7 ml 100% Salpetersäure in 290 ml Eisessig 18 h bei Raumtemperatur und fällt mit Wasser. Man erhält 47 g (94%) N-[2-Nitro-4-(2,2,2-trifluorethoxy)phenyl]-acetamid (Schmp. 117-118°C).

c) Man hydrolysiert 47 g voranstehender Verbindung analog Beispiel 21c und erhält 38,7 g (97%) 2-Nitro-4-(2,2,2-trifluorethoxy)-anilin (Schmp. 84-85°C).

d) Man hydriert 37 g voranstehender Verbindung analog Beispiel 21d) und erhält 41 g (94%) 4-(2,2,2-Trifluorethoxy)-1,2-phenylendiamin-dihydrochlorid vom Schmp. 230-233°C (Zersetzung).

e) Analog Beispiel 21e) erhält man aus 36 g voranstehender Verbindung 30 g (94%) der Titelverbindung (Schmp. 288-290°C).

24. 5-Chlordifluormethoxy-2-merkapto-1H-benzimidazol

a) 10,0 g N-[4-(Chlordifluormethoxy)phenyl]-acetamid (Schmp. 101-103°C, aus 4-Chlordifluormethoxyanilin und Essigsäureanhydrid) und 12,3 ml 100% Salpetersäure werden in 80 ml Dichlormethan 4 h bei 20°C gerührt. Man

neutralisiert mit wäßriger Kaliumhydrogencarbonatlösung, engt die organische Schicht ein und erhält 11,4 g (96%) N-(4-Chlordifluormethoxy-2-nitrophenyl)-acetamid (Schmp. 89-91°C).

b) Man tropft bei 5°C zu 10,5 g voranstehender Verbindung in 200 ml Methanol 8,6 ml einer 30%igen Lösung von Natriummethylat in Methanol, rührt 2 h ohne Kühlung, versetzt mit Eiswasser, stellt auf pH 8 und erhält 8,7 g (97%) 4-Chlordifluormethoxy-2-nitroanilin (Schmp. 40-42°C).

c) Man hydriert 8,5 g voranstehender Verbindung an 0,8 g 10%iger Palladiumkohle drucklos in 200 ml Methanol, versetzt mit konzentrierter Salzsäure, filtriert, engt ein und verrührt mit Diisopropylether. Man erhält 8,5 g (97%) 4-Chlordifluormethoxy-1,2-phenylendiamin-dihydrochlorid.

d) Aus 8,5 g voranstehender Verbindung werden analog Beispiel 21e) 6,3 g (72%) der Titelverbindung vom Schmp. 268-270°C (Zersetzung) erhalten.

25. 5-Difluormethoxy-2-merkapto-1H-benzimidazol

a) 11,8 g N-(4-Difluormethoxyphenyl)-acetamid [L.M.Jagupol'skii et al., J.General Chemistry (USSR) 39, 190 (1969)] werden in 200 ml Dichlormethan mit 12,1 ml 100%iger Salzsäure 1,5 h bei Raumtemperatur gerührt. Analog Beispiel 21b) erhält man 13,3 g (92%) N-[(4-Difluormethoxy--2-nitro)phenyl]-acetamid (Schmp. 71-73°C).

b) Analog Beispiel 24b erhält man daraus in 96%iger Ausbeute 4-Difluormethoxy-2-nitroanilin (Schmp. 68-70°C).

c) Analog Beispiel 24c erhält man in 94% Ausbeute 4-Difluormethoxy-1,2-phenylendiamin-dihydrochlorid.

d) Analog Beispiel 24e erhält man in 78% Ausbeute die Titelverbindung vom Schmp. 250-252°C (aus Isopropanol).

26. 5,6-Bis(difluormethoxy)-2-merkapto-1H-benzimidazol

a) In eine Lösung von 100 g Brenzkatechin, 220 g Natriumhydroxid und 60 g Natriumdithionit in 500 ml Wasser und 400 ml Dioxan leitet man bei 50-55°C 275 g Chlordifluormethan analog L.N. Sedova et al., Zh. Org. Khim. 6, 568 (1970) ein. Man erhält nach Destillation bei 61-62°C/1,0-1,1kPa eine Mischung von 1,2-Bis(difluormethoxy)benzol und 2-Difluormethoxyphenol, die durch Chromatographie an Kieselgel mittels Cyclohexan/Essigsäureethylester (4:1) getrennt werden.

b) Eine Lösung von 15 g 1,2-Bis(difluormethoxy)benzol und 15 ml 100 %iger Salpetersäure in 150 ml Dichlormethan wird 7 h bei Raumtemperatur gerührt. Man neutralisiert mit Kaliumhydrogencarbonatlösung, trennt die organische Schicht ab und chromatographiert an Kieselgel mittels Cyclohexan/Essigsäureethylester (4:1). Man erhält 1,2-Bis(difluormethoxy)-4-nitrobenzol. Dieses hydriert und acetyliert man analog Beispiel 21a zu N-[3,4-Bis(difluormethoxy)phenyl]acetamid (Schmp. 81-83°C). Analog Beispiel 21 erhält man ferner N-[4,5-Bis(difluormethoxy)-2-nitrophenyl]acetamid (Schmp. 65-67°C), N-[4,5-Bis(difluormethoxy)-2-nitro]anilin (Schmp. 107-109°C), 4,5-Bis(difluormethoxy)-1,2-phenylendiamin-dihydrochlorid und die Titelverbindung vom Schmp. 285-287°C (Zersetzung; aus Isopropanol).

27. 5-Difluormethoxy-2-merkapto-6-methoxy-1H-benzimidazol

a) In eine Lösung von 55,5 g Guajacol und 130 g Natriumhydroxid in 300 ml Wasser und 300 ml Dioxan werden bei 60°C ca. 58 g Chlordifluormethan eingeleitet. Man filtriert die Mischung bei 10°C, trennt die organische Schicht ab, trocknet mit wasserfreiem Kaliumcarbonat und destilliert. Man erhält 56 g (73%) 1-Difluormethoxy-2-methoxybenzol vom Siedepunkt 75-76°C/0,9kPa.

b) Zu einer Lösung von 47 g voranstehender Verbindung in 230 ml Dichlormethan wird bei 0-5°C eine Lösung von 33,8 ml 100%iger Salpetersäure in 90 ml Dichlormethan getropft, nach 30 Min. mit 250 ml Eiswasser versetzt und mit Kaliumhydrogencarbonat neutralisiert. Die getrocknete organische Phase wird im Vakuum eingeengt und der Rückstand aus Cyclohexan

umkristallisiert. Man erhält 53 g (90%) 1-Difluormethoxy-2-methoxy-5-nitrobenzol (Schmp. 48-49°C). Dieses wird analog Beispiel 21a hydriert und acetyliert. Man erhält in 90% Ausbeute N-(3-Difluormethoxy-4-methoxyphenyl)acetamid (Schmp. 129-130°C).

c) 46 g voranstehender Verbindung werden mit 33 ml 100%iger Salpetersäure in Dichlormethan analog voranstehender Vorschrift nitriert. Man erhält in 99% Ausbeute N-(5-Difluormethoxy-4-methoxy-2-nitrophenyl)acetamid (Schmp. 116-117°C).

d) 54 g voranstehender Verbindung werden in 810 ml Methanol 1 h mit 44,8 ml 30%iger methanolischer Natriummethylatlösung bei Raumtemperatur gerührt. Man engt im Vakuum ein, versetzt mit Eiswasser und Eisessig bis pH 8 und erhält in 99% Ausbeute 5-Difluormethoxy-4-methoxy-2-nitroanilin (Schmp. 144-145°C).

e) 25 g voranstehender Verbindung werden in 300 ml Methanol an 1,25 g 10%iger Palladiumkohle entsprechend Beispiel 21d hydriert. Man erhält 26 g (88%) 3-Difluormethoxy-4-methoxy-1,2-phenylendiamindihydrochlorid vom Schmp. 218-220°C (Zersetzung).

f) 25 g voranstehender Verbindung werden mit 19 g Kalium-O-ethyldithiocarbonat entsprechend Beispiel 21e umgesetzt. Man erhält 20 g (89%) der Titelverbindung vom Schmp. 280-282°C (Zersetzung; aus Isopropanol).

28. 5-Difluormethoxy-6-fluor-2-merkapto-1H-benzimidazol

a) Analog Beispiel 27a erhält man aus 2-Fluorphenol und Chlordifluormethan 1-Difluormethoxy-2-fluorbenzol (Sdp. 76°C/10 kPa; n_D^{20} = 1,4340)

b) Zu 30 g der voranstehenden Verbindung in 300 ml Dichlormethan tropft man bei -10°C 38,4 ml 100%ige Salpetersäure, rührt 1 h bei -10°C und 2,5 h bei 0°C. Man versetzt mit Eiswasser, stellt neutral und chromatographiert über Kieselgel mit Essigester/Cyclohexan (4:1). Man erhält 34 g eines Öles, das ca. 90% 1-Difluormethoxy-2-fluor-4-nitrobenzol und 10% 1-Difluormethoxy-2-fluor-5-nitrobenzol (NMR-Spektrum) enthält.

c) 30 g voranstehender Mischung wird analog Beispiel 21a hydriert und acetyliert. Nach Umkristallisieren aus Toluol erhält man 21 g (65%) N-(4-Difluormethoxy-3-fluorphenyl)acetamid vom Schmp. 112-113°C.

d) Zu 20 g voranstehender Verbindung in 200 ml Dichlormethan werden bei 20°C 22,5 ml 100%ige Salpetersäure in 30 Min. zugetropft und 15 h bei Raumtemperatur nachgerührt. Analog Beispiel 27c erhält man in 89% Ausbeute N-(4-Difluormethoxy-5-fluor-2-nitrophenyl)acetamid vom Schmp. 72-74°C (aus Cyclohexan). Durch mehrstündiges Rühren mit 1 m Salzsäure in Methanol bei 60°C erhält man in 95% Ausbeute 4-Difluormethoxy-5-fluor-2-nitroanilin vom Schmp. 95-97,5°C und analog Beispiel 27e) in 85% Ausbeute 4-Difluormethoxy-5-fluor-1,2-phenylendiamin-dihydrochlorid. Zersetzung ab 210°C.

e) 15 g voranstehender Verbindung werden mit 11,8 g Kalium-O-ethyldithiocarbonat entsprechend Beispiel 21e umgesetzt. Man erhält 11,1 g (84%) der Titelverbindung vom Schmp. 275-276°C (Zersetzung, aus Isopropanol).

29. 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol

a) Man hydriert 30 g 4-Amino-2,2-difluor-5-nitro-1,3-benzodioxol in 300 ml Methanol an 0,5 g 10%iger Palladiumkohle in einer Umlaufhydrierungsappatur bei Atmosphärendruck und Raumtemperatur, versetzt mit 2,5 Äquivalenten methanolischer Chlorwasserstofflösung, filtriert, engt die Lösung im Vakuum ein, versetzt mit Isopropanol und Ether und erhält 35 g (97 %) 2,2-Difluor-1,3-benzodioxol-4,5-diamin-dihydrochlorid vom Schmp. 232-233°C (Zersetzung).

b) Man versetzt 30 g voranstehender Verbindung in 300 ml Ethanol mit 24 g Kalium-O-ethyldithiocarbonat (umkristallisiert aus Isopropanol) und 9,2 g Natriumhydroxid in 55 ml Wasser und erhitzt 15 h unter Rückfluß zum Sieden. Man gießt auf 1,5 l Wasser, stellt mit Natronlauge auf pH 14, klärt mit Aktivkohle, fällt mit konzentrierter Salzsäure in der Wärme und saugt den Niederschlag in der Kälte ab. Man erhält 24 g (91 %) der Titelverbindung vom Schmp. 365-370°C (Zersetzung).

30. 6,6,7-Trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol

a) Zu 50 g 2,2,3-Trifluor-2,3-dihydro-1,4-benzodioxin wird bei 5°C in 1 h eine Mischung von 39,5 ml 69%iger Salpetersäure und 46 ml 97%iger Schwefelsäure getropft. Man rührt 1 h bei 10°C, 1 h bei 20°C und 5 Min. bei 40°C und gießt auf 200 g Eis, extrahiert mit Dichlormethan, wäscht mit Wasser, trocknet mit Magnesiumsulfat und destilliert im Vakuum. Man erhält 58 g (94 %) einer Mischung von 2,2,3-Trifluor-2,3-dihydro-6-nitro-(und 7-nitro)-1,4-benzodioxin vom Sdp. 68,5°C (0,15 mbar) und n_D^{20} 1,5080. Ein Gaschromatogramm mit einer 10 m Fused Silica Säule (Fa. Chrompack) zeigt zwei Peaks im Verhältnis 2:3.

b) Man hydriert 35 g des Isomerengemisches in 400 ml Ethanol an 3 g 10 %-iger Palladiumkohle bei Atmosphärendruck und 20-30°C in einer Umlaufhydrierungsapparatur, filtriert und engt im Vakuum ein. Man erhält 30,5 g (100 %) einer flüssigen Mischung von 6-Amino-(und 7-Amino)-2,2,3-trifluor-2,3-dihydro-1,4-benzodioxin.

c) Zu 28 g der voranstehenden Isomerenmischung tropft man bei 20-30°C eine Mischung aus 15,3 g Essisäureanhydrid und 15 ml Eisessig, rührt 30 Min. bei 30°C, setzt 1 ml Wasser zu, rührt 30 Min. bei 30°C und destilliert das Lösungsmittel im Vakuum ab. Durch Umkristallisation aus Toluol erhält man 19 g einer Fraktion des Gemisches der isomeren Acetaminoderivate vom Schmp. 128-133°C.

d) Zu 17 g des Isomerengemisches der Acetaminoderivate, suspendiert in 200 ml Dichlormethan, tropft man bei -6° bis -8°C 14 ml 100%ige Salpetersäure, gelöst in 60 ml Dichlormethan, rührt 2 h bei 0°C und dann über Nacht bei Raumtemperatur. Man gießt auf 110 g Eis, trennt die organische Phase ab, wäscht mit Wasser und engt im Vakuum ein. Der Rückstand (19,8 g) wird aus 20 ml Ethanol umkristallisiert. Man erhält 15,5 g einer Mischung von 6-Acetamino-2,2,3-trifluor-2,3-dihydro-7-nitro-1,4-benzodioxin und 7-Acetamino-2,2,3-trifluor-2,3-dihydro-6-nitro-1,4-benzodioxin.

e) Man suspendiert 14,5 g des voranstehenden Produktgemisches in 80 ml Methanol und tropft unter Erwärmung auf 30°C 30 ml 5m Natronlauge zu. Man rührt noch 0,5 h bei Raumtemperatur, gießt auf 200 g Eis und erhält 11,7 g einer Mischung von 6-Amino-2,2,3-trifluor-2,3-dihydro-7-nitro-1,4-benzodioxin und 7-Amino-2,2,3-trifluor-2,3-dihydro-6-nitro-1,4-benzodioxin. Eine Probe wird an einer Kieselgelsäule mit Cyclohexan/Essigsäureethylester (4:1) in zwei reine Isomeren mit den Schmelzpunkten 110,5-111,5°C und 120-121°C getrennt, deren NMR-Spektren an einem 60 MHz-Gerät in Deuterochloroform praktisch identisch sind.

f) 10,9 g des voranstehenden Isomerengemisches werden in 300 ml Methanol bei Raumtemperatur und Atmosphärendruck an 1 g 10%iger Palladiumkohle in 2,5 h hydriert. Man setzt 30 ml 4 m Chlorwasserstoff in Methanol zu, filtriert, engt im Vakuum ein und verrührt mit 100 ml Ether. Man erhält 12,6 g (98 %) 2,2,3-Trifluor-2,3-dihydro-1,4-benzodioxin-6,7-diamin-dihydrochlorid (Schmp. >250°C).

g) 12 g voranstehender Verbindung und 8,5 g Kalium-O-ethyldithiocarbonat (umkristallisiert aus Isopropanol) werden in 120 ml Ethanol mit 20,5 ml 4 m wäßriger Kaliumhydroxidlösung versetzt und 17 h unter Rückfluß zum Sieden erhitzt. Man gießt auf 300 g Eis, stellt mit Kaliumhydroxidlösung auf pH 12-13, klärt mit Aktivkohle und fällt mit konzentrierter Salzsäure. Nach erneuter Fällung mit Säure aus alkalischer wäßrig-alkoholischer Lösung erhält man 10 g (93 %) der Titelverbindung vom Schmp. 309-310°C (Zersetzung).

31. 6-Chlor-6,7,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol

a) Zu 18 g 2-Chlor-2,3,3-trifluor-2,3-dihydro-1,4-benzodioxin tropft man bei 5°C eine Mischung von 18,3 ml 65%iger Salpetersäure und 15,4 ml 97%ige Schwefelsäure, rührt 2 h bei 5-10°C und gießt auf Eis. Man extrahiert mit Methylenchlorid und erhält 21,3 g einer Mischung von 2-Chlor-2,3,3-trifluor-2,3-dihydro-6-nitro-(und 7-nitro)-1,4-benzodioxin als Öl.

b) Analog Beispiel 30b) erhält man daraus in 95% Ausbeute eine ölige Mischung von 2-Chlor-2,3,3-trifluor-2,3-dihydro-1,4-benzodioxin-6-(und 7-)amin, welche entsprechend Beispiel 30c) zu einer Mischung der entsprechenden Acetaminoderivate quantitativ umgesetzt wird.

c) 19 g der voranstehenden Mischung wird in 190 ml Dichlormethan mit 16 ml 100%iger Salpetersäure gerührt und das Reaktionsprodukt durch Chromatographie an Kieselgel mittels Cyclohexan/Essigsäureethylester (4:1) gereinigt. Man erhält 15 g einer Mischung von 6-Acetamino-2-chlor-2,3,3-trifluor-6,7-dihydro-7-nitro-1,4-benzodioxin und 7-Acetamino-2-chlor-2,3,3-trifluor-6,7-dihydro-6-nitro-1,4-benzodioxin als hellgelbes Öl.

d) Zu 14,5 g der voranstehenden Mischung in 100 ml Methanol tropft man bei 5°C 10,2 ml einer 30%igen Lösung von Natriummethylat in Methanol, rührt 1,5 h ohne Kühlung, gießt auf Eis, neutralisiert mit verdünnter Salzsäure, extrahiert mit Dichlormethan und engt im Vakuum ein. Man erhält 12,7 g einer Mischung von 6-Amino-2-chlor-2,3,3-trifluor-2,3-dihydro-7-nitro-1,4-benzodioxin und 7-Amino-2-chlor-2,3,3-trifluor-2,3-dihydro-6-nitro-1,4-benzodioxin als orangefarbenes Öl.

e) 12,4 g der voranstehenden Mischung werden analog Beispiel 30f) hydriert. Man erhält 12,6 g (99%) 2-Chlor-2,3,3-trifluor-2,3-dihydro-1,4-benzodioxin-6,7-diamin-dihydrochlorid.

f) 12,4 g der voranstehenden Verbindung werden analog Beispiel 30g) mit 9,1 g Kalium-O-ethyldithiocarbonat und Kaliumhydroxidlösung in Ethanol umgesetzt. Man erhält 9,6 g (74%) der Titelverbindung vom Schmp. 288-290°C (Zersetzung).

32. 2-Chlormethyl-4,5-dimethoxy-pyridinium-chlorid

a) 2-Chlormethyl-4,5-dimethoxy-pyridinium-chlorid

Zu einer auf 0°C gekühlten Lösung von 5 g 2-Hydroxymethyl-4,5-dimethoxypyridin in 40 ml Methylenchlorid tropft man innerhalb einer Stunde

3 ml Thionylchlorid, gelöst in 10 ml Methylenchlorid zu, rührt anschließend 4 Stunden bei 20°C, wobei sich die Reaktionsmischung rot färbt, setzt 5 ml Toluol zu und engt am Rotationsverdampfer vollständig ein (30°C / 5 mbar). Der ölige Rückstand wird in 50 ml warmem Isopropanol gelöst, mit wenig Tonsil® geklärt, filtriert und erneut eingeengt. Man nimmt in 10 ml Toluol auf und bringt die Lösung mit Petrolether zur Kristallisation. Nach Abkühlung im Eisbad wird abgesaugt, mit Petrolether gewaschen und getrocknet. Man erhält 4,6 g (70 % d.Th.) der Titelverbindung 2-Chlormethyl-4,5-dimethoxy-pyridinium-chlorid als farblosen Feststoff; Zers. bei 160-61°C.

b) 2-Hydroxymethyl-4,5-dimethoxy-pyridin

19 g 4,5-Dimethoxy-2-methylpyridin-1-oxid werden innerhalb von 30 Minuten in der Weise zu 60 ml auf 80°C erwärmten Essigsäureanhydrid zudosiert, daß die Temperatur nicht über 100°C steigt. Nach weiteren 45 Minuten bei 85°C wird überschüssiges Essigsäureanhydrid im Vakuum abdestilliert und der ölige dunkle Rückstand, der im wesentlichen aus dem Zwischenprodukt 2-Acetoxymethyl-4,5-dimethoxypyridin besteht, mit 80 ml 2n Natronlauge 1 Stunde lang bei 80°C gerührt. Nach Verdünnen mit 80 ml Wasser und Abkühlung wird achtmal mit je 100 ml Methylenchlorid extrahiert, die vereinigten organischen Phasen zweimal mit 1n Natronlauge gewaschen, getrocknet, eingeengt und der kristalline, bräunliche Rückstand aus Toluol umkristallisiert. Man erhält 14 g (74 % d.Th.) 2-Hydroxymethyl-4,5-dimethoxy-pyridin vom F. 122-24°C.

c) 4,5-Dimethoxy-2-methylpyridin-1-oxid

Zu einer Suspension von 16,9 g 5-Methoxy-2-methyl-4-nitropyridin-1-oxid in 170 ml trockenem Methanol werden 20 ml einer 30 %-igen Natriummethylatlösung zugetropft, 15 Stunden bei 20°C und anschließend 4 Stunden bei 50°C gerührt. Man stellt durch vorsichtige Zugabe von konzentrierter Schwefelsäure unter Eiskühlung auf pH 7, engt ein, rührt den Rückstand mit 200 ml Methylenchlorid aus, filtriert von unlöslichen Bestandteilen, versetzt mit 10 ml Toluol und engt erneut zur Trockne ein. Man erhält 15,2 g (98 % d.Th.) 4,5-Dimethoxy-2-methylpyridin-1-oxid als

farbloses Kristallisat vom F. 118-121°C.

d) 5-Methoxy-2-methyl-4-nitropyridin-1-oxid

Zu 35 ml auf 60°C erwärmte 65 %-ige Salpetersäure werden 21,2 g 5-Methoxy-2-methylpyridin-1-oxid in der Weise zudosiert, daß die Temperatur der Reaktionsmischung 80°C nicht übersteigt. Man rührt 1 Stunde bei 80°C, setzt zur vollständigen Umsetzung noch 13 ml 100 %-ige Salpetersäure zu und rührt weitere 2 Stunden bei 60-70°C. Zur Aufarbeitung gießt man auf 300 g Eis. Der ausgefallene gelbe Niederschlag wird über ein Nutsche filtriert, mit Wasser gewaschen und getrocknet. Der trockene Feststoff wird mit 200ml Methylenchlorid ausgekocht, filtriert und getrocknet. Durch Konzentrierung des Filtrats wird weiteres DC-reines Produkt isoliert. Man erhält 22,3 g (87 % d.Th.) 5-Methoxy-2-methyl-4-nitropyridin-1-oxid vom F. 201-202°C; gelbe Kristalle.

e) 5-Methoxy-2-methylpyridin-1-oxid

Zu einer Lösung von 60,9 g 5-Methoxy-2-methylpyridin in 300 ml Eisessig werden bei 60°C 120 g 30 %-ige Wasserstoffperoxidlösung innerhalb von 1 Stunde zugetropft und 3 Stunden nachgerührt. Nach Zerstörung von überschüssigen Perverbindungen durch Zugabe von aktivem Mangandioxid wird filtriert, eingeengt, der Rückstand in 500 ml Essigsäureethylester heiß geklärt, erneut eingeengt und bei 0,3 mbar destilliert. Man erhält 54 g (77 % d.Th.) 5-Methoxy-2-methylpyridin-1-oxid als rasch erstarrendes Öl (Sdp. 130°C); F. 80-84°C.

f) 5-Methoxy-2-methylpyridin

Zu einer Lösung von 84 g Kaliumhydroxid in 400 ml Methanol und 500 ml Dimethylsulfoxid werden innerhalb einer Stunde 150 ml 3-Hydroxy-6-methylpyridin zudosiert. Nach Entfernung des Methanols am Rotationsverdampfer tropft man unter Eiskühlung 213 g Methyliodid, gelöst in 100 ml Dimethylsulfoxid zu, rührt 15 Stunden bei 20°C und unterwirft das Reaktionsgemisch einer Wasserdampfdestillation. Das Destillat wird am Extraktor kontinuierlich mit Methylenchlorid extrahiert und der Extrakt

eingeengt. Man erhält 85 g (56 % d.Th.) 5-Methoxy-2-methylpyridin als farbloses Öl.

33. 2-Chlormethyl-4,5-dimethoxy-3-methylpyridinium-chlorid

a) 2-Chlormethyl-4,5-dimethoxy-3-methylpyridinium-chlorid

Nach der in Beispiel 32a) beschriebenen Arbeitsweise erhält man durch Umsetzung von 2,7 g 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridin mit 4 g Thionylchlorid in 25 ml Methylenchlorid nach 1 Stunde Reaktionszeit und nach einer vereinfachten Aufarbeitungsmethode, nämlich durch Zusatz von 10 ml Toluol, abdestillieren des Methylenchlorids und überschüssigen Thionylchlorids, Absaugung des ausgefallenen Kristallisats und Trocknung 3,45 g (99 % d.Th) der Titelverbindung als farblose Kristalle; Zers. bei 125-26°C.

b) 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridin

4,5 g 4,5-Dimethoxy-2,3-dimethylpyridin-1-oxid werden in 20 ml Essigsäureanhydrid 30 Minuten auf 110°C erwärmt und anschließend am Rotationsverdampfer eingeengt. Der ölige Rückstand, der aus dem Zwischenprodukt 2-Acetoxymethyl-4,5-dimethoxy-3-methylpyridin besteht, wird in 30 ml 3n Natronlauge 2 Stunden bei 80°C gerührt, nach Abkühlung fünfmal mit je 30 ml Methylenchlorid extrahiert, die vereinigten organischen Phasen zweimal mit 2n Natronlauge gewaschen, getrocknet, eingeengt, der Rückstand mit Petrolether verrührt, abgesaugt und getrocknet. Man erhält 4,0 g (89 % d.Th.) 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridin vom F. 91-92°C.

c) 4,5-Dimethoxy-2,3-dimethylpyridin-1-oxid

6,3 g 4,5-Dimethoxy-2,3-dimethylpyridin werden in 120 ml Methylenchlorid gelöst, sukzessive 20 g m-Chlorperoxibenzoesäure zugegeben, erst 2 Stunden bei 20°C und anschließend 4 Stunden bei 40°C gerührt. Nach Zusatz von 20 ml 5n Natronlauge wird dreimal mit einem Gemisch aus einer 5 %-igen Natriumthiosulfat- und 5 %-igen Natriumcarbonatlösung gewa-

schen, die Wasserphasen zweimal mit Methylenchlorid rückextrahiert, die vereinigten organischen Phasen über Magnesiumsulfat getrocknet und eingeengt. Man erhält 4,6 g (66 % d.Th.) 4,5-Dimethoxy-2,3-dimethylpyridin-1-oxid. Der Rf-Wert in Methylenchlorid/Methanol 19:1 beträgt 0,25.

d) 4,5-Dimethoxy-2,3-dimethylpyridin

Nach der in Beispiel 32f) beschriebenen Arbeitsweise erhält man durch Umsetzung von 9,18 g 5-Hydroxy-4-methoxy-2,3-dimethylpyridin in 50 ml Dimethylsulfoxid zuerst mit 3,6 g Natriumhydroxid, anschließend mit 8,95 g Methyliodid 7,4 g (74 % d.Th.) 4,5-Dimethoxy-2,3-dimethylpyridin als farbloses, allmählich kristallisierendes Öl, F. 36-38°C.

e) 5-Hydroxy-4-methoxy-2,3-dimethylpyridin

1000 g 4-Methoxy-2,3-dimethylpyridin-1-oxid werden bei 100°C unter Rühren innerhalb von 7 Stunden zu 3 l Essigsäureanhydrid zudosiert und weitere 3 Stunden bei 100°C nachgerührt. Man läßt abkühlen, engt bei 70°C/10 mbar vollständig ein und destilliert anschließend bei 10^{-2} mbar. Die Fraktion mit einem Siedeintervall von 95-145°C (Gemisch aus dem Zwischenprodukt 5-Acetoxy-4-methoxy-2,3-dimethylpyridin und 2-Acetoxymethyl-4-methoxy-3-methylpyridin) wird abgenommen (952 g) und zu 3,5 l auf 50°C erwärmte 2n Natronlauge innerhalb von 30 Minuten zugegeben.
Man rührt bei 50°C bis zur Bildung einer klaren Lösung (ca. 3 Stunden), läßt abkühlen und extrahiert dreimal mit je 1 l Methylenchlorid. Die vereinigten organischen Phasen werden zweimal mit je 0,5 l 1n Natronlauge rückextrahiert und anschließend die vereinigten Wasserphasen mit halbkonzentrierter Salzsäure unter Rühren auf pH 7,5 gestellt. Man filtriert vom ausgefallenen Feststoff, wäscht nach und trocknet bis zur Gewichtskonstanz. Man erhält 5-Hydroxy-4-methoxy-2,3-dimethylpyridin vom F. 274-76°C.

34. 2-Chlormethyl-3,4-dimethoxy-pyridinium-chlorid

a) 2-Chlormethyl-3,4-dimethoxy-pyridiniumchlorid

Nach der in Beispiel 32a beschriebenen Arbeitsweise erhält man durch Umsetzung von 3,38 g 2-Hydroxymethyl-3,4-dimethoxypyridin mit 2 ml Thionylchlorid in 30 ml Methylenchlorid nach 2,5 Stunden Reaktionszeit und nach der in Beispiel 33a beschriebenen Art der Aufarbeitung 4,2 g (93% d.Th.) der Titelverbindung als farblosen Feststoff vom F. 151-152°C (Zers.)

b) 2-Hydroxymethyl-3,4-dimethoxypyridin

4,8 g 2-Acetoxymethyl-3,4-dimethoxypyridin werden nach Zusatz von 15 ml 2n Natronlauge bei 80°C kräftig gerührt, wobei sich aus dem anfänglichen Zweiphasengemisch eine homogene Lösung bildet. Nach 2 h läßt man abkühlen, extrahiert fünfmal mit je 30 ml Methylenchlorid, wäscht die vereinigten organischen Phasen zweimal mit je 5 ml 0,3 n Natronlauge, trocknet über Kaliumcarbonat, filtriert, engt ein und verrührt den Destillationsrückstand mit Petrolether. Man erhält 3,6 g (96% d.Th.) 2-Hydroxymethyl-3,4-dimethoxypyridin als farblosen Feststoff vom F. 87-89°C.

c) 2-Acetoxymethyl-3,4-dimethoxypyridin

Zu 25 ml Essigsäureanhydrid werden bei 85°C innerhalb von einer Stunde 4,8 g (28 mMol) 3,4-Dimethoxy-2-methylpyridin-1-oxid zudosiert, eine Stunde bei der selben Temperatur gerührt, im Vakuum vollständig eingeengt und der braune, ölige Rückstand in einer Kugelrohrdestille bei 1 Pa destilliert. Man erhält 5,3 g (90% d.Th.) 2-Acetoxymethyl-3,4-dimethoxypyridin; Sdp. 125-130°C.

d) 3,4-Dimethoxy-2-methylpyridin-1-oxid

4,5 g (25 mMol) 3-Methoxy-2-methyl-4-nitropyridin-1-oxid werden in 75 ml trockenem Methanol nach Zusatz von 4,7 ml 30%iger Natriummethylatlösung 16 Stunden bei 40°C gerührt. Anschließend kühlt man ab, stellt mit konz. Schwefelsäure auf pH 7, filtriert, engt im Vakuum vollständig ein, nimmt den öligen, rötlichen Rückstand in 50 ml Toluol auf, filtriert erneut von unlöslichen Bestandteilen und engt das Filtrat zur Trockene ein. Der gelbe, ölige Rückstand kristallisiert im Eisbad und wird abschließend mit

30 ml Petrolether (50/70) bei 40°C ausgerührt. Nach Filtration und Trocknung im Exsiccator erhält man 5,2 g (88% d.Th.) 3,4-Dimethoxy-2-methylpyridin-1-oxid in Form blaßgelber Kristalle vom F. 111-113°C.

e) 3-Methoxy-2-methyl-4-nitropyridin-1-oxid

Zu 5,4 g 3-Methoxy-2-methylpyridin-1-oxid in 12 ml Eisessig werden bei 80°C innerhalb von 6h in vier Portionen von je 2 ml 8 ml konz. Salpetersäure zugegeben, über Nacht bei der selben Temperatur gerührt, nochmals in drei Portionen innerhalb von 6 Stunden 8 ml Salpetersäure zugegeben und weitere 15 Stunden gerührt. Nach Abkühlung gießt man auf Eis (40g), stellt mit 10n Natronlauge auf pH 6, filtriert vom ausgefallenen Nebenprodukt (3-Methoxy-2-methyl-4-nitropyridin) und extrahiert viermal mit 50 ml Methylenchlorid. Nach Trocknung werden die vereinigten organischen Phasen vollständig eingeengt und der Rückstand aus wenig Methylenchlorid/Petrolether umkristallisiert. Man erhält 4,2 g (57% d.Th.) der Titelverbindung in Form gelber Kristalle vom F. 103-104°C.

f) 3-Methoxy-2-methylpyridin-1-oxid

15,3 g (0,124 Mol) 3-Methoxy-2-methylpyridin werden in 100 ml Eisessig gelöst und bei 80°C in 4 Portionen 40 ml 30%iges Wasserstoffperoxid innerhalb von 6 Stunden zugegeben. Man rührt weitere drei Stunden und engt anschließend im Vakuum (1,5 kPa) ein, setzt zweimal je 50 ml Essigsäure zu und engt jeweils vollständig ein. Nach negativem Nachweis auf Perverbindungen wird im Kugelrohrofen destilliert. Die bei 120°C (1,5 Pa) destillierende Fraktion wird in wenig Diethylether ausgerührt, der Feststoff filtriert und getrocknet. Man erhält 12 g (60% d.Th.) 3-Methoxy-2-methylpyridin-1-oxid in Form farbloser Kristalle vom F. 72-78°C.

g) 3-Methoxy-2-methylpyridin

Nach der in Beispiel 32f beschriebenen Arbeitsweise erhält man durch Umsetzung von 13,7 g (125 mMol) 3-Hydroxy-2-methylpyridin mit 9,2 ml Methyliodid unter Zusatz von 46 ml 3m methanolischer Kaliumhydroxidlösung nach einer Reaktionszeit von 3 Stunden 15,5 g (90% d.Th.) 3-Methoxy-2-methylpyridin als farbloses Öl.

Gewerbliche Anwendbarkeit

Die Dialkoxypyridine der allgemeinen Formel I und ihre Salze besitzen wertvolle pharmakologische Eigenschaften, die sie gewerblich verwertbar machen. Sie hemmen deutlich die Magensäuresekretion von Warmblütern und weisen darüberhinaus eine ausgezeichnete Magen- und Darmschutzwirkung bei Warmblütern auf. Diese Magen- und Darmschutzwirkung wird bereits bei der Verabreichung von Dosen beobachtet, die unterhalb der säuresekretionshemmenden Dosen liegen. Darüberhinaus zeichen sich die erfindungsgemäßen Verbindungen durch das Fehlen wesentlicher Nebenwirkungen und eine große therapeutische Breite aus.

Unter "Magen- und Darmschutz" wird in diesem Zusammenhang die Verhütung und Behandlung gastrointestinaler Krankheiten, insbesondere gastrointestinaler entzündlicher Krankheiten und Läsionen (wie z.B. Ulcus ventriculi, Ulcus duodeni, Gastritis, hyperazider oder medikamentös bedingter Reizmagen) verstanden, die beispielsweise durch Mikroorganismen, Bakterientoxine, Medikamente (z.B. bestimmte Antiphlogistika und Antirheumatika), Chemikalien (z.B. Ethanol), Magensäure oder Streßsituationen verursacht werden können.

Ein weiterer Vorteil der erfindungsgemäßen Verbindungen ist ihre vergleichsweise große chemische Stabilität.

In ihren ausgezeichneten Eigenschaften erweisen sich die erfindungsgemäßen Verbindungen überraschenderweise den aus dem Stand der Technik bekannten Verbindungen deutlich überlegen. Aufgrund dieser Eigenschaften sind die Dialkoxypyridine und ihre pharmakologisch verträglichen Salze für den Einsatz in der Human- und Veterinärmedizin hervorragend geeignet, wobei sie insbesondere zur Behandlung und/oder Prophylaxe von Krankheiten des Magens und Darms und solcher Krankheiten, die auf einer überhöhten Magensäuresekretion beruhen, verwendet werden.

Ein weiterer Gegenstand der Erfindung sind daher die erfindungsgemäßen Verbindungen zur Anwendung bei der Behandlung und/oder Prophylaxe der vorstehend genannten Krankheiten.

Ebenso umfaßt die Erfindung die Verwendung der erfindungsgemäßen Verbindungen zur Herstellung von Arzneimitteln, die zur Behandlung und/oder Prophylaxe der vorstehend genannten Krankheiten eingesetzt werden.

Ein weiterer Gegenstand der Erfindung sind Arzneimittel, die ein oder mehrere Dialkoxypyridine der allgemeinen Formel I und/oder ihre pharmakologisch verträglichen Salze enthalten.

Die Arzneimittel werden nach an sich bekannten, dem Fachmann geläufigen Verfahren hergestellt. Als Arzneimittel werden die erfindungsgemäßen pharmakologisch wirksamen Verbindungen (=Wirkstoffe) entweder als solche, oder vorzugsweise in Kombination mit geeigneten pharmazeutischen Hilfs- oder Trägerstoffen in Form von Tabletten, Dragees, Kapseln, Suppositorien, Pflastern (z.B. als TTS), Emulsionen, Suspensionen oder Lösungen eingesetzt, wobei der Wirkstoffgehalt vorteilhafterweise zwischen 0,1 und 95% beträgt.

Welche Hilfs- bzw. Trägerstoffe für die gewünschten Arzneimittelformulierungen geeignet sind, ist dem Fachmann aufgrund seines Fachwissens geläufig. Neben Lösemitteln, Gelbildnern, Suppositoriengrundlagen, Tabletten-Hilfsstoffen und anderen Wirkstoffträgern können beispielsweise Antioxidantien, Dispergiermittel, Emulgatoren, Entschäumer, Geschmackskorrigentien, Konservierungsmittel, Lösungsvermittler, Farbstoffe oder insbesondere Permeationspromotoren und Komplexbildner (z.B. Cyclodextrine) verwendet werden.

Die Wirkstoffe können oral, parenteral oder percutan appliziert werden.

Im allgemeinen hat es sich in der Humanmedizin als vorteilhaft erwiesen, den oder die Wirkstoffe bei oraler Gabe in einer Tagesdosis von etwa 0,01 bis etwa 20, vorzugsweise 0,05 bis 5, insbesondere 0,1 bis

1,5 mg/kg Körpergewicht, gegebenenfalls in Form mehrerer, vorzugsweise 1 bis 4 Einzelgaben zur Erzielung des gewünschten Ergebnisses zu verabreichen. Bei einer parenteralen Behandlung können ähnliche bzw. (insbesondere bei der intravenösen Verabreichung der Wirkstoffe) in der Regel niedrigere Dosierungen zur Anwendung kommen. Die Festlegung der jeweils erforderlichen optimalen Dosierung und Applikationsart der Wirkstoffe kann durch jeden Fachmann aufgrund seines Fachwissens leicht erfolgen.

Sollen die erfindungsgemäßen Verbindungen und/oder Salze zur Behandlung der oben genannten Krankheiten eingesetzt werden, so können die pharmazeutischen Zubereitungen auch einen oder mehrere pharmakologisch aktive Bestandteile anderer Arzneimittelgruppen, wie Antacida, beispielsweise Aluminiumhydroxyd, Magnesiumaluminat; Tranquilizer, wie Benzodiazpine, beispielsweise Diazepam; Spasmolytika, wie z.B. Bietamiverin, Camylofin; Anticholinergica, wie z.B. Oxyphencyclimin, Phencarbamid; Lokalanaesthetika, wie z.B. Tetracain, Procain; gegebenenfalls auch Fermente, Vitamine oder Aminosäuren enthalten.

Hervorzuheben ist in diesem Zusammenhang insbesondere die Kombination der erfindungsgemäßen Verbindungen mit anderen, die Säuresekretion hemmenden Pharmaka, wie beispielsweise H_2-Blockern (z.B. Cimetidin, Ranitidin), ferner mit sogenannten peripheren Anticholinergika (z.B. Pirenzepin, Telenzepin, Zolenzepin) sowie mit Gastrin-Antagonisten, mit dem Ziel, die Hauptwirkung in additivem oder überadditivem Sinn zu verstärken und/oder die Nebenwirkungen zu eliminieren oder zu verringern.

Pharmakologie

Die ausgezeichnete Magenschutzwirkung und die magensekretionshemmende Wirkung der erfindungsgemäßen Verbindungen läßt sich tierexperimentell am Modell Shay-Ratte nachweisen. Die untersuchten erfindungsgemäßen Verbindungen sind wie folgt mit Nummern versehen worden:

Lfd. Nr.	Name der Verbindung
1	2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol
2	2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol
3	2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol
4	2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol
5	2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Der Einfluß der untersuchten Verbindungen auf die durch Pylorusligatur (4h; sog. Shay-Ratte) und orale Gabe von 100 mg/kg Acetylsalicylsäure ausgelöste Magenläsionsbildung sowie die Magensekretion (HCl) während 4 h bei der Ratte, ist in der folgenden Tabelle dargestellt.

Magenschutzwirkung und Magensekretionshemmung

Lfd. Nr.	n [Anzahl d.Tiere]	Magenschutzwirkung (Ratte) Hemmung d. Läsionsindexes, ED50+) [mg/kg, p.o.]	Hemmung der HCl-Sekretion d. Magens (Ratte; Summe 4 h) % Hemmung der HCl-Sekretion ++)	ED25+) [mg/kg, p.o.]	ED50+) [mg/kg, p.o.]
1	40	0,6	15	1,0	~ 3
2	48	0,8	25	0,7	1,7
3	56	0,6	18	~ 1	3,4
4	40	3,5	28	3,0	6,5
5	72	~ 1	25	1,0	3,0

+) ED25 bzw. ED50 = Dosis, die den Läsionsindex bzw. die HCl-Sekretion (4h) des Rattenmagens bei der behandelten Gruppe gegenüber der Kontrollgruppe um 25 bzw. 50 % mindert.

++) nach Gabe der antiulcerösen ED50

Die Prüfung der antiulcerogenen Wirkung erfolgte nach der Methode der sogenannten Shay-Ratte:

Die Ulcusprovokation erfolgt bei 24 Stunden nüchtern gehaltenen Ratten (weiblich, 180-200 g, 4 Tiere je Käfig auf hohem Gitterrost) durch Pylorusligatur (unter Diethylethernarkose) und orale Applikation von 100 mg/10 ml/kg Acetylsalicylsäure. Die zu prüfenden Substanzen werden oral (10 ml/kg) eine Stunde vor der Pylorusligatur verabreicht. Der Wundverschluß wird mittels Michelklammern vorgenommen. 4 Stunden danach erfolgt die Tötung der Tiere im Etherrausch durch Atlas-Dislokation und die Resektion des Magens. Der Magen wird längs eröffnet und auf einer Korkplatte fixiert, nachdem zuvor die Menge

des sezernierten Magensaftes (Volumen) und später sein HCl-Gehalt (Titration mit Natronlauge) bestimmt wurde; mit einem Stereomikroskop werden bei 10-facher Vergrößerung Anzahl und Größe (=Durchmesser) vorhandener Ulcera ermittelt. Das Produkt aus Schweregrad (gemäß nachfolgender Punkteskala) und Anzahl der Ulcera dient als individueller Läsionsindex.

Punkteskala:

keine Ulcera		0
Ulcusdurchmesser	0,1 - 1,4 mm	1
	1,5 - 2,4 mm	2
	2,5 - 3,4 mm	3
	3,5 - 4,4 mm	4
	4,5 - 5,4 mm	5
	> 5,5 mm	6

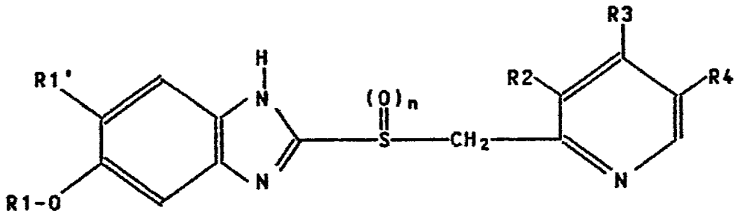
Als Maß für den antiulcerogenen Effekt dient die Minderung des mittleren Läsionsindex jeder behandelten Gruppe gegenüber dem der Kontrollgruppe (=100%). Die ED25 bzw. ED50 bezeichnen diejenigen Dosen, die den mittleren Läsionsindex bzw. die HCl-Sekretion gegenüber der Kontrolle um 25% bzw. 50% mindern.

Toxizität

Die LD50 aller geprüften Verbindungen liegt oberhalb von 1000 mg/kg [p.o.] bei der Maus.

Patentansprüche

1. Dialkoxypyridine der allgemeinen Formel I



(I),

worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest und

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindungen.

2. Verbindungen der Formel I nach Anspruch 1,

worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest,

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen

gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindungen.

3. Verbindungen der Formel I nach Anspruch 1,

worin

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindung.

4. Verbindungen der Formel I nach Anspruch 2, worin R1 1,1,2,2-Tetrafluorethyl, Trifluormethyl, 2,2,2-Trifluorethyl oder Difluormethyl, R1' Wasserstoff, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

5. Verbindungen der Formel I nach Anspruch 3, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Difluormethylendioxyrest oder einen Methylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

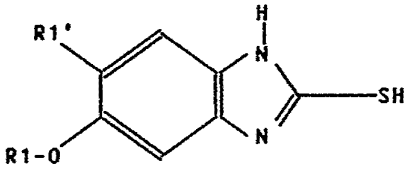
6. Verbindungen der Formel I nach einem der Ansprüche 1 bis 5, worin n die Zahl 0 bedeutet, und ihre Säureadditionssalze.

7. Verbindungen der Formel I nach einem der Ansprüche 1 bis 5, worin n die Zahl 1 bedeutet, und ihre Salze mit Basen.

8. Verbindung ausgewählt aus der Gruppe bestehend aus
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol und
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfiyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol
und ihren Salzen.

9. Verfahren zur Herstellung von Dialkoxypyridinen der Formel I nach Anspruch 1 und ihren Salzen, dadurch gekennzeichnet, daß man

a) Mercaptobenzimidazole der Formel II mit Picolinderivaten III,



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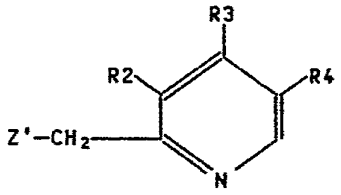
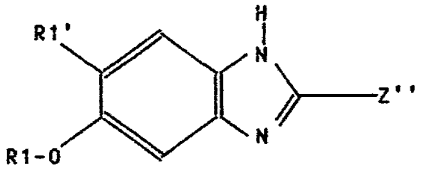


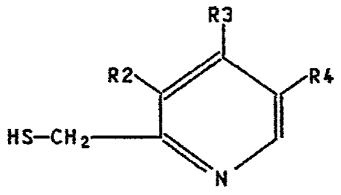
(III),

oder

b) Benzimidazole der Formel IV mit Mercaptopicolinen V,



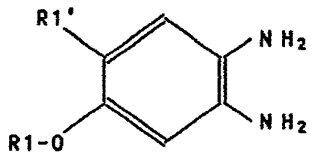
(IV)



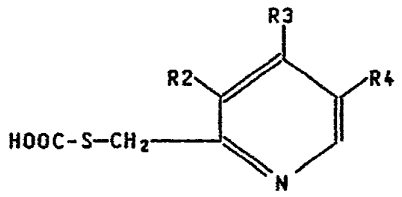
(V),

oder

c) o-Phenylendiamine der Formel VI mit Ameisensäurederivaten VII

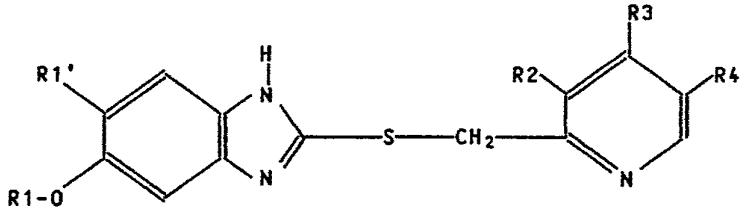


(VI)



(VII),

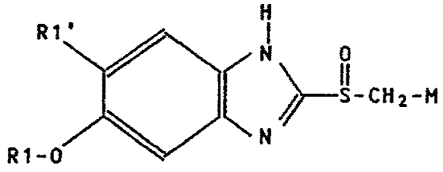
umsetzt und gegebenenfalls anschließend die nach a), b) oder c) erhaltenen 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII



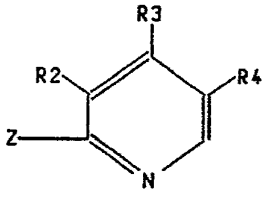
(VIII),

oxidiert und/oder in die Salze überführt,
oder daß man

d) Benzimidazole der Formel IX mit Pyridinderivaten X



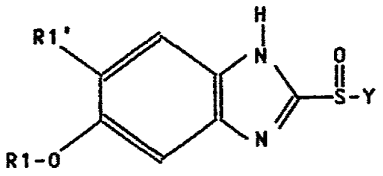
(IX)



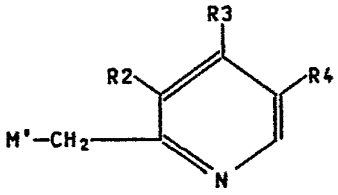
(X),

oder

e) Sulfinylderivate der Formel XI mit 2-Picolinderivaten XII



(XI)



(XII),

umsetzt und gegebenenfalls anschließend in die Salze überführt, wobei Y, Z, Z' und Z'' geeignete Abgangsgruppen darstellen, M für ein Alkalimetallatom (Li, Na oder K) steht, M' für das Äquivalent eines Metallatoms steht und R1, R1', R2, R3, R4 und n die in Anspruch 1 angegebenen Bedeutungen haben.

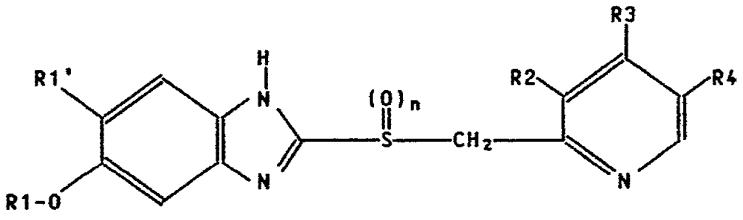
10. Arzneimittel enthaltend ein oder mehrere Dialkoxypyridine nach einem oder mehreren der Ansprüche 1 bis 8 und/oder ihre pharmakologisch verträglichen Salze.

11. Dialkoxypyridine nach einem der Ansprüche 1 bis 8 und ihre pharmakologisch verträglichen Salze zur Anwendung bei der Behandlung und/oder Prophylaxe von Krankheiten des Magens und/oder Darms und solcher Krankheiten, die auf einer erhöhten Magensäuresekretion beruhen.

12. Verwendung von Dialkoxypyridinen nach einem der Ansprüche 1 bis 8 und ihren pharamkologisch verträglichen Salzen zur Herstellung von Arzneimitteln für die Behandlung und/oder Prophylaxe von Krankheiten des Magens und/oder Darms und solchen Krankheiten, die auf einer erhöhten Magensäuresekretion beruhen.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung von Dialkoxypyridinen der allgemeinen Formel I



(I),

worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest und

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,

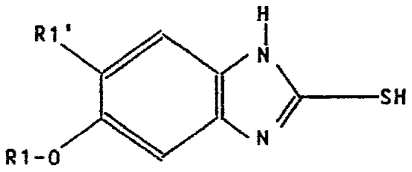
R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

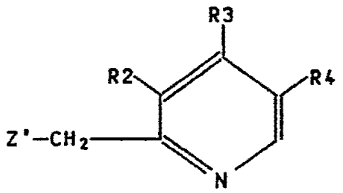
n die Zahlen 0 oder 1 darstellt,

und ihren Salzen, dadurch gekennzeichnet, daß man

a) Mercaptobenzimidazole der Formel II mit Picolinderivaten III,



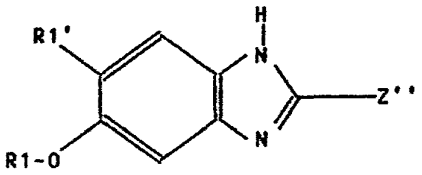
(II)



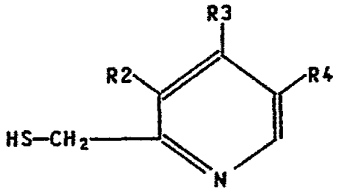
(III),

oder

b) Benzimidazole der Formel IV mit Mercaptopicolinen V,



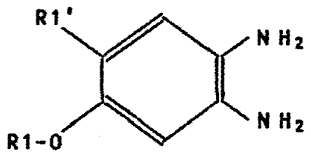
(IV)



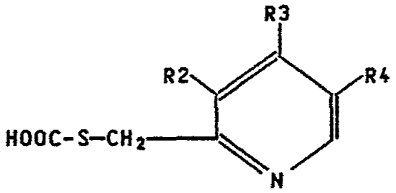
(V),

oder

c) o-Phenylendiamine der Formel VI mit Ameisensäurederivaten VII

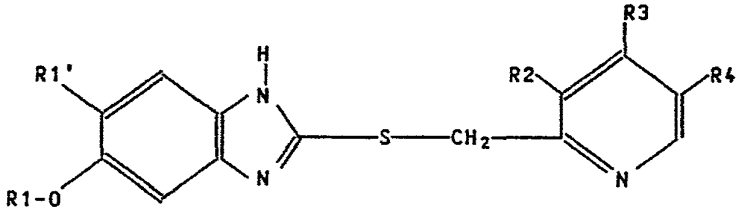


(VI)



(VII),

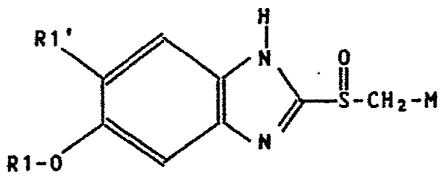
umsetzt und gegebenenfalls anschließend die nach a), b) oder c) erhaltenen 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII



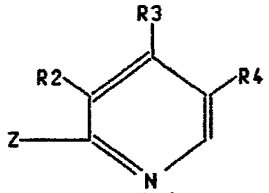
(VIII),

oxidiert und/oder in die Salze überführt,
oder daß man

d) Benzimidazole der Formel IX mit Pyridinderivaten X



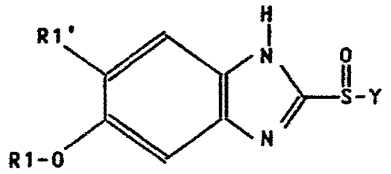
(IX)



(X),

oder

e) Sulfinylderivate der Formel XI mit 2-Picolinderivaten XII



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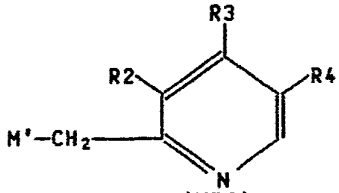

(XII),

umsetzt und gegebenenfalls anschließend in die Salze überführt, wobei Y, Z, Z' und Z'' geeignete Abgangsgruppen darstellen, M für ein Alkalimetallatom (Li, Na oder K) steht, M' für das Äquivalent eines Metallatoms steht und R1, R1', R2, R3, R4 und n die oben angegebenen Bedeutungen haben.

2. Verfahren nach Anspruch 1,
worin
R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest,
R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest,
R3 einen 1-3C-Alkoxyrest,
einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und
n die Zahlen 0 oder 1 darstellt.

3. Verfahren nach Anspruch 1,
worin
R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1

gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt.

4. Verfahren nach Anspruch 1, worin R1 1,1,2,2-Tetrafluorethyl, Trifluormethyl, 2,2,2-Trifluorethyl oder Difluormethyl, R1' Wasserstoff, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt.

5. Verfahren nach Anspruch 1, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Difluormethylendioxyrest oder einen Methylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt.

6. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1, worin R1, R1', R2, R3 und R4 die in Anspruch 1 angegebenen Bedeutungen haben und n die Zahl 0 bedeutet, dadurch gekennzeichnet, daß man Mercaptobenzimidazole der Formel II mit Picolinderivaten III umsetzt und gegebenenfalls anschließend in die Säureadditionssalze überführt.

7. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1, worin R1, R1', R2, R3 und R4 die in Anspruch 1 angegebenen Bedeutungen haben und n die Zahl 1 bedeutet, dadurch gekennzeichnet, daß man die 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII oxidiert und gegebenenfalls anschließend in die Salze mit Basen überführt.

8. Verfahren zur Herstellung von Arzneimitteln, dadurch gekennzeichnet, daß man eine Verbindung der Formel I nach Anspruch 1 oder ein pharmakologisch verträgliches Salz davon mit einem pharmazeutischen Hilfs- und/oder Trägerstoff vermischt.

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EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
D,A	EP-A-0 074 341 (HÄSSLE) -----		C 07 D 401/12 C 07 D 491/04 A 61 K 31/44

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Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt.

Recherchenort	Abschlußdatum der Recherche	Prüfer
DEN HAAG	17-09-1985	DE BUYSER F.A.F.

KATEGORIE DER GENANNTEN DOKUMENTEN

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur
T : der Erfindung zugrunde liegende Theorien oder Grundsätze

E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
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& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

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Said pharmaceutical form is constituted by a tablet comprising: (a) a centre core containing an active principle provided with antiinflammatory and analgesic activity, with ulcerogenic side effects; (b) a layer coating of said core, containing a second active principle provided with protective action for said gastric and duodenal mucosa, which is immediately released.

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ORAL SOLID PHARMACEUTICAL FORM WITH SEQUENTIAL ACTION FOR THE ADMINISTERING OF DRUGS WITH ULCEROGENIC SIDE EFFECT.

The present invention relates to a new pharmaceutical form with antiinflammatory and analgesic activity, avoiding the ulcerogenic side effect of the antiinflammatory and analgesic active principle.

More particularly, the present invention relates to an oral solid pharmaceutical form with antiinflammatory and analgesic activity, with sequential action, showing an effect of protection of the gastric and duodenal mucosa against the action of the active principles having ulcerogenic side effect.

It is known that during these last years several non-steroidic drugs with antiinflammatory and analgesic action, denominated as FANS (Non Steroidic Antiinflammatory Drugs, NSAD) have been prepared and tested.

It is known too that for all these drugs as a side effect a damaging action on the gastric and duodenal mucosa has been evidenced, which makes unadvisable the prolonged use thereof.

In order to overcome this problem, several modifications and administering forms have been suggested for these drugs, e.g., the formation of salts with alkaline metals, the formation of complexes with Al, Mg or Cu, the prepara-

tion of inclusion compounds with B-cyclodextrins and the like.

Notwithstanding the attention devoted to this problem, and the large number of solutions proposed, the problem of the ulcerogenic action of antiinflammatory drugs is to be considered as being still open, and always of great interest in the pharmaceutical field.

A noticeable step forward has been done with the contemporary administering, in the 1 : 1 ratio, of FANS and sucralfate, which allows an antiinflammatory activity similar to that exerted by the same FANS alone to be obtained, with a considerable reduction in the damaging effects on the gastric and duodenal mucosa (Italian Patent Application Nr. 23205 A.83).

Sucralfate [3,4,5,6-tetra-(polyhydroxyalumino)-α-D-glucopyranosyl sulphate - 2,3,4,5-tetra-(polyhydroxyalumino)-β-D-fructofuranoside sulphate] is a product prepared during these last years, and successfully tested in the management of gastric and duodenal ulcer (R. Nagashima et al., Arzneim. Forsch., 1980: 30: 84/8; 1980: 30: 88/91 "Selective Binding of Sucralfate to Ulcer Lesion").

We have now found that if, instead of contemporaneously administering the mixture of the two active principles, the administering in sequence of sucralfate first, and of FANS then is carried out, a more efficacious protection of the mucosa is obtained. The result in practice is such as to allow the same protection level with lower amounts of sucralfate to be obtained. This administering form causes however the drawback that a double administering is to be carried out, with a suitable time interval.

Purpose of the present invention is to provide a solid pharmaceutical form which allows the contemporary admin-

istering of the two drugs above mentioned, or of other similar drugs, and the release of them in a sequential fashion.

This purpose is achieved by means of the pharmaceutical form sequentially relasing the active principles according to the present invention, which is characterized in that it is constituted by a tablet comprising:

a) a centre core containing an active principle providing an anti-inflammatory and analgesic activity with side ulcerogenic effects;

b) a layer coating for said core, containing a second active principle, providing a protective action of the gastric and duodenal mucosa, which is released immediately.

These and other characteristics and advantages of the pharmaceutical form according to the present invention shall be evidenced in greater detail by the following detailed disclosure, and by the related Figure 1, which are reported to the purpose of illustrating and not of limiting the invention itself.

Referring to the numerical indices of fig. 1, the centre core (1) of the pharmaceutical form according to the present invention is prepared by making into a paste the antiinflammatory and analgesic active principle, suitably formulated, with an alcoholic solution of ethylcellulose; the paste is granulated, dried, blended with lubricating and disintegrating substances, and then transformed into tablets.

The coating layer (2) is prepared by mixing sucralfate in suitable formulations, and is applied to the core (1) by means of the double-compression technique, i.e., by compressing two coating layers respectively positioned on and under the core.

The coating layer can contain as mucose protecting ac-

tive principles, in addition to sucralfate, also mucin, cellulose derivatives, natural or synthetic polymeric materials, alone, or as different combinations with each other.

The coating layer is so formulated, as to release an extremely subdivided dispersion of sucralfate before that the FANS composing the core comes in contact with the gastric and duodenal mucosa.

The action of this farmaceutical form is hence developed in two sequential steps, whose sequence is evidenced by observations related to tests carried out on animal. The steps of this action are:

A) Disintegration quick and of microgranular type, in the acidic medium of the stomach, of the coating layer, with formation of a wide dispersion of the protective agent composing it. The active principle of the coating has hence the time and the possibility of lining the gastric and intestinal mucosa, protecting it from the subsequent contact with the ulcerogenic drug contained in the core.

B) Slow disintegration of the core in a medium wherein the protective active substance has already lined the mucosa.

In this way, the lesioning action of the drug contained in the core is limited by the action of the protective drug.

Several compositions containing sucralfate : FANS in weight ratios comprised within the range of from 1: 4 to 8 : 1 have been tested on rats by means of the test of pylorus ligature according to the technique Linda J. et al., J. Pharmac., 1978, 30, 244 - 246 "Inhibitors of Gastric Lesions in the Rat".

The testing has been carried out on Charles River Wistar rats of 230 - 270 g of weight and in the number of 8 rats per each group. The rats, fasting from 15 hours, have been submitted to etheric anesthesia and then to the liga

ture of the pylorus. The rats have been treated, immediately after the recovery, by means of gastric probe, with the FANS alone, with the FANS in the sucralfate-FANS form with sequential action according to the present invention, and by means of the administering of sucralfate first, and then, after a 10 minutes interval, of FANS.

The single active principles have been administered as aqueous suspension in sodium-CMC at 0.5% p.o.

Six hours later than the intervention, the rats have been sacrificed and the stomach, after having been withdrawn, has been cut along the line of the greater curvature. The stomach, after having been slightly washed with bidistilled water has been spread out and mounted on a support for the evaluation of induced ulceration. The alterations detected on the gastric mucosa have been quantified on the basis of their type and largeness, with a value ranging from 0 to 1 (ulcerating index, UI), according to the following empirical scale:

0 = mucose not damaged (control submitted to surgical handling and to placebo)

0.25 = diffused accentuated hyperemia

0.50 = diffused erosion

0.75 = diffused hemorrhagic ulceration

1 = diffused hemorrhagic ulceration with perforation and damaging of the whole gastric mucosa.

The activity of the form of sucralfate and FANS with sequential action according to the invention has been expressed as percentage inhibition of the lesion relatively to that observed in the control group as treated with the ligature of pylorus and administering of FANS only, and compared to that obtained from the contemporary administering of sucralfate and FANS. The ID_{50} (Inhibiting Dosis 50) was

computated by the probit method.

In Table 1 the values of ID_{50} of sucralfate for various FANS are reported, in the case of the contemporary administering of FANS and sucralfate, and in the case of the administering in the form with sequential activity according to the present invention.

TABLE 1

Inhibiting Dosis 50 of sucralfate for the ulcerogenic activity of some FANS (mg)

FANS	Contemporary administering of sucralfate and of FANS	Administering of the sucralfate-FANS form with sequential action
Sodium indoprofen betainate (200 mg/kg as indoprofen)	206	85.6
Diclofenac Na (50 mg/kg)	157	96.6
Indomethacin (100 mg/kg)	204	97

It results from Table 1 in a clear way that the administering of the form of sucralfate-FANS with sequential action is capable of protecting to a significantly greater extent the gastric mucosa against the lesioning power of FANS.

To illustrative, but not limitative, purpose of the present invention, the following Example is reported, relating to a formulation of the pharmaceutic form with sequential action (the numbers indicate parts by weight):

a) Formulation of the core of sodium indoprofen betainate

Sodium indoprofen betainate	290
Ethylcellulose	5
Carboxymethyl starch	12

Magnesium stearate	3

b) Preparation of the core

Indoprofen betainate is made into a paste with an alcoholic solution of ethylcellulose, the paste is granulated and dried. The dried granulate is mixed with the lubricant agent (magnesium stearate) and then with the disintegrating agent (carboxymethyl starch), and is compressed to form tablets of slightly crowned shape, with punches of 9 mm in diameter.

c) Formulation of the coating layer

Sucralfate	100
Crosslinked carboxymethylcellulose	10
Microcrystalline cellulose	40
Magnesium carbonate	10
CL Polyvinylpirrolidone	5
Magnesium stearate	2

The components of the formulation are mixed in a V-mixer.

d) Application of sucralfate coating on the core of sodium indoprofen betainate.

The application of the coating layer on the core is carried out by means of the double-compression technique, by compressing two layers of coating positioned on the core and under it, a coated tablet of suitable diameter being obtained, wherein the outer coating is constituted by sucralfate, and the inner core is constituted by indoprofen betainate (see figure 1).

Claims

1. Solid pharmaceutical form, for administration by oral way, with sequential release of the contained active principles, characterized in that it is constituted by

(a) a centre core containing an active principle displaying antiinflammatory and analgesic activity, with ulcerogenic side effects;

(b) a coating layer for said core, containing a second active principle displaying a protective action for the gastric and duodenal mucosa, which is immediately released.

2. Pharmaceutical form according to claim 1, characterized in that the active principle contained in said core is constitutend by FANS (Non Steroidic Antiinflammatory drugs, NSAD), such as ASA, Indoprofen, Naproxen, Ketoprofen, Indomethacin, Diflunisal, Diclofenac or derivatives.

3. Pharmaceutical form according to claim 1, characterized in that said core shows a slow disintegration, or constitutes a system with bioeroded matrix and however of the type with properties of controlled release of the contained active principle.

4. Pharmaceutical form according to claim 1, characterized in that said core containes active principles provided with anti-inflammatory and analgesic activity, with ulcerogenic side effects, combined with each other or with other medicaments.

5. Pharmaceutical form according to claim 1, characterized in that said coating layer is constituted by active principles capable of performing a protective action on the gastric and duodenal mucosa such as, e.g., sucralfate, mucin, cellulose derivatives, natural or synthetic polymeric materials capable of forming a protective lining.

6. Pharmaceutical form according to claim 1, characterized in that said coating layer shows a disintegration quick and of the microgranular type in the acidic medium of the stomach, determining an immediate dispersion of the contained protective agent.

7. Pharmaceutical form according to claim 1, characterized in that sucralfate or another mucose-protecting agent and FANS are contained in a weight ratio comprised within the range of from 1 : 4 to 8 : 1.

8. Pharmaceutical form for oral usage according to claims from 1 to 7 and method for the preparation thereof, which is carried out by means of the double-compression technique, i.e., by compressing around said core containing the active principle provided with antiinflammatory and analgesic activity with ulcerogenic side effects, said coating layer containing an active principle provided with protective action for the gastric and duodenal mucosa.

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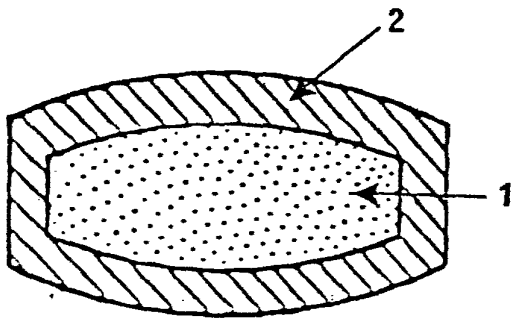

FIGURE 1

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EUROPEAN SEARCH REPORT

0167958
Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X,Y	FR-M- 3 715 (L. NOUVEL) * Page 1, column 1, paragraphs 1,2,7; column 2, paragraph 5; claims *	1-7	A 61 K 9/24
D,P Y	DE-A-3 434 707 (LISAPHARMA) * Whole document *	1,2	
A	EP-A-0 064 485 (AB HÄSSLE) * Abstract; page 1, paragraph 2; claims *	1-7	

TECHNICAL FIELDS SEARCHED (Int Cl.4)
A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24-02-1987	BERTE M.J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
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More particularly, the present invention relates to an oral solid pharmaceutical form with antiinflammatory and analgesic activity, with sequential action, showing an effect of protection of the gastric and duodenal mucosa against the action of the active principles having ulcerogenic side effect.

It is known that during these last years several non-steroidic drugs with antiinflammatory and analgesic action, denominated as FANS (Non Steroidic Antiinflammatory Drugs, NSAD) have been prepared and tested.

It is known too that for all these drugs as a side effect a damaging action on the gastric and duodenal mucosa has been evidenced, which makes unadvisable the prolonged use thereof.

In order to overcome this problem, several modifications and administering forms have been suggested for these drugs, e.g., the formation of salts with alkaline metals, the formation of complexes with Al, Mg or Cu, the prepara-

tion of inclusion compounds with B-cyclodextrins and the like.

Notwithstanding the attention devoted to this problem, and the large number of solutions proposed, the problem of the ulcerogenic action of antiinflammatory drugs is to be considered as being still open, and always of great interest in the pharmaceutical field.

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Referring to the numerical indices of fig. 1, the centre core (1) of the pharmaceutical form according to the present invention is prepared by making into a paste the antiinflammatory and analgesic active principle, suitably formulated, with an alcoholic solution of ethylcellulose; the paste is granulated, dried, blended with lubricating and disintegrating substances, and then transformed into tablets.

The coating layer (2) is prepared by mixing sucralfate in suitable formulations, and is applied to the core (1) by means of the double-compression technique, i.e., by compressing two coating layers respectively positioned on and under the core.

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tive principles, in addition to sucralfate, also mucin, cellulose derivatives, natural or synthetic polymeric materials, alone, or as different combinations with each other.

The coating layer is so formulated, as to release an extremely subdivided dispersion of sucralfate before that the FANS composing the core comes in contact with the gastric and duodenal mucosa.

The action of this farmaceutical form is hence developed in two sequential steps, whose sequence is evidenced by observations related to tests carried out on animal. The steps of this action are:

A) Disintegration quick and of microgranular type, in the acidic medium of the stomach, of the coating layer, with formation of a wide dispersion of the protective agent composing it. The active principle of the coating has hence the time and the possibility of lining the gastric and intestinal mucosa, protecting it from the subsequent contact with the ulcerogenic drug contained in the core.

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In this way, the lesioning action of the drug contained in the core is limited by the action of the protective drug.

Several compositions containing sucralfate : FANS in weight ratios comprised within the range of from 1: 4 to 8 : 1 have been tested on rats by means of the test of pylorus ligature according to the technique Linda J. et al., J. Pharmac., 1978, 30, 244 - 246 "Inhibitors of Gastric Lesions in the Rat".

The testing has been carried out on Charles River Wistar rats of 230 - 270 g of weight and in the number of 8 rats per each group. The rats, fasting from 15 hours, have been submitted to etheric anesthesia and then to the liga

ture of the pylorus. The rats have been treated, immediately after the recovery, by means of gastric probe, with the FANS alone, with the FANS in the sucralfate-FANS form with sequential action according to the present invention, and by means of the administering of sucralfate first, and then, after a 10 minutes interval, of FANS.

The single active principles have been administered as aqueous suspension in sodium-CMC at 0.5% p.o.

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computated by the probit method.

In Table 1 the values of ID_{50} of sucralfate for various FANS are reported, in the case of the contemporary administering of FANS and sucralfate, and in the case of the administering in the form with sequential activity according to the present invention.

TABLE 1

Inhibiting Dosis 50 of sucralfate for the ulcerogenic activity of some FANS (mg)

FANS	Contemporary administering of sucralfate and of FANS	Administering of the sucralfate-FANS form with sequential action
Sodium indoprofen betainate (200 mg/kg as indoprofen)	206	85.6
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It results from Table 1 in a clear way that the administering of the form of sucralfate-FANS with sequential action is capable of protecting to a significantly greater extent the gastric mucosa against the lesioning power of FANS.

To illustrative, but not limitative, purpose of the present invention, the following Example is reported, relating to a formulation of the pharmaceutic form with sequential action (the numbers indicate parts by weight):

a) Formulation of the core of sodium indoprofen betainate

Sodium indoprofen betainate	290
Ethylcellulose	5
Carboxymethyl starch	12

Magnesium stearate	3

b) Preparation of the core

Indoprofen betainate is made into a paste with an alcoholic solution of ethylcellulose, the paste is granulated and dried. The dried granulate is mixed with the lubricant agent (magnesium stearate) and then with the disintegrating agent (carboxymethyl starch), and is compressed to form tablets of slightly crowned shape, with punches of 9 mm in diameter.

c) Formulation of the coating layer

Sucralfate	100
Crosslinked carboxymethylcellulose	10
Microcrystalline cellulose	40
Magnesium carbonate	10
CL Polyvinylpirrolidone	5
Magnesium stearate	2

The components of the formulation are mixed in a V-mixer.

d) Application of sucralfate coating on the core of sodium indoprofen betainate.

The application of the coating layer on the core is carried out by means of the double-compression technique, by compressing two layers of coating positioned on the core and under it, a coated tablet of suitable diameter being obtained, wherein the outer coating is constituted by sucralfate, and the inner core is constituted by indoprofen betainate (see figure 1).

Claims

1. Solid pharmaceutical form, for administration by oral way, with sequential release of the contained active principles, characterized in that it is constituted by

(a) a centre core containing an active principle displaying antiinflammatory and analgesic activity, with ulcerogenic side effects;

(b) a coating layer for said core, containing a second active principle displaying a protective action for the gastric and duodenal mucosa, which is immediately released.

2. Pharmaceutical form according to claim 1, characterized in that the active principle contained in said core is constitutend by FANS (Non Steroidic Antiinflammatory drugs, NSAD), such as ASA, Indoprofen, Naproxen, Ketoprofen, Indomethacin, Diflunisal, Diclofenac or derivatives.

3. Pharmaceutical form according to claim 1, characterized in that said core shows a slow disintegration, or constitutes a system with bioeroded matrix and however of the type with properties of controlled release of the contained active principle.

4. Pharmaceutical form according to claim 1, characterized in that said core containes active principles provided with anti-inflammatory and analgesic activity, with ulcerogenic side effects, combined with each other or with other medicaments.

5. Pharmaceutical form according to claim 1, characterized in that said coating layer is constituted by active principles capable of performing a protective action on the gastric and duodenal mucosa such as, e.g., sucralfate, mucin, cellulose derivatives, natural or synthetic polymeric materials capable of forming a protective lining.

6. Pharmaceutical form according to claim 1, characterized in that said coating layer shows a disintegration quick and of the microgranular type in the acidic medium of the stomach, determining an immediate dispersion of the contained protective agent.

7. Pharmaceutical form according to claim 1, characterized in that sucralfate or another mucose-protecting agent and FANS are contained in a weight ratio comprised within the range of from 1 : 4 to 8 : 1.

8. Pharmaceutical form for oral usage according to claims from 1 to 7 and method for the preparation thereof, which is carried out by means of the double-compression technique, i.e., by compressing around said core containing the active principle provided with antiinflammatory and analgesic activity with ulcerogenic side effects, said coating layer containing an active principle provided with protective action for the gastric and duodenal mucosa.

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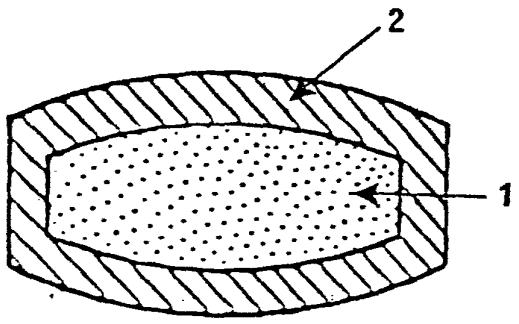

FIGURE 1

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(54) Oral solid pharmaceutical form with sequential action for the administering of drugs with ulcerogenic side effect.

(57) Oral solid pharmaceutical form with antiinflammatory and analgesic activity, with sequential action, with protective effect on the gastric and duodenal mucosa against the action of the active principles having ulcerogenic effect, contained in the same pharmaceutical form.

Said pharmaceutical form is constituted by a tablet comprising: (a) a centre core containing an active principle provided with antiinflammatory and analgesic activity, with ulcerogenic side effects; (b) a layer coating of said core, containing a second active principle provided with protective action for said gastric and duodenal mucosa, which is immediately released.

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EUROPEAN SEARCH REPORT

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Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X,Y	FR-M- 3 715 (L. NOUVEL) * Page 1, column 1, paragraphs 1,2,7; column 2, paragraph 5; claims *	1-7	A 61 K 9/24
D,P Y	DE-A-3 434 707 (LISAPHARMA) * Whole document *	1,2	
A	EP-A-0 064 485 (AB HÄSSLE) * Abstract; page 1, paragraph 2; claims *	1-7	

TECHNICAL FIELDS SEARCHED (Int Cl.4)
A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24-02-1987	BERTE M.J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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E : earlier patent document, but published on, or after the filing date
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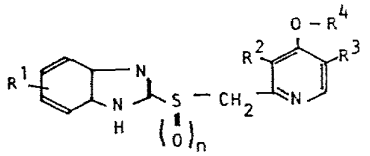
(54) **Pyridine derivatives and their production.**

(57) The compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a $C_{2\text{-}5}$ fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof is novel, and useful for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis.

Pyridine Derivatives and Their Production

This invention relates to pyridine derivatives useful as e.g. anti-ulcer agents and to a method of preparing them.

As the pyridine derivatives having anti-ulcer activity, those disclosed in USP. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/79) and USP. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/83) etc. have been known.

However, while these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents. Besides, these compounds are possessed of such drawbacks in the physico-chemical properties as being unstable and readily decomposed.

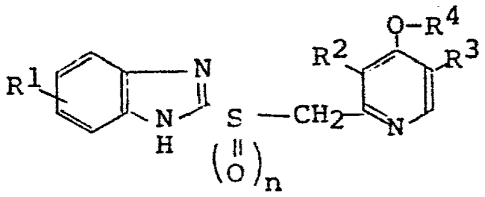
It is considered that gastrointestinal ulcer is induced by unbalance between aggressive factors, e.g. hydrochloric acid, pepsin, and defensive factors, e.g. mucus secretion and mucosal blood flow. Therefore, a medicine having both an action of inhibiting gastric acid secretion and an action of enhancing protection of gastric mucosa has been desired.

The present inventors diligently studied with the purpose of preparing an anti-ulcer agent having excellent actions of inhibiting gastric acid secretion, of

protecting gastric mucosa and of anti-ulceration. They found that a certain type of pyridine derivatives meet the said purpose, and they conducted further study to accomplish the present invention.

The present invention relates to

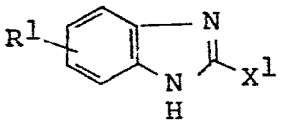
(1) pyridine derivatives of the formula (I)



(I)

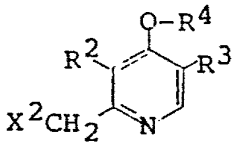
wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl, and n denotes 0 or 1, or their pharmacologically acceptable salts and

(2) a method for preparing a compound (I) or its pharmacologically acceptable salt, which comprises allowing a compound of the formula (II)



(II)

wherein R^1 is of the same meaning as defined above, to react with a compound of the formula (III)



(III)

wherein R^2, R^3 and R^4 are of the same meaning as defined above, one of X^1 and X^2 is SH and the other

is a leaving group and, when necessary, by subjecting the reaction product to oxidation.

In the above formulae, C_{2-5} fluorinated alkyl groups shown by R^4 are exemplified by 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 2,2,3,3-tetrafluoropropyl 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl and 2,2,3,3,4,4,5,5-octafluoropentyl.

Examples of the leaving groups X^1 and X^2 in the above formulae are halogen, preferably chlorine, bromine or iodine, or a reactive esterified hydroxy group, e.g. an arylsulfonyloxy, for example, phenylsulfonyloxy or tosyloxy, or a C_{1-4} alkylsulfonyloxy, for example, methanesulfonyloxy, or an organic phosphoryloxy, for example, diphenylphosphoryloxy, dibenzylphosphoryloxy or di-C_{1-4} alkylphosphoryloxy (e.g. dimethylphosphoryloxy) and the like.

R^1 may be located at 4- or 5-position, and preferably at 5-position.

A sulfide derivative (I) (n = 0), among the object compounds of this invention, can be prepared by allowing a compound (II) to react with a compound (III). It is convenient to conduct this reaction in the presence of a base. The base is exemplified by alkali metal hydride e.g. sodium hydride and potassium hydride; alkali metal e.g. metallic sodium; sodium alcoholate e.g. sodium methoxide and sodium ethoxide; alkali metal carbonate e.g. potassium carbonate and sodium carbonate; and organic amines e.g. triethylamine. The solvent used for the reaction is exemplified by alcohols e.g. methanol and ethanol, as well as dimethylformamide. The amount of a base used for the reaction is usually in a little excess to the equivalent, but it may be in a large excess. Specifically, it is about 1-10 equivalents, more preferably about 1-4 equivalents. The reaction temperature ranges usually from about 0°C to about the boiling point of the solvent then used, more preferably from about 20°C

to about 80°C. The reaction time ranges from about 0.2 to about 24 hours, more preferably from about 0.5 to about 2 hours.

A sulfinyl derivative (I) (n = 1), which is also among the object compounds of this invention, can be prepared by subjecting a compound (I) (n = 0) to oxidation. The oxidizing agent to be employed here is exemplified by peracid e.g. m-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid, or sodium bromite or sodium hypochlorite or hydrogen peroxide. The solvent used for the reaction is exemplified by halogenated hydrocarbon e.g. chloroform and dichloromethane, ethers e.g. tetrahydrofuran and dioxane, amides e.g. dimethylformamide, alcohols, e.g. methanol, ethanol, propanol, and t-butanol or water, and these solvents may used singly or in admixture. The oxidizing agent is used preferably in approximately equivalent or a little excess amount relative to the compound (I) (n = 0). Specifically, it is about 1 to about 3 equivalents, more preferably about 1-1.5 equivalent. The reaction temperature ranges from that under ice-cooling to about the boiling point of the solvent then employed, usually from that under ice-cooling to room temperature, more preferably from about 0°C to about 10°C. The reaction time usually ranges from about 0.1 to about 24 hours, more preferably from about 0.1 to about 4 hours.

The object compound (I) produced by the above reaction can be isolated and purified by conventional means e.g. recrystallization and chromatography.

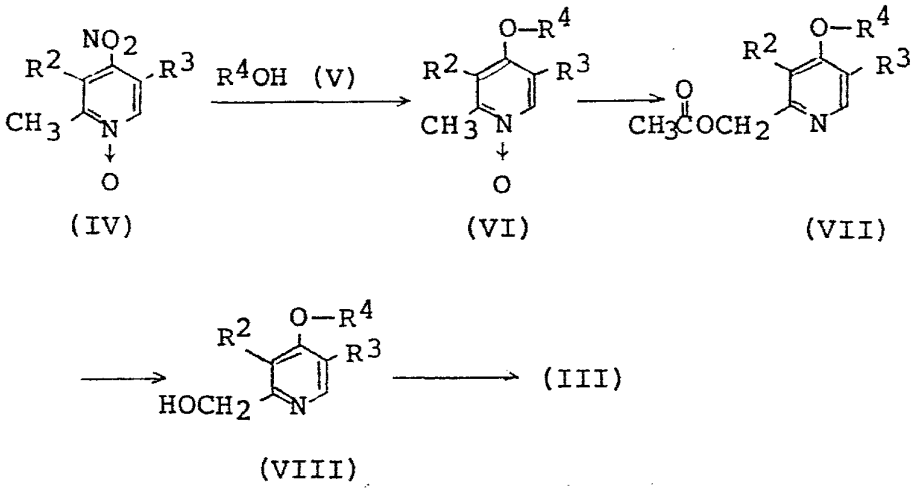
The compound (I) of this invention may be led to pharmacologically acceptable salts thereof by per se conventional means, the salts being exemplified by hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate.

Among the compounds (I), those of n = 0 give stable

salts, while those of n = 1 may exist as an aqueous solution though unstable.

The process of preparing the starting material (III) is described as follows.

Process 1)



(IV) (VI) (VII) (VIII) (III)

A nitro compound of the formula (IV) [wherein R^2 and R^3 are of the same meaning as defined above] is allowed to react with an alcohol derivative R^4OH (V) [wherein R^4 is of the same meaning as defined above] in the presence of a base to give an alkoxy derivative of the formula (VI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The base is exemplified by alkali metal e.g. lithium, sodium and potassium; alkali metal hydride e.g. sodium hydride and potassium hydride; alcoholate e.g. potassium t-butoxide and sodium propoxide; alkali metal carbonate or hydrogen carbonate e.g. potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate; or alkali hydroxide e.g. sodium hydroxide and potassium hydroxide. The solvent used for the reaction is exemplified by, besides R^4OH itself, ethers such as tetrahydrofuran and dioxane as well as ketones such as acetone and methyl ethyl ketone, aceto-

nitrile, dimethylformamide and hexamethylphosphoric acid triamide. The reaction temperature is suitably selected within the range from those under ice-cooling to those near the boiling point of the solvent used. The reaction time ranges usually from about 1 to about 48 hours.

The thus-obtained compound (VI) is subjected to heating (about 80 to about 120°C) in the presence of acetic anhydride singly or together with a mineral acid e.g. sulfuric acid and perchloric acid to give a 2-acetoxymethylpyridine derivative of the formula (VII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction time ranges usually from about 0.1 to about 10 hours.

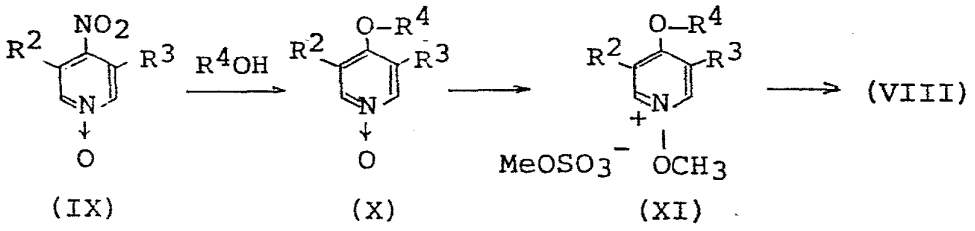
Then, the compound (VII) is subjected to alkali-hydrolysis to give a 2-hydroxymethyl pyridine derivative of the formula (VIII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The alkali is exemplified by sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. The solvent used for the reaction is exemplified by methanol, ethanol and water. The reaction temperature ranges usually from about 20°C to about 60°C. The reaction time is within the range of from about 0.1 to about 2 hours.

The compound (VIII) is further subjected to reaction with a chlorinating agent such as thionyl chloride, or an esterifying agent, e.g. an organic sulfonic acid chloride such as methanesulfonyl chloride or p-toluenesulfonyl chloride, or an organic phosphoric acid chloride such as diphenylphosphoryl chloride to give the compound (III). The amount of the chlorinating agent used for the reaction is usually in equivalent to a large excess relative to the compound (VIII). The solvent used for the reaction is exemplified by chloroform, dichloromethane and tetrachloroethane. The reaction temperature is usually within the range of from about 20°C to about

80°C, and the reaction time is about 0.1 to about 2 hours.

The amount of the organic sulfonic acid chloride or organic phosphoric acid chloride used for the reaction is usually in equivalent to a little excess, and the reaction is usually conducted in the presence of a base. The base is exemplified by organic base e.g. triethylamine and tributylamine, or inorganic base e.g. sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The amount of a base used for the reaction is usually in equivalent to a little excess. The solvent used for the reaction is exemplified by chloroform, dichloromethane, carbon tetrachloride or acetonitrile. The reaction temperature ranges usually from that under ice-cooling to about the boiling point of the solvent then used. The raction time ranges usually from a few minutes to a few hours. It is usually preferable to use the thus-produced compound (III) immediately for the reaction with a compound (II).

Process 2)



(IX) (X) (XI)

By a reaction similar to the above-described process (1), a compound of the formula (IX) [wherein R^2 and R^3 are of the same meaning as defined above] is led to a compound of the formula (X) [wherein R^2, R^3 and R^4 are of the same meaning as defined above].

Then, the compound (X) is subjected to methylation with dimethyl sulfate to give a compound of the formula

(XI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction can be conducted usually without solvent. The reaction temperature ranges from about 100°C to about 120°C, and the reaction time is within the range of from about 0.1 to about 4 hours.

Further, the compound (XI) is allowed to react with a radical source such as ammonium persulfate or any other persulfate in methanol to give the above-mentioned compound (VIII). The reaction temperature is within the range of from about 20°C to about 80°C, and the reaction time ranges from about 0.5 to about 4 hours.

Pharmacological actions of the compounds of the present invention are described as follows.

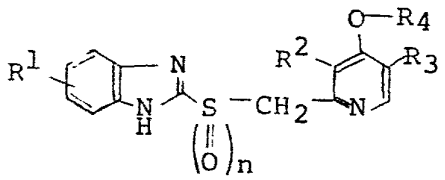
As the models of gastrointestinal ulcers, restraint and water-immersion stress-induced ulcer, indomethacin-induced ulcer and ethanol-induced gastric mucosal lesions have been used. However, as a model mimicking human gastric ulcer, indomethacin-induced gastric antral ulcer was reported in "Gastroenterology" (Satoh et al. 81, p. 719, 1981), which is considered to be of value as an experimental model. Therefore, the following are data of anti-ulcer actions of the object compounds (I) and of some representable known compounds, on the ulcer model in the above-mentioned literature reference.

Experimental Method:

Male Sprague-Dawley rats of 7-weeks old were fasted for 24 hours. These animals were administered test compounds into stomach by using a gastric tube. After 30 minutes, indomethacin, 30 mg/kg subcutaneously, was administered. During 30-90 minutes after the administration of indomethacin, these animals had free access to chow pellets (Japan Clea, CE-2). At 5 hours after the administration of indomethacin, 1 ml of 1% Evans blue was injected to the animals via the tail vein, followed by sacrificing these animals with carbon dioxide gas. The

stomach was removed together with the lower part of esophagus and the duodenum. The esophagus was clipped, 10 ml of 1% formalin solution was instilled into the stomach from the duodenum, and then the duodenum was clipped. The whole stomach was immersed in 1% formalin solution. About 15 minutes later, the stomachs were opened along the greater curvature. Area of the lesions occurred in the gastric antral mucosa was measured under a dissecting microscope with a square-grid eye piece (x10). The sum total of the individual lesions in each animal was measured, and the average value per group was calculated. Based on the difference between the average value of each group and that of the control group, the inhibition rate was determined. The test compound on indomethacin was suspended in a 5% gum arabic solution, and administered in a volume of 2 ml/kg.

Experimental Results:



R^1	R^2	R^3	R^4	n	Anti-ulcer action[a] ID_{50} (mg/kg, p.o.)
H	H	H	CH_2CF_3	1	2.4
H	CH_3	H	CH_2CF_3	1	<1.0
H	H	H	$CH_2CF_2CF_3$	1	1.3
H	CH_3	H	$CH_2CF_2CF_3$	1	<1.0
H	H	H	$CH_2CF_2CF_2H$	1	1.3
H	CH_3	H	$CH_2CF_2CF_2H$	1	<1.0

R^1	R^2	R^3	R^4	n	Anti-ulcer action[a] ID_{50} (mg/kg, p.o.)
H	CH_3	H	$CH_2CF_2CF_3$	0	3.7
5-OCH_3	CH_3	CH_3	CH_3 *1		21.0
5-CF_3	CH_3	H	CH_3 *2		5.5

*1 The compound disclosed in Example 23 of USP. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/1979)

*2 The compound disclosed in Example 3 of USP. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/1983)

a) Using 6 rats per group, each of the test compounds was administered in a dose of 1, 3, 10 and 30 mg/kg to determine ID_{50}.

As shown by the above data, the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5-20 times or more. Besides, the compound (I) of this invention shows excellent actions of inhibiting gastric acid secretion, protecting gastric mucous membrane and preventing ulceration.

Stating about the toxicity of the compound (I) of this invention, oral administration of the compound employed for the experiment of anti-ulceration (compound of R^1 = H, R^2 = CH_3, R^3 = H, R^4 = $CH_2CF_2CF_3$, n = 1) to mice even in a dose of 2000 mg/kg caused no fatal effect, thus the compound (I) being low in toxicity.

As described in the foregoing, the compound (I) of this invention has an anti-ulcer action, a gastric acid secretion controlling action and a mucous membrane protecting action, furthermore is of low toxicity and is

relatively stable as a chemical substance. The compound (I) of this invention can thus be used for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis in mammalian animals (e.g. mouse, rat, rabbit, dog, cat and man).

When the compound (I) of this invention is used as an anti-ulcer agent for the therapy of digestive ulcers in mammalian animals, it can be administered orally in a dosage form of capsules, tablets, granules, etc. by formulating with a pharmacologically acceptable carrier, excipient, diluent, etc. The daily dose is about 0.01-30 mg/kg, more preferably about 0.1-3 mg/kg.

Incidentally, the compound of this invention (I) (n = 0) is useful as a starting material for preparing the compound (I) (n = 1).

The processes of producing the starting compounds to be employed in the method of this invention as well as those of producing the compound (I) of this invention are specifically explained by the following Reference Examples and Working Examples.

Reference Example 1

In 2,2,3,3-tetrafluoropropanol (10 ml) was dissolved 2,3-dimethyl-4-nitropyridine-1-oxide (2 g). To the solution was added potassium t-butoxide (1.6 g) little by little at room temperature. The mixture was then heated at 80-90°C for 22 hours. The reaction solution was diluted with water, which was subjected to extraction with chloroform. The extract was dried on magnesium sulfate, and then concentrated. The concentrate was chromatographed on a column of silica gel (70 g). Elution was conducted with methanol-chloroform (1:10), and then subjected to recrystallization from ethyl acetate-hexane to yield 2.6 g of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 138-139°C.

After the manner similar to the above, compounds (VI) were prepared from compounds (IV).

Compound (VI)			
R^2	R^3	R^4	Melting point (°C)
H	H	CH_2CF_3	148-150
CH_3	CH_3	CH_2CF_3	138-139

Reference Example 2

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethyl phosphoric acid triamide (2.07 g) was heated at 70-80°C for 4.5 days under stirring, then insolubles were filtered off. The filtrate was concentrated, to which was added water. The mixture was subjected to extraction with ethyl acetate. The extract solution was dried on magnesium sulfate, followed by removing the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from ethyl acetate-hexane to yield 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 148-149°C.

After the manner similar to the above, compounds (VI) were prepared from starting compounds (IV).

Compound (VI)			
R^2	R^3	R^4	Melting point (°C)
CH_3	H	CH_2CF_3	131.0-131.5
H	CH_3	CH_2CF_3	153-154
H	H	$CH_2CF_2CF_3$	79-81

Compound (VI)			
R^2	R^3	R^4	Melting point (°C)
H	CH_3	$CH_2CF_2CF_3$	140-142
H	H	$CH_2CF_2CF_2H$	Oily
H	CH_3	$CH_2CF_2CF_2H$	143.5-144.5
CH_3	H	$CH_2CF_2CF_2H$	138-139

Reference Example 3

Concentrated sulfuric acid (two drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide (2.6 g) in acetic anhydride (8 ml). The mixture was stirred at 110°C for 4 hours, which was then concentrated. The residue was dissolved in methanol (20 ml), to which was added sodium hydroxide (1.2 g) dissolved in water (5 ml). The mixture was stirred at room temperature for 30 minutes, which was concentrated. To the residue was added water, and the mixture was subjected to extraction with ethyl acetate. The extract was dried on magnesium sulfate, followed by removal of the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from isopropyl ether to yield 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine as yellow crystals, m.p. 67-68°C.

After the manner similar to the above, compounds (VIII) were prepared from compounds (VI).

Compound (VIII)			
R^2	R^3	R^4	Melting point (°C)
H	H	CH_2CF_3	Oily
CH_3	H	CH_2CF_3	93.5-94.0
H	H	$CH_2CF_2CF_3$	Oily
CH_3	H	$CH_2CF_2CF_3$	Oily
H	CH_3	$CH_2CF_2CF_3$	87-89
H	H	$CH_2CF_2CF_2H$	88-89
H	CH_3	$CH_2CF_2CF_2H$	98-99
CH_3	H	$CH_2CF_2CF_2H$	67-68

Reference Example 4

To a solution of 3,5-dimethyl-4-nitropyridine-1-oxide (2.0 g) in 2,2,3,3,3-pentafluoropropanol (10 g) was added at 0°C little by little potassium t-butoxide (2 g) over 15 minutes. The mixture was stirred at 60°C for 18 hours. To the reaction mixture was added chloroform, which was subjected to filtration with celite. The filtrate was chromatographed on a column of silica gel (80 g), eluted with ethyl acetate-hexane (1:1), then with 20% methanol-ethyl acetate, and recrystallized from ether-hexane to yield 2.6 g of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as crystals, m.p. 89-91°C.

After the manner similar to the above, compounds (X) were prepared from compounds (IX).

Compound (X)			
R^2	R^3	R^4	Melting point (°C)
CH_3	H	CH_2CF_3	82-94
CH_3	CH_3	CH_2CF_3	138-139

Reference Example 5

A mixture of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide (2.5 g) and dimethyl sulfate (1 ml) was heated at 120°C for 30 minutes, to which was then added methanol (12.5 ml). To the mixture was added dropwise at 80°C ammonium persulfate (4.3 g) dissolved in water (20 ml)-methanol (10 ml) over 30 minutes, which was stirred for further 30 minutes. The resultant solution was concentrated. To the residue was added ice, which was neutralized with sodium carbonate, followed by extraction with chloroform. The extract was dried on sodium sulfate, followed by removing the solvent by evaporation to give 2.2 g of 3,5-dimethyl-2-hydroxymethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine as an oily substance.

After the manner similar to the above, compounds (VIII) were prepared from compounds (X).

Compound (VIII)			
R^2	R^3	R^4	Melting point (°C)
H	CH_3	CH_2CF_3	116-119
CH_3	CH_3	CH_2CF_3	62-63

Example 1

To a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine (350 mg) in chloroform (10 ml) was added thionyl chloride (0.2 ml). The mixture was refluxed for 30 minutes, which was then concentrated. The residue was dissolved in methanol (5 ml). The solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml), which was refluxed for 30 minutes. From the resultant was removed methanol by evaporation. To the residue was added water, which was subjected to extraction with ethyl acetate. The extract was washed with a dilute sodium hydroxide solution, followed by drying on magnesium sulfate. From the resultant was removed the solvent by evaporation. The residue was then chromatographed on a column of silica gel (20 g), eluted with ethyl acetate-hexane (2:1), and then recrystallized from ethyl acetate-hexane to yield 370 mg of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole·$\frac{1}{2}$ hydrate as colorless plates, m.p. 145-146°C.

After the manner similar to the above, compounds (I) (n = 0) were prepared by allowing compounds (II) with compounds (III).

Compound (I) (n=0)				
R^1	R^2	R^3	R^4	Melting point (°C)
H	H	H	CH_2CF_3	138-139
H	CH_3	H	CH_2CF_3	149-150
H	H	CH_3	CH_2CF_3	168-170
H	CH_3	CH_3	CH_2CF_3	151.5-152.0
H	H	H	$CH_2CF_2CF_3$	125-126

Compound (I) (n=0)					
	R^1	R^2	R^3	R^4	Melting point (°C)
	H	H	CH_3	$CH_2CF_2CF_3$	151-152
	H	H	H	$CH_2CF_2CF_2H$	Oily *3
	H	CH_3	H	$CH_2CF_2CF_2H$	134-135
	H	H	CH_3	$CH_2CF_2CF_2H$	148-149
	H	CH_3	CH_3	$CH_2CF_2CF_3$	158-160
*4	5-CF_3	CH_3	H	CH_2CF_3	92-93
	5-OCH_3	CH_3	H	CH_2CF_3	159-160
	5-OCH_3	H	H	CH_2CF_3	152-153

*3 NMR spectrum ($CDCl_3$) δ:4.35(S),4.39(t,t,J=1.5 and 12 Hz), 5.98 (1H,t,t,J=52.5 and 4 Hz), 6.81 (1H,d,d,J=2 and 6 Hz) 6.95 (1H,d,J=2Hz), 7.1-7.3 (2H,m), 7.4-7.7 (2H,m), 8.50 (1H,d,J=6 Hz)

*4: $\frac{1}{4}H_2O$ (crystal water)

Example 2

To a solution of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyrid-2-yl]methylthiobenzimidazole (2.2 g) in chloroform (20 ml) was added dropwise under ice-cooling over a period of 30 minutes m-chloroperbenzoic acid (1.3 g) dissolved in chloroform (15 ml). The solution was washed with a saturated aqueous solution of sodium hydrogen carbonate, then dried on magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (50 g), eluted with ethyl acetate, and then recrystallized from acetone-isopropyl ether to give 1.78 g of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyrid-2-yl]methylsulfinylbenzimidazole as pale yellow prisms, m.p. 161-163°C (decomp.).

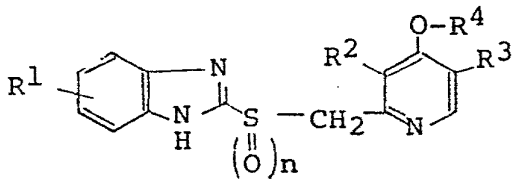
After the manner similar to the above, compounds (I) (n = 1) were prepared from compounds (I) (n = 0).

Compound (I) (n=1)				
R^1	R^2	R^3	R^4	Melting point (°C)
H	H	H	CH_2CF_3	176-177
H	CH_3	H	CH_2CF_3	178-182(d)
H	H	CH_3	CH_2CF_3	175-177(d)
H	CH_3	CH_3	CH_2CF_3	177-178(d)
H	H	H	$CH_2CF_2CF_3$	148-150(d)
H	H	CH_3	$CH_2CF_2CF_3$	145-148(d)
H	H	H	$CH_2CF_2CF_2H$	132-133
H	CH_3	H	$CH_2CF_2CF_2H$	147-148(d)
H	H	CH_3	$CH_2CF_2CF_2H$	136-139(d)
H	CH_3	CH_3	$CH_2CF_2CF_3$	157-159
5-CF_3	CH_3	H	CH_2CF_3	161-162(d)
5-OCH_3	CH_3	H	CH_2CF_3	140.5-142(d)
5-OCH_3	H	H	CH_2CF_3	162-163(d)

(Note) (d): decomposition

What we claim is:

1. A compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, and a pharmacologically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is hydrogen.

3. A compound according to claim 1 or 2, wherein R^2 is methyl.

4. A compound according to any of claims 1 to 3, wherein R^3 is hydrogen.

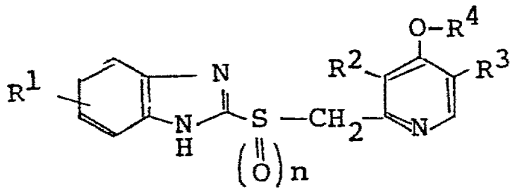
5. A compound according to any of claims 1 to 4, wherein R^4 is a C_{2-3} fluorinated alkyl.

6. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

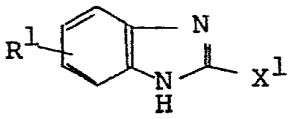
7. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

8. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

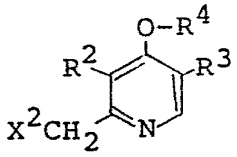
9. A method for producing a pyridine derivative of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof, which comprises allowing a compound of the formula



wherein R^1 is of the same meaning as defined above, to react with a compound of the formula

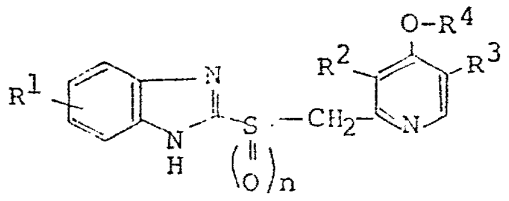


wherein R^2, R^3 and R^4 are of the same meaning as defined above, and one of X^1 and X^2 is SH and the other is a leaving group, and when necessary, by subjecting the reaction product to oxidation.

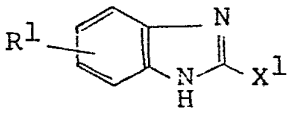
10. A method according to claim 9, wherein X^1 is SH and X^2 is halogen.

Claims for contracting state: AT (Austria)

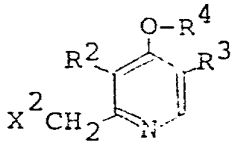
1. A method for producing a pyridine derivative of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof, which comprises allowing a compound of the formula



wherein R^1 is of the same meaning as defined above, to react with a compound of the formula



wherein R^2, R^3 and R^4 are of the same meaning as defined above, and one of X^1 and X^2 is SH and the other is a leaving group, and when necessary, by subjecting the reaction product to oxidation.

2. A method according to claim 1, wherein X^1 is SH and X^2 is halogen.

European Patent Office

EUROPEAN SEARCH REPORT

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Application number

EP 85 30 5458

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl.4)
A	EP-A-0 005 129 (HÄSSLE)		C 07 D 401/12 A 61 K 31/44
A	EP-A-0 080 602 (BYK GULDEN)		

TECHNICAL FIELDS SEARCHED (Int Cl.4)

C 07 D 401/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29-11-1985	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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& : member of the same patent family, corresponding document

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(54) Pharmaceutical formulations of acid labile substances for oral use.

(57) Pharmaceutical preparation containing an acid labile compound together with an alkaline reacting compound or an alkaline salt of an acid labile compound optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

EP 0 244 380 A2

Pharmaceutical formulations of acid labile substances for oral use

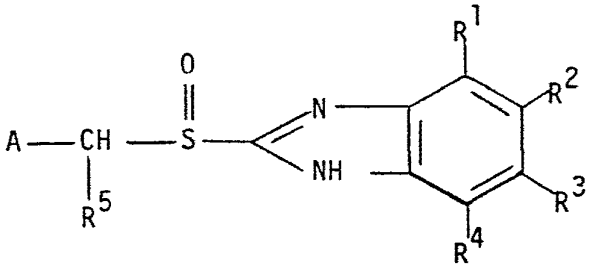
Field of the Invention

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use, to a method for the manufacture of such preparations and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

Background of the Invention

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



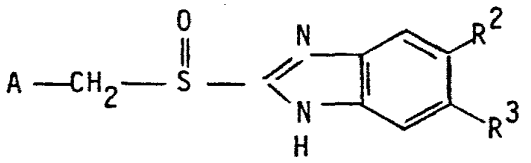
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4 are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylamino-benzyl)sulfinyl]-benzimidazole.

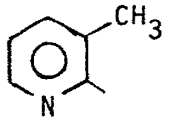
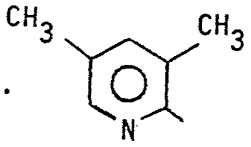
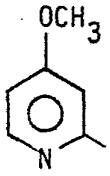
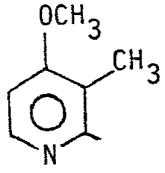
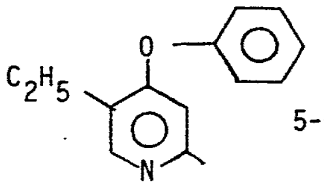
The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-85850258,6, EP-A1-0 080 602, EP-0127 736, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2- (2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-di--methylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into an active inhibitor of H^+K^+-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

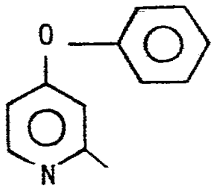
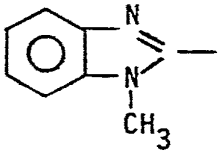
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
1.		5-$COOCH_3$;6-CH_3	11	150
2.		5-CH_3;H	5.4	1700
3.		5-CF_3;H	1.9	122
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620

Cont.

Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

Substituted sulfoxides, such as for instance the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+--ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidily decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a

combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestive is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

Outline of the invention

According to the present invention it has been found that the known acid labile compounds with the general formula I above in which R^1, R^2, R^3 and R^4 are the same or different and are

(a) hydrogen

(b) halogen, e.g. F, Cl, Br, I

(c) -CN

(d) -CHO

(e) $-CF_3$

(f) $-\overset{O}{\overset{\|}{C}}-R^{11}$

(g) $-O-C-R^{12}$

(h) $-CH(OR^{13})_2$

(i) $-(Z)_n-B-D$

(j) aryl containing up to 10 carbon atoms

(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms

(l) -alkylthio containing 1-6 carbon atoms

(m) $-NO_2$

(n) -alkylsulfinyl containing 1-6 carbon atoms

(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups

$(-\overset{O}{\overset{\|}{C}}-)$, whereby if R^1 and R^2, R^2 and R^3 or R^3 and

R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same or different, are

(a) aryl containing up to 10 carbon atoms
(b) alkoxy containing 1-4 carbon atoms
(c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is (a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is -O- or $-\overset{\overset{O}{\|}}{C}-$;

n is 0 or 1;

B is (a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms

(c) alkenylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is
(a) H
(b) -CN
(c) $-\overset{O}{\overset{\|}{C}}-R^9$
(d) $-(Y)_m-(\overset{O}{\overset{\|}{C}})_r-R^{10}$

wherein

R^9 is
(a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;

r is 0 or 1;

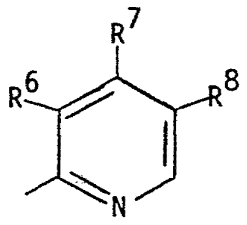
Y is
(a) -O-
(b) -NH-
(c) $-NR^{10}-$;

R^{10} is
(a) H
(b) alkyl containing 1-3 carbon atoms
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part

(d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

A is especially a pyridyl group in which R^6 and R^8 are the same or different, are



(a) H or
(b) alkyl containing 1-6 carbon atoms;

R^7 is
(a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms
(d) alkenyloxy containing 2-5 carbon atoms
(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) aryl containing up to 10 carbon atoms
(h) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or

(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$

$-O-(CH_2)_p-$

$-S-(CH_2)_v-$

$-CH_2(CH_2)_p-$

$-O-CH=CH-$

$-NH-CH=CH-$

$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{N}}-CH=CH-$

wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2- (4-methoxy-3,5 dimethyl--2-pyridinyl methyl sulfinyl -1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2- (2-dimethyl-aminobenzyl)sulfinyl -benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good

stability of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Detailed description of the invention

Cores

The acid labile active compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as

aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances such as $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3\ 4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; organic pH-buffering substances such as trishydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound such as the sodium, potassium, magnesium, calcium etc. salts of acid labile compounds,either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets or tablets, by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3,4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering substances such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering substances.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrollidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or the like. The thickness of the separating layer is not less than 2 µm, for small spherical pellets preferably not less than 4 µm, for tablets preferably not less than 10 µm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet another layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, pigments, titanium dioxide talc and other additives may also be included into the separating layer.

In the case of gelatin capsules the gelatin capsule itself serves as separating layer.

Enteric coating layer

The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the

trade name Eudragit^{R} L 12,5 or Eudragit^{R} L 100,(Röhm Pharma) or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit^{R} L 100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex^{R} (Pfizer) phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin

capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is usually administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as for example the individual requirement of the patients, the mode of administration and the disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the vovel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1 - 3 exemplify the invention.

Example 1

Uncoated pellets

I	Lactose powder	253	g
	Lactose anhydrous	167	g
	Hydroxypropyl cellulose	25	g

II	Compound 1, Table I	50	g
	Sodium lauryl sulphate	5	g
	Disodium hydrogen phosphate	1.5	g
	Sodium dihydrogen phosphate	0.1	g
	Distilled water	125	g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methyl-cellulose	20	g
	Distilled water	400	g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

	Subcoated pellets	500	g
IV	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table I.

Uncoated pellets

I	Compound 2, Table I sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture I.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose	20	g
	Aluminium hydroxide/magnesium carbonate	4	g
	Distilled water	400	g
	Pellets subcoated with III	500	g
IV	Hydroxypropyl methylcellulose	20	g
	Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500	g
V	Hydroxypropyl methylcellulose phthalate	57	g
V	Cetyl alcohol	3	g
V	Acetone	540	g
V	Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
Total	160 mg

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite $[Al_2O_3.6MgO.CO_2.12H_2O]$	0.3 mg

Separating layer (outer)

Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

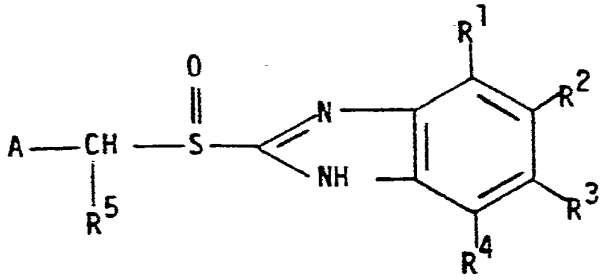
Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

CLAIMS

1. An oral, pharmaceutical preparation containing an acid labile compound as the active ingredient characterized in that it is composed of core material containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1, wherein the acid labile compound has the general formula I.



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$, $-O-\overset{O}{\overset{\|}{C}}$-lower alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

3. A preparation according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance $[Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O]$, wherein n not is an integer and less than two.

4. A preparation according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.

5. A preparation according to claim 4 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl--pyrrolidone.

6. A preparation according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

7. A preparation according to claim 6 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

8. A preparation according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

9. A preparation according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

10. A preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

11. A preparation according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

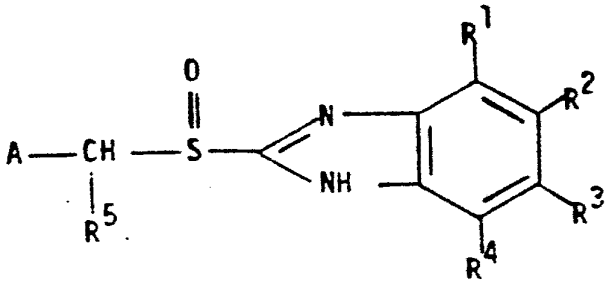
12. Process for the preparation of an oral pharmaceutical formulation containing an acid labile compound in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating layer.

13. Use of the preparation according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

CLAIMS FOR THE CONTRACTING STATES AT, ES, GR.

1. A process for the preparation of an oral, pharmaceutical formulation containing an acid labile compound as the active ingredient characterized in that the cores containing the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

2. A process according to claim 1, wherein the acid labile compound has the general formula I.



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$, $-O-\overset{O}{\overset{\|}{C}}$-lower alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl] -benzimidazole.

3. A process according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite

substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$], wherein n not is an integer and less than two.

4. A process according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.

5. A process according to claim 4 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl--pyrrolidone.

6. A process according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

7. A process according to claim 6 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

8. A process according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

9. A process according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

10. A process according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

11. A process according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

12. Use of the formulation prepared according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

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(54) Pharmaceutical formulations of acid labile substances for oral use.

(57) Pharmaceutical preparation containing an acid labile compound together with an alkaline reacting compound or an alkaline salt of an acid labile compound optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

EP 0 244 380 A3

0244380

European Patent Office

Application Number

EP 87 85 0126

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP-A-0 124 495 (AB HÄSSLE) * Page 2, line 19 - page 5, line 5; page 6, line 16 - page 7, line 10; claims *	1,8,10-13	A 61 K 9/32 A 61 K 9/52 A 61 K 9/54
D,X	EP-A-0 173 664 (AB HÄSSLE) * Page 1, line 1 - page 3, line 12; page 9, line 3 - page 10; page 21, line 26 - page 22, line 27; page 27, lines 1-31; page 37, line 19- page 38, line 12 *	1,2,6-13	
D,Y	EP-A-0 080 602 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GmbH) * Page 2, lines 1-21; page 3, lines 6-13; page 17, lines 10-20; page 18, lines 1-17; page 20, lines 4-34 *	1-13	
Y	GB-A- 760 403 (ABBOTT LABORATORIES) * Page 1, lines 11-34; page 2, lines 31-70; page 6, lines 3-18 *	1,2,10-13	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
Y	FR-A-2 272 639 (A. WARREN et al.) * Page 1, lines 1-3; page 2, line 19 - page 3, line 20; page 4, lines 19-22 *	3-9	A 61 K C 07 D
A	DE-A-3 233 764 (R.P. SCHERER GmbH) * Page 6, line 7 - page 7, paragraph 3; page 8, last paragraph *	1-13	
A	PATENT ABSTRACTS OF JAPAN, vol. 8, no. 106 (C-223)[1543], 18th May 1984; & JP-A-59 20 219 (SHINETSU KAGAKU KOGYO K.K.) 01-02-1984	1-13	

-/-

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	03-08-1988	MUELLNERS W.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

0244380

Application Number

EP 87 85 0126

European Patent Office

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	GB-A-1 190 387 (THE GREEN CROSS CORP.) * Page 1, lines 19-38; page 2, lines 33-44; claim 1 *	1-13	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	03-08-1988	MUELLNERS W.

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& : member of the same patent family, corresponding document

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(54) Nonsteroidal anti-inflammatory drug composition containing h1 blockers, h2 blockers, beta adrenergic agonists or combinations thereof and an alkalizing agent, and process for administration.

(57) A nonsteroidal anti-inflammatory drug composition containing as protectants against gastrointestinal injury, H_1 blockers, H_2 blockers, beta-adrenergic agonists, or combinations thereof, and an alkalizing agent and a process for administering such compositions.

EP 0 320 550 A1

NONSTEROIDAL ANTI-INFLAMMATORY DRUG COMPOSITION CONTAINING H_1 BLOCKERS, H_2 BLOCKERS, BETA-ADRENERGIC AGONISTS OR COMBINATIONS THEREOF AND AN ALKALIZING AGENT, AND PROCESS FOR ADMINISTRATION.

This invention relates to nonsteroidal anti-inflammatory compositions containing, as protectants against gastrointentinal injury caused by said nonsteroidal anti-inflammatory drug (hereinafter sometimes referred to as NSAID), a protectant selected from the group consisting of H_1 blockers, H_2 blockers, beta-adrenergic agonists, and combinations thereof. More particularly, it concerns compositions of this character, that also contain an alkalizing agent, and a process that uses such compositions. The terms H_1 blockers and H_2 blockers are used herein to refer to the histamine H_1- and H_2-receptor blockers, respectively.

H_1 blockers, H_2 blockers, as well as beta-adrenergic agonists, have been shown to offer some protection against gastrointestinal injury that is sometimes caused by the administration of NSAIDs. These, however, have suffered from some very distinct disadvantages. Among such advantages is the delay in relieving the subjective symptoms of gastric distress that is experienced by individuals who have taken such products.

It has now been found that the aforesaid disadvantages may be avoided by also incorporating an alkalizing agent in said NSAID composition containing a gastrointestinal protectant selected from the group consisting of H_1 blockers. H_2 blockers, beta-adrenergic agonists, and combinations thereof. In addition, it has been found that by incorporating said alkalizing agent in the compositions of interest there is often also observed an improvement in the ability of such compositions to protect against gastrointestinal injury that may be caused by said NSAIDs.

It has been suggested in the prior art that the coadministration of cimetidine with an antacid is to be avoided. In this connection, attention is directed to the "Physicians Desk Reference", 40th Edition, 1986, page 1726 and AMA Drug Evaluations" 5th Edition p. 1267. The latter is prepared and published by the American Medical Association, Chicago, Illinois. In contrast to this, applicants did not observe any reduction in efficacy when the alkalizing agents were coadministered with H_2- or H_1-blockers and a NSAID.

It has also been reported in prior art that H_2-receptor blocking agents or antagonists protect against aspirin-induced lesions in certain laboratory animals. One such study is reported in Gastroenterology Vol. 88, NO. 5 part 2. p. 1344. This reference teaches nothing with regard to the use of an alkalizing agent as is characteristic of the present invention.

Cyproheptadine has been evaluated as a protectant against aspirin-induced gastric injury (Indian J. Med. Res. 1980, 71, p. 926-32). Although cyproheptadine may have some H_1-receptor antagonist properties, it does not act exclusively at the H_1-receptor sites but rather acts predominantly at serotonin-receptor sites (Goodman and Gilman "The Pharmacological Basis of Therapeutics", 7th Edition, p. 634). In addition, in the Indian Journal reference, the aspirin and cyproheptadine are not coadministered but are given serially. This is to be contrasted with the present invention in which the H_2- or H_2-receptor blocker or the beta-adrenergic agonist is coadministered with the aspirin. Furthermore, the treatment with cyproheptadine in accordance with the Indian reference is reported as not modifying the gastric acidity. This is also in contrast with the experience in this invention in which significant modification of gastric acidity takes place with the administration of aspirin and gastroprotectants utilized for the present purposes. Still a further distinction of the instant invention over the Indian Journal teaching is the fact that in the latter cyproheptadine was administered by intraperitoneal injection prior to the intragastric administration of the aspirin. This is to be contrasted with the fact that the compositions of the present invention lend themselves to oral administration at which time the NSAID and the H_1- or H_2-receptor blocker are coadministered. Most importantly perhaps, like the other reference discussed above, the Indian Journal reference nowhere suggests the use nor the advantages that follow from its use of an alkalizing agent. This, as will be made clear below, is an essential feature of the present invention.

The NSAIDs form a well-known class of drugs that are anti-inflammatory analgesics. These have the common property of inhibiting the formation of prostaglandins, which have a protective affect on the gastrointestinal mucosa (Goodman and Gilman "The Pharmacological Basis for Therapeutics" 7th Edition, p. 678). It is because of this inhibiting effect that the oral administration of drugs of this class may result in gastrointestinal injury and/or bleeding and is at least part of the problem that the present invention seeks to reduce or eliminate.

A number of NSAIDs are known in the prior art to which the present invention has application. The most commonly known group are the salicylates of which aspirin is the prime example. A further group of NSAIDs that have utility in connection with the instant invention are the proprionic acid derivatives. Included in this group are ibuprofen and naproxen. A further group of NSAIDs, employable herein, are the fenamates

and compounds closely related to them structurally. These may be illustrated by such compounds as mefenamic acid, meclofenamate sodium, diclofenac and its sodium salt. Also belonging to the class NSAIDs with which the present invention is concerned are the indole derivates (e.g. indomethacin); pyrrole alkanoic acid derivatives (e.g. tolmetin); pyrazalone derivates (e.g. phenylbutazone); oxicams (e.g. piroxicam), etc.

The NSAID will be contained in the composition of this invention at concentrations at which it is generally found in therapeutic NSAID compositions intended for oral administration. This will usually be a pharmaceutically acceptable analgesic/anti-inflammatory dose.

A number of H_1- and H_2-receptor blockers are known in the prior art which are useful for the purposes of the present invention. By way of illustrating the H_1-receptor blockers that may be employed herein, mentioned may be made of the following: ethanolamines (e.g. diphenhydramine or its hydrochloride salt; carbinoxamine or its maleate salt); ethylenediamines (e.g. tripelennamine or its hydrochloride or nitrate salts); alkylamines (e.g. chlorpheniramine or its maleate salt, brompheniramine or its maleate salt); piperazines (e.g. hydroxyzine or its hydrochloride or pamoate salts, cyclizine or its hydrochloride or lactate salts, meclizine or sits hydrochloride salts); etc. To exemplify the H_2-receptor blockers that may be advantageously used in the practice of this invention the following are given: cimetidine, ranitidine, famotidine, etc.

The H_1- and H_2-receptors blockers may be used in the form of their bases or in the form of their pharmaceutically acceptable salts. When employed as salts these will usually be acid addition salts wherein the acid portion may be hydrochloride, maleate, ascorbate, citrate, pamoate, lactate, tartrate, sulfate, etc.

The quantity of H_1-receptor blocker that will be contained in the composition of this invention may vary somewhat because of the variations in the anticholinergic activity that these agents exhibit. All that is required is that an effective amount be present so that the H_1-receptor blocker can make its contribution as a protectant against NSAID-induced gastrointestinal injury.

Similarly, the quantity of H_2-receptor blocker in the present composition may also vary. Again, all that is required is that amount employed be an effective protectant quantity which will enable the H_2-receptor blocker to play its part as a gastrointestinal protectant.

A number of beta-adrenergic agonists are known in the prior art which are useful for the purpose of this invention. Of special interest are isoproterenol which is a mixed beta-1 and beta-2 agonist and terbutaline which is a more selective beta-2 agonist. By way of illustrating the other beta-adrenergic agonists that may be employed herein, the following are given: metaproterenol, albuterol, ritodrine. All of these may be employed as such or as pharmaceutically acceptable salts.

As with the other active ingredients contained in the compositions of this invention, the quantity of beta-adrenergic agonist that will be contained therein may also vary somewhat. Again, all that is required is that it be contained in said composition in an amount which will enable the beta-adrenergic agonist to play its part as a gastrointestinal protectant.

As indicated above, it is a feature of the present invention to incorporate in the instant composition an alkalizing agent. Since this composition is intended for oral administration, the akalizing agent employed will be one which is a pharmaceutically acceptable one that may be tolerated at the concentrations at which it is administered. A number of such alkalizing agents are known in this art which are suitable for the present purpose. By way of illustration, the following may be mentioned: sodium bicarbonate, magnesium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide, magnesium trisilicate, aluminum hydroxide, aluminum carbonate, potassium bicarbonate, etc.

The quantitive relationships of the various components of the composition of this invention may be expressed on the basis of the average daily dose of the ingredient contained in the product. This will take the form of weight of the ingredient per kg of body weight of the subject per day (e.g. milligrams or grams/kg of body weight/day). In general, this relationship may be expressed for the various ingredients as follows:

(a) NSAID: from about 10 mg/kg/day to about 100 mg/kg/day; preferred range from about 15 mg/kg/day to about 75 mg/kg/day.

(b) H_2-receptor blocker (when employed): from about 0.01 mg/kg/day to about 1g/kg/day; preferred range from about 0.01 mg/kg/day to about 10 mg/kg/day.

(c) H_1-receptor blocker (when employed): from about 2.5 ug/kg/day to about 500 mg/kg/day; preferred range from about 0.1 mg/kg/day to about 50 mg/kg/day.

(d) beta-adrenergic agonist (when employed): from about 0.30 ug/kg/day to about 500 mg/kg/day; preferred range from about 0.01 mg/kg/day to about 10 mg/kg/day.

(e) alkalizing agent: from about 0.02 mEq/kg/day to about 10 mEq/kg/day; preferred range from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

The compositions of the present invention may also be made up in unit dosage forms. Each unit doage form will be sized and contain the ingredients in such amount that they may be taken orally in comfortable and convenient manner. Given below are the quantities of each type of active ingredient, when present in the composition, that will be contained in each:

TABLE I

Ingredient	mg. per Unit dose General
NSAID	about 200 mg to about 600 mg.
H_1 Blocker	about 0.01 mg to about 70 mg.
H_2 Blocker	about 0.5 mg to about 350 mg
Beta-Adrenergic Agonist	about 0.7 mg to about 70 mg.
Alkalizing Agent	about 2 mEq to about 10 mEq

The present products may be made into capsules, tablets, powders or caplets and may be film-coated, enteric-coated or formulated into sustained-release dosage forms or liquid dosage compositions. When formed into tablets or caplets they may contain adjuvants that facilitate the tableting of the product or enhance its elegance or dissolution rates. Generally illustrative of the adjuvants that may be contained in the various dosage forms encompassed in the present invention, the following may be mentioned: disintegrating agents, binders, lubricants, fillers, glidents, surfactants, flavoring agents, sweeteners, solvents, liquid carriers, suspending agents, preservatives, etc. More particularly, the adjuvants that may be contained in the various dosage forms over and above the active ingredients are as follows:

Caplet and Tablet

Cellulose, lactose, corn starch, stearic acid, water, gelatin, talc, sterotix, magnesium stearate, terra alba, sucrose, agar, pectin, Cab-O-Sil, acacia, etc.

Capsule:

Spray-dried lactose, dimethylsiloxane, corn starch, water, magnesium stearate, sucrose, agar, pectin, Cab-O-Sil, etc.

Liquid Dosage Forms:

Polyethylene glycol, sucrose, povidone, sodium citrate, citric acid, flavor, color, quinine, salicylic acid, water, peanut oil, olive oil, sesame oil, etc.

Sustained-release compositions may contain such things as glyceryl monostearate or glyceryl distearate.

In addition, these products may also contain other pharmaceutically active ingredients, such as decongestants, analgesic adjuvants, antihistamines, expectorants, antitussives, diuretics, other analgesics, other anti-inflammatory agents, other antipyretics, other antirheumatics, antioxidants, vasodilators, smooth muscle relaxants, skeletal muscle relaxants, bronchodilators, vitamins, trace minerals, amino acids, biological peptides, etc.

The compositions of this invention are useful in treating conditions and symptoms that are classically treated by the administration of NSAIDs. These include headache pain, pain and inflammation associated with arthritis and other systemic diseases, elevated body temperatures, etc. A variety of regimens may be employed in treating these conditions in accordance with the present invention. This will depend upon the particular unit dosage form that is used in the regimen. In the typical case one or two tablets will be taken every 4 to 6 hours, as needed.

The following examples are given to further illustrate the present invention. It is to be understood, however, that the invention is not limited thereto.

Example 1

Aspirin 325 mg
Diphenhydramine hydrochloride 16.67 mg
Sodium bicarbonate 5 mEq

The above ingredients are mixed in powdered or granular form and loaded into gelatin capsules.

Example 2

Aspirin 325 mg
Ranitidine hydrochloride 3.33 mg
Sodium bicarbonate 5 mEq

Prepared as described in Example 1

Example 3

Aspirin 325 mg
Metaproterenol sulfate 0.83 mg
Sodium bicarbonate 5 mEq

Prepared as described in Example 1

To test the effectiveness of the composition of this invention in protecting the stomach against NSAID-induced muscosal injury each protectant, in combination with an alkalizing agent, is administered orally with aspirin in capsules. For purposes of comparison, the protectant alone or the alkalizing agent alone is administered with the aspirin. A standard dose of 975 mg of aspirin is administered with varying doses of protectant and or alkalizing agent.

All test formulations are prepared on the day of the tests. The capsules are placed in the back of the dog's throat. A catheter, with funnel attached, is positioned in the dog's stomach and 50 ml of deionized water is administered.

Healthy adult beagle dogs of either sex are selected for testing. Dogs are housed individually in stainless steel cages with grid floors to allow excreta to pass through. Room temperature in the holding rooms and test laboratories is maintained between 65 ° F and 85 ° F and relative humidity between 30% and 80%. Room lights remain on from 6:00 AM to 4:00 PM.

Each dog is trained to stand in a stanchion with sling support and to accept a bit tied in its mouth. A gastroscope is then passed through the bit into the dog's stomach. This training requires ten days to two weeks in most dogs.

To determine whether a dog is suitable for test purposes, its stomach is examined for a normal mucosa, and its gastric responsiveness to aspirin is evaluated (as under Test Procedure). An acceptable gastric irritation score in the antrum must be 5 or greater (on a scale of 0-7) 2 hours after dosage.

Food is withheld from test dogs for 24 hours before the test and during the test and water is allowed ad lib. The dogs are moved into a holding area away from the kennel. Fasted dogs of either sex are examined gastroscopically to ensure that their stomachs have normal healthy mucosal linings. The dogs are dosed orally with test formulations, which are flushed into their stomachs with 50 ml of deionized water. They are then re-examined 20 hours later for gastric petechiae and signs of bleeding according to the following scale:

0 = uniform, pale to dark pink mucosa
1 = darker pink or blotchy mucosa
2 = petechiae and/or light-red streaks
3 = few small lesions
4 = many or connected small lesions (striations)
5 = few large lesions
6 = many large lesions

7 = massive hemorrhagic damage

Severity of bleeding for each treatment and at each time is calculated as the mean gastric irritation score.

In addition to the endoscopic observation of the gastric mucosa of each dog, a qualitative description of gastric fluid is recorded and a pH measurement is made of the gastric fluid. All of these are done 2 hours after administration of the test product.

A base line is established by measuring the various parameters after the administration of 975 mg of aspirin. The normal resting stomach has an irritation score of 0 and a pH of 5 to 5.5. Aspirin given alone, produced injury with scores of approximately 5.5 after 2 hours. The gastric pH at this time was about 3.1.

The results of these tests are summarized in Tables II, III and IV below. Table II summarizes the results obtained with an H_1 blocker and alkalizing agents; Table III the results obtained with H_2 blockers and an alkalizing agent; and Table IV the results obtained with beta-adrenergic agonists and alkalizing agents. These tables also include the data obtained with the protectant or alkalizing agent alone. With each of the test compositions set forth in these tables, 975 mg of aspirin was simultaneously administered. The aspirin was contained in the same capsule along with the other test ingredients.

In these tests the active ingredients were administered in the following forms:

diphenhydramine: [hydrochloride]
ranitidine: [hydrochloride]
cimetidine: [free base]
terbutaline: [sulfate]
albuterol: [free base]
isoproterenol: [hydrochloride]

Table II

Non-steroidal Anti-inflammatory Compositions Protected Against Gastrointestinal Injury with Combinations of H_1 Blocker and Alkalizing Agents.

Data Summary

	2-Hour Data		
	(N)	Irritation Score	pH
Control	13	0	5.7
Aspirin 975 mg	8	5.5	3.3
Diphenhydramine (12.5 mg) + Aspirin (975 mg)	4	5.5	1.4
" (25.0 mg) + Aspirin (975 mg)	4	5.75	2.1
" (50.0 mg) + Aspirin (975 mg)	5	4.0	3.6
Magnesium Oxide (12 mEq) + Aspirin (975 mg)	12	3.50	---
Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	6	2.0	5.5
Diphenhydramine (25 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	4	1.0	5.8
Diphenhydramine (25 mg) + Sodium Bicarb. (15 mEq) + Aspirin (975 mg)	4	1.25	6.0
Diphenhydramine (12.5 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	4	3.00	2.7
Diphenhydramine (12.5 mg) + Sodium Bicarb. (15 mEq) + Aspirin (975 mg)	4	3.25	3.4
Diphenhydramine (6.25 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	3	5.33	1.8

Table III

Non-steroidal Anti-inflammatory Composition Protected Against Gastrointestinal Injury with Combinations of Certain H_2 Blockers and Alkalizing Agents.

Data Summary

	2-Hour Data		
	(N)	Irritation Score	pH
Control	13	0	5.7
Aspirin (975 mg)	8	5.5	3.3
Ranitidine (10 mg) + Aspirin (975 mg)	6	3.50	5.3
" (20 mg) + Aspirin (975 mg)	8	1.88	5.9
" (50 mg) + Aspirin (975 mg)	6	0.67	6.1
$NaHCO_3$ (12 mEq) + Aspirin (975 mg)	11	4.1	3.8
" (15mEq) + Aspirin (975 mg)	6	2.0	5.5
Ranitidine (10 mg) + $NaHCO_3$ (10 mEq) + Aspirin (975 mg)	5	3.00	5.3
Ranitidine (50 mg) + $NaHCO_3$ (10 mEq) + Aspirin (975 mg)	5	0.60	6.7
Cimetidine (50 mg) + Aspirin (975 mg)	5	2.40	5.6
Cimetidine (150 mg) + Aspirin (975 mg)	6	0.33	6.0
Cimetidine (50 mg) + $NaHCO_3$ (4.8 mEq) + Aspirin (975 mg)	6	2.83	4.4
Cimetidine (50 mg) + $NaHCO_3$ (9.6 mEq) + Aspirin (975 mg)	6	2.83	3.9
Cimetidine (50 mg) + $NaHCO_3$ (14.4 mEq) + Aspirin (975 mg)	6	1.33	5.1
Cimetidine (150 mg) + Sodium Bicarb. (15 mEq) + Aspirin (975 mg)	6	0.67	7.2

Note: At the highest dose tested, the alkalizing agent gave added protection against aspirin-induced injury and reduction in pH.

Table IV

Non-steroidal Anti-inflammatory Compositions Protected Against Gastrointestinal Injury with Combinations of Certain Beta Agonists and Alkalizing Agents.			
Data Summary			
	2-Hour Data		
	(N)	Irritation Score	pH
Control	13	0	5.7
Aspirin (975 mg)	8	5.5	3.3
Terbutaline (1.25 mg) + Aspirin (975 mg)	4	4.0	2.9
" (2.50 mg) + Aspirin (975 mg)	4	2.0	3.8
" (5.00 mg) + Aspirin (975 mg)	8	1.4	4.0
" (10.0 mg) + Aspirin (975 mg)	5	1.2	4.6
Albuterol (2.0 mg) + Aspirin (975 mg)	4	2.8	2.7
" (4.0 mg) + Aspirin (975 mg)	4	1.5	4.8
" (8.0 mg) + Aspirin (975 mg)	4	1.0	5.4
Isoproterenol (7.5 mg) + Aspirin (975 mg)	9	3.9	3.5
" (15.0 mg) + Aspirin (975 mg)	9	2.7	3.8
" (30.0 mg) + Aspirin (975 mg)	10	1.3	5.0
Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	6	2.0	5.5
Magnesium Oxide (12 mEq) + Aspirin (975 mg)	12	3.5	
Terbutaline (5.0 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	4	1.0	5.8
Terbutaline (5.0 mg) + Magnesium Oxide (15 mEq) + Aspirin (975 mg)	4	2.0	6.3
Terbutaline (1.25 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	4	3.2	2.0
Albuterol (2.0 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	4	0.75	5.7
Isoproterenol (30 mg) + Sodium Bicarbonate (15 mEq) + Aspirin (975 mg)	5	1.2	7.4

Note: The concomitant use of these drugs may permit the use of a lower dose of the beta agonist without compromising objective or subjective tolerance.

Claims

1. A nonsteroidal anti-inflammatory drug composition having reduced potential for gastrointestinal injury induced by said anti-inflammatory drug, comprising an anti-inflammatory amount of said anti-inflammatory drug, a gastrointestinal protective amount of a protectant selected from the group consisting of histamine H_1-receptor blockers, histamine H_2-receptor blockers, beta-adrenergic agonists and combinations thereof, and effective alkalizing amount of an alkalizing agent.

2. A composition according to claim 1 wherein said protectant is an histamine H_1-receptor blocker.

3. A composition according to claim 1 wherein said histamine H_1-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof.

4. A composition according to claim 1 wherein said histamine H_1- receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

5. A composition according to claims, 1, 2, 3, or 4 having a daily average dose for the active ingredients as follows:

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;

(b) histamine H_1-receptor blocker; from about 2.5 ug/kg/day to about 500 mg/kg/day; and

(c) alkalizing agent; from about 0.02 mEq/kg/day to 10 mEq/kg/day.

6. A composition according to claims 1, 2, 3, or 4 having a daily average dose for the active ingredients as follows:

(a) nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;

(b) histamine H_1-receptor blocker; from about 0.1 mg/kg/day to about 50 mg/kg/day; and
(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

7. A nonsteroidal anti-inflammatory composition according to claims 1, 2, 3 or 4 in unit dosage form containing the active ingredients in the following amounts per unit dose:
(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;
(b) histamine H_1-receptor blocker; from 0.01 mg to about 70 mg; and
(c) alkalizing agent; from about 2 mEq to about 10 mEq.

8. A composition according to claim 1 wherein said protectant is an histamine H_2-receptor blocker.

9. A composition according to claim 8 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof.

10. A composition according to claim 8 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen, and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

11. A composition according to claims 8, 9, or 10 having a daily average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;
(b) histamine H_2-receptor blocker; about 0.01 mg/kg/day to about 1 g/kg/day; and
(c) alkalizing agent; from about 0.02 mEq/kg/day to about 10 mEq/kg/day.

12. A composition according to claims 8, 9, or 10 having a daily average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;
(b) histamine H_2-receptor blocker; from about 0.01 mg/kg/day to about 10 mg/kg/day; and
(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

13. A nonsteroidal anti-inflammatory composition according to claims 8, 9 or 10 in unit dosage form containing the active ingredients in the following amounts per unit dose:
(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;
(b) histamine H_2-receptor blocker; from 0.5 mg to about 350 mg; and
(c) alkalizing agent; from about 2 mEq to about 10 mEq.

14. A composition according to claim 1 wherein said protectant is a beta-adrenergic agonist.

15. A composition according to claim 14 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol, and pharmaceutically acceptable salts thereof.

16. A composition according to claim 14 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alka- lizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

17. A composition according to claims 14, 15 or 16 having a daily average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;
(b) beta-adrenergic agonist from about 0.3 ug/kg/day to about 500 mg/kg/day; and
(c) alkalizing agent; from about 0.02 MEq/kg/day to about 10 mEq/kg/day.

18. A composition according to claims 14, 15, and 16 having a daily average dose for the active ingredients as follows:
(a) nonsteroidal anti-inflammatory drug; from about 15 mg/kg/day to about 75 mg/kg/day;
(b) beta-adrenergic agonist from about 0.1 mg/kg/day to about 10 mg/kg/day; and
(c) alkalizing agent; from about 0.04 MEq/kg/day to about 2 mEq/kg/day.

19. A nonsteroidal anti-inflammatory composition according to claims 14, 15 or 16 in unit dosage form containing the active ingredients in the following amounts per unit dose:
(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;
(b) beta-adrenergic agonist; from 0.7 mg to about 70 mg; and

(c) alkalizing agent; from about 2 mEq to about 10 mEq.

20. A process for administering a therapeutically effective amount of a nonsteroidal anti-inflammatory composition which comprises administering said anti-inflammatory compound in the compositions defined in claims 1, 2, 3, 4, 8, 9, 10, 14, 15 or 16.

Claims for the following contracting States: ES, GR

1. A method of preparing a nonsteroidal anti-inflammatory drug composition having reduced potential for gastrointestinal injury induced by said anti-inflammatory drug, comprising combining an anti-inflammatory amount of said anti-inflammatory drug, a gastrointestinal protective amount of a protectant selected from the group consisting of histamine H_1-receptor blockers, histamine H_2-receptor blockers, beta-adrenergic agonists and combinations thereof, and adding an effective alkalizing amount of an alkalizing agent.

2. A method according to claim 1 wherein said histamine H_1-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof.

3. A method according to claim 2 wherein said histamine H_1-receptor blocker is diphenhydramine or a pharmaceutically acceptable salt thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

4. A method according to claims 1 to 3 wherein there are combined into units for a daily average dose for the active ingredients as follows:

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;

(b) histamine H_1-receptor blocker; from about 2.5 ug/kg/day to about 500 mg/kg/day; and

(c) alkalizing agent; from about 0.02 mEq/kg/day to 10 mEq/kg/day.

5. A method according to any one of claims 1 to 3 having a daily average dose for the active ingredients as follows:

(a)nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;

(b) histamine H_1-receptor blocker; from about 0.1 mg/kg/day to about 50 mg/kg/day; and

(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

6. A method according to claim 1 of preparing a nonsteroidal anti-inflammatory composition in unit dosage form comprising combining the active ingredients in the following amounts per unit dose;

(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;

(b) histamine H_1-receptor blocker; from 0.01 mg to about 70 mg; and

(c) alkalizing agent; from about 2 mEq to about 10 mEq.

7. A method according to claim 1 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof.

8. A method according to claim 7 wherein said histamine H_2-receptor blocker is selected from the group consisting of ranitidine, cimetidine, and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen, and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

9. A method according to either of claims 7 and 8 comprising forming a daily average dose by combining the active ingredients as follows :

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;

(b) histamine H_2-receptor blocker; about 0.01 mg/kg/day to about 1 g/kg/day; and

(c) alkalizing agent; from about 0.02 mEq/kg/day to about 10 mEq/kg/day.

10. A method according to either of claims 7 and 8 comprising forming a daily average dose by combining the active ingredients as follows:

(a) nonsteroidal anti-inflammatory agent; from about 15 mg/kg/day to about 75 mg/kg/day;

(b) histamine H_2-receptor blocker; from about 0.01 mg/kg/day to about 10 mg/kg/day; and

(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

11. A method according to either of claims 7 and 8 comprising forming a nonsteroidal anti-inflammatory composition in a unit doage form by combining the active ingredients in the following amounts per unit dose:

(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg.

(b) histamine H_2-receptor blocker; from 0.5 mg to about 350 mg; and

(c) alkalizing agent; from about 2 mEq to about 10 mEq.

12. A method according to claim 1 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol, and pharmaceutically acceptable salts thereof.

13. A method according to claim 12 wherein said protectant is selected from the group consisting of metaproterenol, terbutaline, albuterol, isoproterenol and pharmaceutically acceptable salts thereof, said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin and ibuprofen and said alkalizing agent is selected from the group consisting of sodium bicarbonate and magnesium oxide.

14. A method of according to either of claims 12 and 13 comprising forming a daily average dose by combining the active ingredients as follows :

(a) nonsteroidal anti-inflammatory drug; from about 10 mg/kg/day to about 100 mg/kg/day;

(b) beta-adrenergic agonist from about 0.3 ug/kg/day to about 500 mg/kg/day; and

(c) alkalizing agent; from about 0.02 mEq/kg/day to about 10 mEq/kg/day.

15. A method according to either of claims 12 and 13 comprising forming a daily average dose by combining the active ingredients as follows :

(a) nonsteroidal anti-inflammatory drug; from about 15 mg/kg/day to about 75 mg/kg/day;

(b) beta-adrenergic agonist; from about 0.1 mg/kg/day to about 10 mg/kg/day; and

(c) alkalizing agent; from about 0.04 mEq/kg/day to about 2 mEq/kg/day.

16. A method of preparing a nonsteroidal anti-inflammatory composition in unit dosage form by combining the active ingredients in the following amounts per unit dose:

(a) nonsteroidal anti-inflammatory drug; from about 200 mg to about 600 mg;

(b) beta-adrenergic agonist; from 0.7 mg to about 70 mg; and

(c) alkalizing agent; from about 2 mEq to about 10 mEq.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number
EP 87 31 1171

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	GB-A-2 082 456 (BRISTOL-MYERS COMP.) * Page 2, lines 50-55; page 9, line 9 - page 10, line 16 * --	1-19	A 61 K 33/08 A 61 K 33/00// (A 61 K 33/08, 33:00, 31:60, 31:415, 31:34, 31:19, 31:135)
X	EP-A-0 248 150 (BRISTOL-MYERS COMP.) * Page 3, lines 29-33; page 11, lines 1-40 * --	1-19	
A	GB-A-2 105 193 (GLAXO GROUP LTD.) * Whole document * --	1-19	
A	US-A-4 522 826 (ABRAHAM SUNSHINE) * Whole document * --------	1-19	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-19

Claims searched incompletely:

Claims not searched: 20

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
The Hague	31-08-1988	BRINKMANN

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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(54) Non-steroidal anti-inflammatory compositions protected against gastrointestinal injury with a combination of certain H1 and H2 receptor blockers.

(57) A pharmaceutical composition and process for administering non-steroidal drugs which are protected against injury to the gastrointestinal tract by a combination of certain H_1 and H_2 receptor blockers.

EP 0 320 551 A1

NON-STEROIDAL ANTI-INFLAMMATORY COMPOSITIONS PROTECTED AGAINST GASTROINTESTINAL INJURY WITH A COMBINATION OF CERTAIN H_1 AND H_2 RECEPTOR BLOCKERS

This invention relates to non-steroidal anti-inflammatory drug (hereinafter referred to as NSAID) compositions containing protectants against NSAID-induced gastrointestinal injury and to processes for administering such composition. More particularly, it concerns compositions and processes of the aforesaid type that employ certain combinations of histamine receptor blockers as the protectants. The compositions of this invention are useful in treating conditions and symptoms that are classically treated by the administration of NSAIDs e.g. headache pain, pain and inflammation associated with arthritis and other systemic diseases, elevated body temperatures etc.

Aspirin and other NSAIDs have long been the most popular drugs for the management of pain, inflammation and fever. However, one of the drawbacks in their use is the gastrointestinal injury and/or bleeding that sometimes accompanies their administration to individuals. This becomes a problem where large and sustained doses of NSAIDs must be given to control the symptoms, as for example, in the case of the management of arthritis.

It has now been found that NSAID-induced gastrointestinal injury can be significantly reduced when a combination of histamine receptor blockers and particularly a combination of H_1 and H_2 receptor blockers are administered concurrently with the NSAID.

As pointed out in U.S. Patent 4996571 H_1 and H_2 receptor blockers form two well-known classes of pharmacologically active drugs that serve as blocking agents for histamine at H_1 and H_2 histamine receptor sites, respectively. Histamine receptor sites have been differentiated on the basis of the classes of antihistamines that can serve to block these sites. The fact that a drug is identified as an antihistamine does not necessarily mean that it will be effective in blocking all the known histamine receptor sites but may in fact be selective so that it will act at one site e.g. H_1 site but not at another e.g. H_2 site.

It has been reported in prior art that H_2 receptor blocking agents or antagonists protect against aspirin-induced lesions in certain laboratory animals. One such study is a report in Gastroenterology Vol. 88, No. 5 part 2. p. 1344. It has also been reported that cyproheptadine has been evaluated as a protectant against aspirin induced gastrointestinal injury (Indian J. Med. Res. 1980, 71, p. 926-32). Although the cyproheptadine may have some H_1-receptor antagonist properties, it does not act exclusively at the H_1 receptor sites but rather acts predominantly at the serotonin receptor sites.

Aside from the above the present invention has further significant distinctions from the teachings in the Indian Journal. For one thing in this reference the aspirin and the cyproheptadine are not coadministered as would be the case in the present invention. Furthermore the treatment in this reference with cyproheptadine is reported as not modifying the gastric acidity. This is contrary to the observations made in connection with the present invention. Moreover, the cyproheptadine was administered by intraperitoneal injection prior to the intragastric administration of the aspirin. In contrast to this the compositions of the present invention lend themselves to oral administration at which time the NSAID and the combination H_1 and H_2 receptor blockers are coadministered.

As will be pointed out in more detail below it has been found that by employing certain combinations of H_1 and H_2 histamine receptor blockers as further defined herein that these two act synergistically in their protective effect against NSAID-induced gastrointestinal injury. This was an unexpected result and would not have been anticipated on the basis of the present state of the art.

A number of H_1 and H_2 receptor blockers are known in the prior art which are useful for the purposes of the present invention. However, not all of the H_1 receptors blockers are equally effective in practicing this invention. Those that are useful should also exhibit anticholinergic properties.

By way of illustrating the H_1 receptor blockers that may be employed herein mention may be made of the following: ethanolamines (e.g. diphenhydramine or its hydrochloride salt; carbinoxamine or its maleate salt); ethylenediamines (e.g. tripelennamine or its hydrochloride or citrate salts); alkylamines (e.g. chlorpheniramine or its maleate salt, brompheniramine or its maleate salt); piperazines (e.g. hydroxyzine or its hydrochloride or pamoate salts, cyclizine or its hydrochloride or lactate salts, etc. To exemplify the H_2 receptor blockers that may be advantageously used in the practice of this invention the following are given: cimetidene, ranitidine, famotidine, etc.

Generally any combination of H_1, and H_2 receptor blockers as outlined above are useful for the purpose of this invention. Nevertheless certain combinations of H_1 and H_2 receptor blockers have been found to be particularly efficacious. Thus the combination of chlorpheniramine plus ranitidine, diphenhydramine plus ranitidine, chlorpheniramine plus cimetidine, and diphenhydramine plus cimetidine are the combinations of

choice in the present invention.

The H_1 and H_2 receptors blockers may be used in the form of their bases or in the form of their pharmaceutically acceptable salts. When employed as salts these will usually be acid addition salts wherein the acid portion may be hydrochloric, maleic, ascorbic, citric, pamoic, lactic, tartaric, etc.

The NSAIDs form a well-known class of drugs that are anti-inflammatory analgesics. These have the common property of inhibiting the formation of prostagladins which have a protective affect on the gastrointestinal mucosa. See Goodman and Gilman "The Pharmacological Basis for Therapeutics" 7th Edition, p. 678. It is because of this inhibiting effect that the oral administration of drugs of this class tend to result in gastrointestinal injury and/or bleeding and is at least part of the problem that the present invention seeks to reduce or eliminate.

A number of NSAIDs are known in the prior art to which the present invention has application. The most commonly known group are the salicylates of which aspirin is the prime example. A further group of NSAIDs that have utility in connection with the instant invention are the proprionic acid derivatives. Included in this group are ibuprofen, naproxen. A further group of NSAIDs, employable herein are the fenamates and compounds closely related to them structurally. These may be illustrated by such compounds as mefenamic acid, meclofenamate sodium, diclofenac and its sodium salt. Also belonging to the class NSAIDs with which the present invention is concerned are the indole derivatives (e.g. indomethacin); pyrrole alkanoic acid derivatives (e.g. tolmetin); pyrazalone derivatives (e.g. phenylbutazone); oxicams (e.g. piroxicam), etc.

It is contemplated that in the practice of the present invention the NSAID and the histamine receptor blockers will be administered concurrently in a convenient product form. The essential ingredients of such products will be the H_1 and H_2 receptor blockers and the NSAID. Over and above this these products may also contain other ingredients which will to a large extent depend upon the particular dosage form of the product, e.g. tablets, capsules, powders, suspensions etc.

The quantity of H_1 receptor blocker that will be contained in the composition of this invention may vary somewhat. All that is required is that an effective amount be present so that the H_1 receptor blocker can make its contribution as a protectant against NSAID induced gastrointestinal injury.

Similarly the quantity of H_2 receptor blocker in the present composition may also vary, Again, all that is required is that amount employed be an effective quantity which will enable the H_2 receptor blocker to play its part as protectant.

The NSAID will be contained in the composition of this invention at levels at which it is generally found in therapeutic NSAID compositions intended for oral administration. This will usually be a pharmaceutically acceptable analgesic/anti-inflammatory dose.

The quantitative relationship of the NSAID and the H_1 and H_2 receptor blockers contained in the present products may be expressed on the basis of the daily average dose of the ingredient, e.g. mg/kg of body weight/day. In this case the average daily dose for the ingredients will have the values in the range set forth in the following table:

Ingredient	General Range	Preferred Range
NSAID	about 10 mg/kg/day to about 100 mg/kg/day	about 15 mg/kg/day to about 75 mg/kg/day
H_1 Receptor Blocker	about 2.5 ug/kg/day to about 500 mg/kg/day	about 100 ug/kg/day to about 50 mg/kg/day
H_2 Receptor Blocker	about 10 ug/kg/day to about 1 g/kg/day	about 0.010 mg/kg/day to about 10 mg/kg/day

The unit dosage forms for the present products will be formulated for convenient oral administration. Each such unit will generally contain from about 200 mg to about 600 mg of NSAID, from about 0.1 mg to about 70 mg of H_1 receptor blocker and from 0.5 mg to about 350 mg of H_2 receptor blocker. In formulating these products pharmaceutically acceptable doses of the aforesaid ingredients within the ranges set out above will be employed.

Depending upon the dosage form employed the products of this invention may also contain other adjuvants that may be useful in formulating or administering the particular dosage form. Thus, for example, when administered as a tablet the products of this invention may also contain lubricants, excipients, binding agents, disintegrating agents, flavoring agents, etc. In addition, these products may also contain other

pharmaceutically active ingredients such as: decongestants, analgesic adjuvants, antihistamines, expectorants, antitussives, diuretics, other analgesics, other anti-inflammatory agents, antipyretics, antirheumatics, anti-oxidants, vasodilators, smooth muscle relaxants, skeletal muscle relaxants, bronchodilators, vitamins, trace minerals, amino acids and biological peptides.

The products of this invention may take a variety of forms. As indicated above they may assume the form of tablets. However, the NSAID and the H_1 and H_2 receptor blockers may also be in powdered or granular form contained in edible capsules such as gelatin capsules. The present products may also take the form of suspensions or solutions of the above ingredients in a suitable liquid medium or as powders packaged in suitable paper envelopes.

The following examples are given to further illustrate the present invention. It is to be understood, however, that this invention is not limited thereto.

EXAMPLE 1

Aspirin	325 mg
Ranitidine hydrochloride	3.33 mg
Chlorpheniramine maleate	3.33 mg

The above ingredients are mixed in powdered or granular form and loaded into gelatin capsules.

EXAMPLE 2

Aspirin	325 mg
Cimetidine hydrochloride	16.67 mg
Chlorpheniramine maleate	3.33 mg

Prepared as described in Example 1.

EXAMPLE 3

Aspirin	325 mg
Cimetidine hydrochloride	3.33 mg
Diphenhyramine hydrochloride	16.67 mg

Prepared as described in Example 1.

The following experiments were carried out to test the effectiveness of the combination of H_1 and H_2 receptor blockers in protecting the stomach against NSAID-induced gastrointestinal injury and to compare any protection afforded by the individual H_1 and H_2 receptor blockers. In these studies the H_1 and H_2 receptor blockers are used in the form of the following acid salts: ranitidine HCl, diphenhydramine HCl, chloropheniramine maleate, cimetidine HCl. A standard dose of 975 mg of aspirin is administered orally to dogs along with, respectively, treatment (a) through (h) as indicated below. The stomach lining of the dogs are examined endoscopically and rated as to the degree of injury. The results are given in the table following the description of the methodology.

treatment	cimetidine 50 mg	ranitidine 10 mg	diphenhydramine 50 mg	chlorphenira 10 mg
a	x			
b		x		
c			x	
d				x
e		x	x	
f	x		x	
g		x		x

All test formulations are prepared on the day of the tests. The capsules are placed in the back of the dog's throat. A stomach catheter with attached funnel is positioned in the dog's stomach and 50ml. of deionized water is administered.

Healthy adult beagle dogs of either sex are selected for testing. Dogs are housed individually in stainless steel cages with grid floors to allow excreta to pass through. Room temperature in the holding rooms and test laboratories is maintained between 65° F and 85° F and relative humidity between 30% and 80%. Room lights remain on from 6:00 AM to 4:00 PM.

Each dog is trained to stand in a stanchion with sling support and to accept a bit tied in its mouth. A gastroscope is then passed through the bit into the dog's stomach. This training requires ten days to two weeks in most dogs.

To determine whether a dog is suitable for test purposes, its stomach is examined for a normal mucosa, and its gastric responsiveness to NSAID is evaluated (as under Test Procedure). An acceptable gastric irritation score in the antrum must be 5 or greater, 2 hours after dosage.

Food is withheld from test dogs for 24 hrs. before the test and during the test and water is allowed ad lib. The dogs are moved into a holding area away from the kennel. Fasted dogs of either sex are examined gastroscopically to ensure that their stomachs have normal healthy mucosal linings. The dogs are dosed orally with test formulations, which are flushed into their stomachs with 50 ml. of deionized water. They are then re-examined two and four hours later for gastric petechiae and signs of bleeding according to the following scale:

0 = uniform, pale to dark pink mucosa
1 = darker pink or blotchy mucosa
2 = petechias and/or light red streaks
3 = few small lesions
4 = many or connected small lesions (striations)
5 = few large lesions
6 = many large lesions
7 = massive hemorrhagic damage

Severity of injury for each treatment and at each time is calculated as the mean gastric irritation score.

In addition to the endoscopic observation of the gastric mucosa of each dog a qualitative description of gastric fluid is recorded and a pH measurement is made of the gastric fluid. All of these are done 2 hours after administration of the test product.

A base line is established by measuring the various parameters after the administration of 975 mg of aspirin by itself. The resting stomach has an irritation score of 0 and a pH of 5 to 5.5. Aspirin alone produces injury which scores at approximately 5.6 after 2 hours and the gastric pH at this time is about 3.1. After 4 hours these values are 4.0 for the irritation factor and the pH is about 4.7. This indicates that a certain amount of healing takes place between the 2nd and 4th hour after administration.

The results of these tests with respect to the two hour injury data are summarized in the following table below:

Test Composition	2 Hr. Score	
	Injury	pH
aspirin (975 mg)	5.6	3.1
aspirin (975 mg) + ranitidine HCl (10 mg)	3.5	5.3
aspirin (975 mg) + chlorpheniramine maleate (10 mg)	4.0	4.4
aspirin (975 mg) + cimetidine HCl (50 mg)	2.4	5.6
aspirin (975 mg) + diphenhydramine HCl (50 mg)	4.0	3.6
aspirin (975 mg) + ranitidine HCl (10 mg) + diphenhydramine HCl (50 mg)	0.6	5.4
aspirin (975 mg) + ranitidine HCl (10 mg) + chlorpheniramine maleate (10 mg)	1.6	4.7
aspirin (975 mg) + cimetidine HCl (50 mg) + diphenhydramine HCl (50 mg)	1.0	7.0
Aspirin (975 mg) + Diphenhydramine HCl (25 mg)	5.8	2.1
Aspirin (975 mg) + Ranitidine HCl (10 mg) + Diphenhydramine HCl (25 mg)	2.3	5.2

An examination of these data shows that significantly more, synergistic protection is obtained when a combination of an H_1 and H_2 receptor blocker is employed together with aspirin as compared with the cases in which H_1 or H_2 receptor blocker, respectively, is issued alone.

Claims

1. A NSAID composition having reduced potential for NSAID induced gastrointestinal injury comprising

(a) an analgesic or antiinflammatory amount of a NSAID selected from the group consisting of aspirin and pharmaceutically acceptable salt of aspirin; and

(b) a protective amount of:

(i) an H_1 receptor blocker selected from the group consisting of diphenhydramine and pharmaceutically acceptable salts of diphenhydramine; and

(ii) an H_2 receptor blocker selected from the group consiting of cimetidine, ranitidine, famotidine and pharmaceutically acceptable salts thereof.

2. The composition according to claim 1, wherein, based on the weight of a subject to whom the composition is being administered, the NSAID is present in an amount of from about 10 mg to about 100 mg per kg per day; the H_1 receptor blocker is present in an amount of from about 2.5 ug to about 500 mg per kg per day; and the H_2 receptor is present in an amount of from about 10 ug to about 1 g per kg per day.

3. The composition according to claim 1, wherein the NSAID is present in an amount of from about 200 mg to about 600 mg; the H_1 receptor blocker is present in an amount of from about 0.1 mg to about 70 mg; and the H_2 receptor blocker is present in an amount of from about 0.5 mg to about 350 mg.

4. The composition according to claim 1, wherein the NSAID is 975 mg of aspirin, the H_1 receptor blocker is 50 mg of diphenhydramine HCl, and the H_2 receptor blocker is 10 mg of ranitidine HCl.

5. The composition according to claim 1, wherein the NSAID is 975 mg of aspirin, the H_1 receptor blocker is 50 mg of diphenhydramine HCl and the H_2 receptor blocker is 50 mg of cimetidine HCl.

6. Use in a process for reducing the potential of aspirin or of a pharmaceutically acceptable salt of aspirin, to induce gastrointestinal injury in a subject which comprises preparing a composition based on the weight of the subject,

(a) from about 10 mg to about 100 mg kg per day of an NSAID selected from the group consisting of aspirin and pharmaceutically acceptable salts of aspirin;

(b) from about 2.5 ug to about 500 mg per kg per day of an H_1 receptor blocker selected from the group consisting of diphenhydramine and pharmaceutically acceptable salts of diphenhydramine; and

(c) from about 10 ug to about 1 g per kg per day of an H_2 receptor blocker selected from the group consisting of cimetidine, ranitidine, famotidine, and pharmaceutically acceptable salts thereof.

7. The use according to claim 6 wherein the NSAID and the H_1 and H_2 receptor blockers are prepared in a unit dosage form containing from about 200 mg to about 600 mg of NSAID, from about 0.1 mg to about 70 mg of H_1 receptor blocker and from about 0.5 mg to about 350 mg of H_2 receptor blocker.

8. The use according to claim 6 wherein the NSAID and the H_1 and H_2 receptor blockers are prepared for a subject in a daily average dose based on the weight of the subject, of from about 10 mg per kg per day to about 100 mg per kg per day of NSAID, from about 2.5 ug per kg per day to about 500 mg per kg per day of H_1 receptor blocker, and from about 10 ug per kg per day to about 1 gm per kg per day of H_2 receptor blocker.

9. The use according to claim 6, wherein 975 mg of aspirin, 50 mg of diphenhydramine HCl and 10 mg of ranitidine HCl are combined.

10. The use according to claim 6, wherein 975 mg of aspirin, 50 mg of diphenhydramine HCl and 50 mg of cimetidine HCl are combined.

Claims for the following Contracting States: ES & GR

1. A method of preparing a NSAID composition having reduced potential for NSAID induced gastrointestinal injury comprising combining

(a) an analgesic or antiinflammatory amount of a NSAID selected from the group consiting of aspirin and pharmaceutically acceptable salt of aspirin; and

(b) a protective amount of:

(i) an H_1 receptor blocker selected from the group consisting of diphenhydramine and pharmaceutically acceptable salts of diphenhydramine; and

(ii) an H_2 receptor blocker selected from the group consisting of cimetidine, ranitidine, famotidine and pharmaceutically acceptable salts thereof.

2. A method according to claim 1, wherein, based on the weight of a subject to whom the composition is being administered, there are combined the NSAID in an amount of from about 10 mg to about 100 mg per kg per day; the H_1 receptor blocker in an amount of from about 2.5 ug to about 500 mg per kg per day; and the H_2 receptor in an amount of from about 10 ug to about 1 g per kg per day.

3. The method according to claim 1, wherein there are combined the NSAID in an amount of from about 200 mg to about 600 mg; the H_1 receptor blocker in an amount of from about 0.1 mg to about 70 mg; and the H_2 receptor blocker in an amount of from about 0.5 mg to about 350 mg.

4. The method according to claim 1, wherein there are combined the NSAID as 975 mg of aspirin, the H_1 receptor blocker as 50 mg of diphenhydramine HCl, and the H_2 receptor blocker as 10 mg of ranitidine HCl.

5. The method according to claim 1, wherein there are combined the NSAID as 975 mg of aspirin, the H_1 receptor blocker as 50 mg of

6. Use in a process for reducing the potential of aspirin or of a pharmaceutically acceptable salt of aspirin, to induce gastrointestinal injury in a subject which comprises preparing a composition based on the weight of the subject,

(a) from about 10 mg to about 100 mg per kg per day of an NSAID selected from the group consisting of aspirin and pharmaceutically acceptable salts of aspirin;

(b) from about 2.5 ug to about 500 mg per kg per day of an H_1 receptor blocker selected from the group consisting of diphenhydramine and pharmaceutically acceptable salts of diphenhydramine; and

(c) from about 10 ug to about 1 g per kg per day of an H_2 receptor blocker selected from the group consisting of cimetidine, ranitidine, famotidine, and pharmaceutically acceptable salts thereof.

7. The use according to claim 6 wherein the NSAID and the H_1 and H_2 receptor blockers are prepared in a unit dosage form containing from about 200 mg to about 600 mg of NSAID, from about 0.1 mg to about 70 mg of H_1 receptor blocker and from aboout 0.5 mg to about 350 mg of H_2 receptor blocker.

8. The use according to claim 6 wherein the NSAID and the H_1 and H_2 receptor blockers are prepared for a subject in a daily average dose based on the weight of the subject, of from about 10 mg per kg per day to about 100 mg per kg per day of NSAID, from about 2.5 ug per kg per day to about 500 mg per kg per day of H_1 receptor blocker, and from about 10 ug per kg per day to about 1 gm per kg per day of H_2 receptor blocker.

9. The use according to claim 6, wherein 975 mg of aspirin, 50 mg of diphenhydramine HCl and 10 mg of ranitidine HCl are combined.

10. The use according to claim 6, wherein 975 mg of aspirin, 50 mg of diphenhydramine HCl and 50 mg of cimetidine HCl are combined.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 31 1172

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	DICTIONNAIRE VIDAL, 1961, Office de Vulgarisation Pharmaceutique, Paris; "Allerga-aspirine" ---	1-10	A 61 K 31/60 // (A 61 K 31/60 A 61 K 31:415 A 61 K 31:34 A 61 K 31:135)
Y	GB-A-2 105 193 (GLAXO GROUP LTD) * Page 3, lines 19-35 * ---	1-10	
A	US-A-4 522 826 (A. SUNSHINE) -----	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	31-08-1988	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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(54) Pharmaceutical composition and methods for treating the symptoms of overindulgence.

(57) This invention relates to a pharmaceutical composition for treating the symptoms of overindulgence comprising an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, proton pump inhibitor or a combination thereof and methods of treating the symptoms of overindulgence comprising administering such pharmaceutical compositions.

EP 0 426 479 A1

PHARMCEUTICAL COMPOSITIONS AND METHODS FOR TREATING THE SYMPTOMS OF OVERINDULGENCE

Field of the Invention

This invention relates to pharmaceutical compositions for treating the symptoms of overindulgence. More particularly, the invention comprises treating the symptoms of overindulgence with a combination of non-steroidal anti-inflammatory drug or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition

Background of the Invention

Non-steroidal anti-inflammatory drugs (hereinafter referred to as "NSAID(S)") and acetaminophen (hereinafter referred to as "APAP") are known to be effective analgesics for the treatment of mild to moderate pain Histamine receptor blockers (referred to generically herein as H_1 or H_2 blockers) are effective inhibitors of gastric acid production. Proton pump inhibitors have been recently introduced as effective gastric acid inhibitors

The symptoms of overindulgence due to excessive or inappropriate intake of food and/or alcoholic beverage are well known and include headache as well as indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis These latter symptoms collectively are sometimes referred to as acid indigestion or sour stomach. Indigestion has been variously described and will be defined herein as encompassing one or more of the following symptoms: abdominal pain and/or pressure, heartburn, a sense of abdominal fullness or bloating, excessive belching or flatulence and a vague feeling that digestion has not proceeded naturally (See Friedman, L.S., and K. J. Isselbacher, "Indigestion", Harison's Principles of Internal Medicine , 11th Edition, McGraw Hill Book Company, N.Y., p 171-175, 1986).

The pathophysiology of indigestion is generally believed to be related to increased intraluminal acidity. The effects of alcohol and/or food on the gastrointestinal tract are influenced by a number of factors, including the mental state of the patient, the amount and type of food concurrently ingested, the individual subject's tolerance for alcohol and the presence or absence of disease. Gastric secretions stimulated by alcohol are rich in acid and normal in pepsin content. Stimulation of the antral mucosa by alcohol also leads to increased gastric secretion. Histamine has also been shown to be released in response to the alcohol-gastrin interrelationship. (See Glass, G. B. J., B. L. Slomiany and A. Slomiany, "Biochemical and Pathological Derangements of the Gastrointestinal Tract following Acute and Chronic Ingestion of Ethanol", Biochemistry and Pharmacology of Ethanol , Vol 1, Plenum Press, N.Y., p 551-586, 1979.)

Alcohol in concentrations of about 10% in the stomach results in an acid rich secretion. Alcoholic drinks of 40% concentration and over are quite irritating to the gastric mucosa and cause congestive hyperemia and inflammation of the gastric mucosa and can produce erosive gastritis (See Ritchie, J. M., "The Aliphatic Alcohols", The Pharmacological Basis of Therapeutics , 7th Edition, MacMillan Publishing Co, N.Y., p 372-386, 1985). The irritation produced by alcohol stimulates sensitized visceral afferent nerves which accompany the abdominal sympathetic pathway and is responsible for the symptom of abdominal discomfort which accompanies overindulgence. Inflammation also generally lowers the threshold for pain from visceral distention or exaggerated muscular contraction (See Lorber, S. H., and V. P. Dimoso, Jr., "Diseases of the Gastrointestinal Tract", The Biology of Alcoholism , Vol 3, Clinical Pathology, Plenum Press, N.Y., p 339-357, 1974).

Heartburn or pyrosis is frequently associated with overindulgence and is the result of reflux of acidic gastric content into the lower esophagus after a large meal or excessive alcohol intake. Heartburn is described as a sensation of warmth or burning located substernally or high in the epigastrum with occasional radiation into the neck and occasionally to the arms.

Treatment of the gastric mucosal irritation and heartburn associated with overindulgence due to alcohol has traditionally been directed toward reducing gastric acidity with various oral antacids. Recent introduction of H_2 receptor blocking agents has added another dimension to the treatment regimen and has only lately been considered as a routine therapy for gastric mucosal irritation due to a variety of causes. Histamine is known to stimulate the release of gastric acid. Evidence is available that blocking the histamine gastric response is possible with agents which selectively block the H_1 receptor. Similarly, combinations of H_1 and H_2 receptor blocking agents have been shown to have a synergistic effect on protecting the gastric mucosa. An appropriate treatment of heartburn or pyrosis could encompass a composition containing an H_1 receptor blocking agent, an H_2 receptor blocking agent or a combination of the two depending upon the desired result or severity of the condition.

Headache due to excessive food or alcohol ingestion is a much more obscure subject. While

the etiology of the common headache due to overindulgence may be related to the essential oils, metabolic by-products of ethyl alcohol metabolism or osmotic changes induced by the anhydrous nature of the alcohol itself, specific details of the mechanism are difficult to determine. Should etiologies and mechanisms of headache production be more precisely known, therapy can be more specifically oriented. Meanwhile, treatnient has been directed at avoidance and symptomatic therapy with analgesic compositions, e.g. aspirin or APAP (See Adams, A. D. and J. B. Martin, "Headache", Harrison's Principles of Internal Medicine , 11th Edition, McGraw Hill Book Company, N.Y., p 26-33, 1986).

The treatment of the symptoms of overindulgence often requires the co-administration of an analgesic to relieve the headache along with an agent to reduce gastric acidity which is generally believed to cause the indigestion and heartburn. For example, effervescent products comprising aspirin or APAP combined with an antacid such as sodium or calcium carbonates have been commercially available as treatments for the symptoms of overindulgence.

The concept of combining an agent to reduce or inhibit the production of gastric acid with an analgesic in a single composition has, however, heretofore been overlooked as a method of treating overindulgence. Such a combination would be a significant advance and meet a long felt need for treating the symptoms of overindulgence, permitting a single composition to more effectively treat all the symptoms concurrcntly.

Summary of the Invention

The foregoing object of fulfilling a long felt need for pharmaceutical compositions which can relieve the symptoms of overindulgence defined herein as headache and acid indigestion has now been accomplished in accordance with the compositions and methods of the present invention.

In accordance with the purposes of the invention, as embodied and fully described herein, the invention comprises pharmaceutical compositions for treating the symptoms of overindulgence comprising an analgesic effective amount of an NSAID or APAP and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, a proton pump inhibitor or a combination thereof.

In preferred embodiments the NSAID is selected from the group consisting of propionic acid derivatives including ibuprofen, fenoprofen, naproxen and ketoprofen; fenamic acid derivatives, including meclofenamate and mefenamic acid; oxicams,. including piroxicam; indole acetic acids, including indomethacin, sulindac, tolmetin; and pharmaceutically acceptable salts thereof. The preferred H_1 or H_2 or proton pump inhibitors are selected from the group consisting of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine; the proton pump inhibitor drug omeprazole; and the H_1 receptor blocking drugs, from the group ethanolamines including diphenhydramine, dimenhydrimate, carbinoxamine, from the group ethylenediamines, including tripelennamine, pyrilamine, from the group alkylamines, including cholphenirdmine, from the group piperazines, including hydroxyzine, cyclizine, meclizine, from the group phenothiarinec, including promethazine. In more preferred embodiments the APAP or ibuprofen are used in combination with cimetidine.

As embodied and broadly described herein, the invention further comprises a method for treating the symptoms of overindulgence comprising administering a combination pharmaceutical composition to a patient comprising an analgesic effective amount of APAP or an NSAID and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, a proton pump inhibitor or a combination thereof as is described above.

Detailed Description of Preferred Embodiments of the Invention

Reference will now be made in detail to preferred embodiments of the invention, examples of which are illustrated in the following examples section.

To achieve the object of the invention of providing a pharmaceutical composition for treating the symptoms of overindulgence an analgesic effective amount of APAP or an NSAID is combined with a gastric acid inhibiting effective amount of an H_1 or H_2 blocker or a proton pump inhibitor or a combination thereof.

The treatment of overindulgence is directed to the symptomatic relief of the complaints of acid indigestion and headache. This requires the use of an agent which would treat the headache, abdominal discomfort and reduce the intraluminal gastric acidity. Since no single agent has been found to be capable of treating the multiple symptons of overindulgence, a composition such as is described in this invention is recommended.

APAP, a well-known clinically proven analgesic and antipyretic, produces analgesia by elevating the pain threshold. APAP is indicated as an analgesic for both acute and chronic pain conditions, including arthritic and rheumatic conditions involving musculoskeletal pain, headache, dysmenorrhea, myalgias and neuralgias. APAP is an extremely

safe analgesic, rarely producing side-effects and is especially well tolerated by aspirin-sensitive patients. (Seegers, A. J. M., L. P. Jager, and J. Van Noordwijk, "Effects of Phenacetin Parcetamol and Caffeine on the Erosive Activity of Acetylsalicylic Acid in the Rat Stomach: Dose-Response Relationships, Time Course of Erosion Development and Effects of Acid Secretion", J. Pharmacol , 31:840-848, 1979), have shown that APAP decreases the gastric erosive activity of a strongly ulcerogenic NSAID. (Stern, A. I., D. L. Hogan, L. H. Kahn, and J. 1. Isenberg, "Protective Effect of Acetaminophen Against Aspirin - and Ethanol-Induced Damage to the Human Gastric Mucosa", Gastroenterology , 86:728-733, 1984), have additionally shown that a single dose of APAP prevents a significant amount of gastric mucosal damage caused by both aspirin and alcohol. Further, APAP is particularly well suited as an analgesic in patients with hemostatic disturbances as well as in patients with upper gastrointestinal disorders including ulcers, gastritis and hiatus hernia.

Aspirin and other NSAIDs are commonly used for the treatment of pain and inf lammation of a variety of etiologies. The mechanism of action of this class of drugs is by inhibition of the enzyme of prostaglandin synthetase, both contrally and peripherally. The peripheral prostaglandin synthetase inhibiting activity of aspirin and other NSAIDs is responsible for the anti-inflammatory and analgesic activity as well as for many of the varied side-effects of these drugs. Aspirin is specifically excluded from this invention since aspirin, by itself, causes severe inflammation of the gastric mucosa. In the presence of alcohol, this effect of aspirin is enhanced. Similarly, prolongation of bleeding time induced by aspirin, is enhanced in the presence of alcohol (See Deykin, D., P. Janson and L. McMahon, "Ethanol Potentiation of Aspirin-Induced Prolongation of the Bleeding Time", New England Journal of Medicine , 306:852-854, 1982). For these reasons aspirin is not a rational choice either alone or in combination with other compositions for treating acid indigestion in general and as it relates to overindulgence. While other NSAIDs can by themselves lead to increased stomach upset, this effect is not as severe as with aspirin, and they are thus useful in treating the symptoms of overindulgence in accordance with the combination composition of the invention.

The presence of gastrin, acetylcholine and histamine in the stomach interacting with the histamine receptor on the parietal cell results in the increased secretion of hydrochloric acid. The activity of gastrin and acetylcholine are believed to be influenced by histamine. Inhibition of the histamine receptor prevents the attachment of histamine to the parietal cell and subsequently inhibits acid secretion. Omeprazole, a proton pump inhibitor, irreversibly inhibits the enzyme responsible for acid production.

The histzmine receptors are differentiated by the class of inhibitor so that while the acid secreting histamine receptor is called an H_2 receptor with the inhibitors of this site being called the H_2 receptor blocker, the histamine H_1 receptor site blockers comprise another class of antihistamine drugs. The combination of H_1 and H_2 blockers can synergistically protect the gastrointestinal mucosa from the effects of chemically induced damage such as occurs in alcohol and food related overindulgence.

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts either acetaminophen from 500 to 1000 mg per dose or one of several NSAIDs from the group of: propionic acid derivatives including ibuprofen (the term ibuprofen is meant to include administration of both the racemic mixture of R- and S-enantiomers and the substantially pure S-enantiomer which is the analgesic active form of ibuprofen) from 200 to 400 mg per dose; naproxen from 200 to 500 mg per dose; fenoprofen from 200 to 600 mg per dose; ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose; piroxicam from 10 to 20 mg per dose; indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose; in combination with the H_2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the proton pump inhibitor drugs including omeprazole from 100 to 500 mg per dose; and/or an H_1 receptor blocking drug from the group ethanolamines including diphenhydramine 25 to 200 mg per dose; dimenhydrimate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose; from the group ethylenediamines including tripelennamine frog 25 to 300 mg per dose; pyrilamine from 25 to 300 mg per dose; from the group alkylamines including chorpheniramine from 2 to 24 mg per dose, from the group piperazines including hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose; and from the group phenothiazines including promethazine from 12.5 to 50 mg per dose.

The dosage ranges described above are preferred adult doses and may vary depending upon the age and weight of the patient as would be known by those skilled in the pharmaceutical arts. Further, if a combination of, for example an H_1 and H_2 blocker is used, the dosage for each may be reduced.

To establish the efficacy of the composition of this invention in humans, patients suffering from the symptoms of overindulgence which will include any of the constellation of signs of indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis and headache can be administered acetaminophen or a non-steroidal anti-inflammatory drug with and without histamine receptor blockers (H_1 and/or H_2 blocking agents). To determine efficacy, patients are asked to subjectively estimate onset of relief, duration of relief and time to maximum relief. Appropriate statistical methods are used to show that on the average, acetaminophen or non-steroidal anti-inflammatory agents with H_1 histamine and/or H_2 histamine receptor blocking drugs are more efficacious.

Since appropriate animal models for the evaluation of overindulgence are not available, studies will not be conducted involving laboratory animals.

Other ingredients both active and inactive can be added to the combination pharmaceutical compositions of the invention. For example, flavoring compositions are desirably added to chewable and liquid dosage forms. Further, antidiarrheal, antiflatulent, antispasmodic and/or anticholinergic compositions may be added to the compositions of the invention to reduce and relieve gastrointestinal distress, which may be associated with acid indigestion. Exzmples of antidiarrheals include loperamidc, attapulgite, bismuth subsalicylate, diphenoxylate HCl, polycarbophil, calcium polycarbophil and mixtures thereof. An example of an antiflatulent is simethicone. Examples of antispasmodics include phenobarbital dicyclomine HCl, belladonna alkaloids, and atropine.

Examples

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention. Example 1-14 disclose various formulations for preparing tablets or caplets in accordance with the invention. Various conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed for example by Remington's Pharmaceutle Sciences , flack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985).

Example 1:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 2:

A tablet consisting of:
500 mg of acetaminophen;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 3:

A tablet consisting of:
200 mg of ibuprofen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 4:

A tablet consisting of:
200 mg of ibuprofen;
mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 5:

A tablet consisting of:
200 mg of ibuprofen;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 6:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 7:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine;
25 mg of diphenhydramine; and

other auxiliary agents and coloring agents.

Example 8:

A tablet consisting of:
200 mg of ibuprofen;
350 mg of cimetidine;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 9:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 10:

A tablet consisting of:
200 mg of ibuprofen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 11:

A tablet consisting of:
500 mg of acetaminphen;
60 mg of omeprazole; and
other auxiliary agents and coloring agents.

Example 12:

A tablet consisting of:
200 mg ibuprofen;
mg omeprazole; and
other auxiliary agents and coloring agents.

Example 13:

A tablet consisting of:
500 mg acetaminophen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Example 14:

A tablet consisting of:
200 mg ibuprofen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Various other dosage forms can be applied herein such as a filled gelatin capsule, liquid emulsion/suspension or chewable tablet form employing the dosage actives provided above or other dosage amounts in accordance with the present invention. A liquid suspension of ibuprofen to which cimetidine, diphenhydramine, ranitidine or combinations thereof in the amounts provided above can be added to the ibuprofen suspension disclosed in EP-A-90307001.9.

Method of Treating Patients for the Symptoms of Overindulgence

A patient exhibiting the symptoms or suffering from the symptoms of overindulgence is treated by the oral administration of one tablet of the pharmaceutical composition in accordance with any of Examples 1-14.

The scope of the present invention is not limited by the description, examples and suggested uses herein and modifications can be made without departing from the spirit of the invention. For example, the pharmaceutical compositions of the invention may be provided in a sustained release formulation for prolonged and/or nightime treatment of the symptoms of overindulgence. Application of the compositions and methods of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the presently claimed invention cover the modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

Claims

1. A pharmaceutical composition comprising:
an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and
a gastric acid inhibiting effective amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a

combination thereof.

2. The composition of claim 1 wherein the non-steroidal anti-inflammatory drug is a propionic acid derivative, a fenamic acid derivative, an oxicam, an indole acetic acid or a pharmaceutically acceptable salt thereof.

3. The composition of claim 1 or claim 2 wherein the acetaminophen or non-steroidal anti-inflammatory drug, selected from ibuprofen, fenoprofen, naproxen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin, or a pharmaceutically acceptable salt thereof, is combined with:

one of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine;

the proton pump inhibitor drug omeprazole; or one of the H_1 receptor blocking drugs diphenhydramine, dimenhydrimate, carbinoxamine, tripelennamine, pyrilamine, chorpheniramine, hydroxyzine, cyclizine, meclizine, promethazine;

or a pharmaceutically acceptable salt thereof.

4. The composition of any one of claims 1 to 3 which contains:

acetaminophen from 500 to 1000mg per dose, ibuprofen from 200 to 400 mg per dose, naproxen from 200 to 500 mg per dose, fenoprofen from 200 to 600 mg per dose, ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose, piroxicam from 10 to 20 mg per dose, indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose or a pharmaceutically acceptable salt thereof;

in combination with:

cimetidine from 150 to 800 mg per dose, ranitidine from 50 to 300 mg per dose, famotidine from 5 to 40 mg per dose, omeprazole from 100 to 500 mg per dose, diphenhydramine from 25 to 200 mg per dose, dimenhydrimate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose, tripelennamine from 25 to 300 mg per dose, pyrilamine from 25 to 100 mg per dose, chlorpheniramine from 2 to 24 mg per dose, hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose, promethazine from 12.5 to 50 mg per dose, a pharmaceutically acceptable salt thereof or a combination thereof.

5. The composition of any one of claims 1 to 4 comprising fenoprofen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin or a pharmaceutically acceptable salt thereof, and

(a) cimetidine, ranitidine or famotidine; or

(b) diphenhydramine, dimenhydrimate, carbinoxamine, tripelennamine, pyrilamine, chlorpheniramine, hydroxyzine, cyclizine, meclizine or promethazine; or

(c) a combination of a drug from group (a) and a drug from group (b).

6. The composition of any one of claims 1 to 5 comprising:

a combination of acetaminophen and cimetidine;

a combination of ibuprofen and cimetidine; or

a combination of naproxen anddiphenhydramine.

7. The composition of any one of claims 1 to 6, in oral tablet, caplet, chewable or liquid dosage form.

8. The composition of any one of claims 1 to 7, for use in treating the symptoms of over indulgence.

9. A method for producing the composition of any one of claims 1 to 8 which comprises forming a pharmaceutical composition containing:

an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and

a gastric acid inhibiting amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a combination thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 1995

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	UNLISTED DRUGS, vol. 20, no. 11, November 1968, Chatnam, New Jersey, US * Page 167, paragraph e: "Infacete" *	1-9	A 61 K 31/415 A 61 K 31/34 A 61 K 31/165
X	WO-A-8 503 443 (RICHARDSON-VICKS, INC.) * Pages 25-28, claims 1-27 *	1-9	A 61 K 31/19 A 61 K 31/44 // (A 61 K 31/415
X	GB-A-2 105 193 (GLAXO GROUP LTD) * Page 3, lines 19-35, claims 1-7 *	1-9	A 61 K 31:19 A 61 K 31:165) (A 61 K 31/34 A 61 K 31:165) (A 61 K 31/165 A 61 K 31:135) (A 61 K 31/19 A 61 K 31:135) (A 61 K 31/44 A 61 K 31:19 A 61 K 31:165)

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	28 January 91	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

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(54) Medicaments for treating imflammatory conditions or for analgesia containing a NSAID and canitidine bismuth citrate.

(57) The use is described of both (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in treating or preventing inflammatory conditions and for analgesia. Pharmaceutical compositions containing both (i) and (ii) and methods for the preparation of pharmaceutical compositions containing (i) and (ii) are also described.

EP 0 550 083 A1

The present invention relates to improvements in the treatment of inflammatory conditions and for analgesia. More particularly it relates to the co-administration of a non-steroidal anti-inflammatory drug with a salt formed between ranitidine and a complex of bismuth with a carboxylic acid.

Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin, ibuprofen and piroxicam, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric and/or duodenal ulceration when administered orally. This side effect may be further enhanced in combination with other factors such as stress and smoking. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

In our UK Patent Specification No. 2220937B we describe and claim salts formed between ranitidine and a complex of bismuth with a carboxylic acid, particularly tartaric acid and, more especially, citric acid. One such salt is N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3^+) complex, also known as ranitidine bismuth Citrate.

The salts disclosed in UK Patent Specification No. 2220937B possess the H_2-antagonist antisecretory properties associated with ranitidine, together with antibacterial activity against Helicobacter pylori (formerly Campylobacter pylori). In addition, such salts possess cytoprotective properties and display activity against the human gastric pepsins with preferential inhibition of pepsin 1, a pepsin isozyme associated with peptic ulcer. The salts disclosed in UK Patent Specification No. 2220937B thus possess a particularly advantageous combination of properties for the treatment of gastrointestinal disorders, especially peptic ulcer disease (e.g. gastric and duodenal ulceration) and other gastroduodenal conditions, for example gastritis and non-ulcer dyspepsia.

Tests in animals and humans have now shown that mucosal lesions of the gastrointestinal tract caused by non-steroidal anti-inflammatory drugs are significantly reduced by administering ranitidine bismuth citrate. In particular, we have demonstrated in rats the ability of ranitidine bismuth citrate to prevent indomethacin induced gastric antral ulceration using a modification of the method of Satoh et al., Gastroenterology (1981), 81, 719-725. In this test ranitidine bismuth citrate was markedly more potent than both ranitidine hydrochloride and tripotassium dicitrato bismuthate as DeNol™. A recently published human clinical study (N. Hudson et al., Gut 1992, 33 supplement, s47) also demonstrates that ranitidine bismuth citrate confers substantial protection from aspirin-induced injury to the gastric mucosa.

The present invention thus provides, in one aspect, the use of (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in the manufacture of medicaments for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

In a further, or alternative, aspect the present invention provides the use of ranitidine bismuth citrate in the manufacture of medicaments to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs.

Combination therapy according to the present invention may be used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteo-arthritis and ankylosing spondylitis and for analgesia in conditions such as dysmenorrhoea, especially where the use of the anti-inflammatory drug is limited by gastrointestinal side effects. As stated above, co-administration of ranitidine bismuth citrate with a systematic non-steroidal anti-inflammatory drug may also be used to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs. Such gastrointestinal damage includes duodenal and/or gastric ulceration, non-steroidal anti-inflammatory drug associated gastritis and gastric erosions, and non-steroidal anti-inflammatory drug associated mucosal damage to the small intestine.

Suitable systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

The ranitidine bismuth citrate and the anti-inflammatory drug are preferably co-administered in the form of separate pharmaceutical compositions for simultaneous and/or sequential use. Alternatively the ranitidine bismuth citrate and the anti-inflammatory drug may be administered as a single pharmaceutical composition for oral use comprising effective amounts of the active ingredients.

Thus, according to a further aspect, the invention provides a product containing (i) ranitidine bismuth citrate and (ii) a non-steroidal antiinflammatory drug as a combined preparation for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

When the ranitidine bismuth citrate and the non-steroidal anti-inflammatory are administered as separate preparations, the anti-inflammatory may be provided in any convenient formulation, such as in the manner known in the art and/or commercially for the compound concerned. Administration of both the ranitidine bismuth citrate and the non-steroidal anti-inflammatory by the oral route is preferred, although the anti-inflammatory, where appropriate, may also be given by another route, for example parenterally (e.g. intravenously) or rectally (e.g. by suppository).

The ranitidine bismuth citrate may conveniently be formulated as tablets (including chewable tablets), capsules (of either the hard or soft type), or as a liquid preparation, as described for example in UK Patent Specification Nos. 2220937B and 2248185A. Tablets are generally preferred.

As stated hereinabove, ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug may be administered as a single pharmaceutical composition for oral use. Thus, according to a further aspect the invention provides a pharmaceutical composition, for oral use in human or veterinary medicine, comprising ranitidine bismuth citrate and a non-steroidal anti-inflammatory drug, together, where appropriate, with a pharmaceutically acceptable carrier or excipient.

Suitable additional carriers or excipients include binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). An alkaline salt of the type described in UK Patent Specification No. 2248185A may be added to improve the rate of disintegration and/or dissolution of the composition.

The compositions may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug may be admixed together, if desired, with suitable carriers or excipients. Tablets may be prepared, for example, by direct compression or wet granulation of such a mixture. Capsules may be prepared by filling the blend along with suitable carriers or excipients into gelatin capsules, using a suitable filling machine. Tablets may be coated by methods well known in the art. The preparations may also contain flavouring, colouring and/or sweetening agents as appropriate.

When ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug are administered as a single pharmaceutical composition for oral use the composition is preferably in the form of a capsule or, more particularly, a tablet.

The compositions for use according to the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. Where the ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug are intended for administration as separate compositions these may be presented in the form of, for example, a twin pack.

Thus, according to a further aspect the present invention provides a twin-container pack for use in treating or preventing inflammatory conditions or for analgesia, one of the containers containing ranitidine bismuth citrate and the other containing a non-steroidal anti-inflammatory drug.

The doses at which the ranitidine bismuth citrate and the non-steroidal anti-inflammatory may be administered to man (of approximately 70kg body weight) will depend on the route of administration of the anti-inflammatory and on the nature and severity of the condition being treated. It will also be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient.

A proposed dosage of ranitidine bismuth citrate for use according to the invention is 150mg to 1.5g, preferably 200 - 800mg per unit dose. The unit dose may be administered, for example, 1 to 4 times per day, preferably once or twice per day.

The non-steroidal anti-inflammatory may conveniently be administered at doses within the normal dosage range at which the compound is therapeutically effective, -for example 50mg-1g of aspirin, 10 - 100 mg of indomethacin, 5 - 50 mg of piroxicam, 100-500mg of ibuprofen and 200-800mg of mefenamic acid per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question.

In a further aspect, the present invention provides a method of treating inflammatory conditions or for analgesia in a human or animal subject, which comprises administering to said subject effective amounts of ranitidine bismuth citrate and a non-steroidal anti-inflammatory drug.

In another, or alternative, aspect the present invention provides a method of treating gastrointestinal damage caused by non-steroidal anti-inflammatory drugs in a human or animal subject, which comprises administering to said subject an effective amount of ranitidine bismuth citrate.

References herein to treatment include prophylactic treatment as well as the alleviation of acute symptoms.

The methods of the present invention comprise administering the non-steroidal anti-inflammatory drug and ranitidine bismuth citrate either concurrently or non-concurrently. As used herein, concurrent administration means that the agents are given within 24 hours of each other, whereas non-concurrent administration means that the agents are given more than 24 hours apart. When the agents are administered concurrently, it may be preferable to administer the agents within about 1 hour of each other or, more preferably, within about 5 minutes of each other.

For the methods of the present invention, the duration of administration of the agents during either concurrent or non-concurrent dosing will vary according to the specific condition being treated.

The following examples illustrate pharmaceutical compositions for oral use containing both ranitidine bismuth citrate and a suitable non-steroidal anti-inflammatory drug.

Example 1

TABLETS

		mg/tablet
(a)	Ranitidine bismuth citrate	400.00
	Ibuprofen	400.00
	Lactose	200.00
	Hydroxypropyl methylcellulose	5.00
	Sodium starch glycollate	30.00
	Magnesium stearate	10.00
	Compression weight	1045.00

The ranitidine bismuth citrate and ibuprofen are sieved through a 250μm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using 15.0mm punches.

		mg/tablet
(b)	Ranitidine bismuth citrate	400.00
	Indomethacin	50.00
	Microcrystalline cellulose	114.00
	Anhydrous sodium carbonate	30.00
	Magnesium stearate	6.00
	Compression weight	600.00

The ranitidine bismuth citrate and indomethacin are blended with the microcrystalline cellulose, sodium carbonate and magnesium stearate and compressed using 12.5mm punches.

Example 2

CAPSULES

		Capsule
(a)	Ranitidine bismuth citrate	200.00
	Ibuprofen	400.00
	Starch 1500**	196.00
	Magnesium stearate	4.00
	Fill weight	800.00

** A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

The ranitidine bismuth citrate and ibuprofen are sieved through a 250μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

		mg/capsule
(b)	Ranitidine bismuth citrate	200.00
	Indomethacin	50.00
	Starch 1500	48.50
	Magnesium stearate	1.50
	Fill weight	300.00

The ranitidine bismuth citrate and indomethacin are sieved through a 250μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 2 hard gelatin capsules using a suitable filling machine.

Example 3

INHIBITION OF INDOMETHACIN-INDUCED GASTRIC LESIONS IN THE RAT

The ability of ranitidine bismuth citrate to prevent indomethacin-induced gastric antral ulceration was compared with that of ranitidine hydrochloride and De-Nol™.

Female rats, which had been fasted for 24 hours and then re-fed, received ranitidine bismuth citrate (1 to 100mg/kg), ranitidine hydrochloride (10 to 100mg/kg) or De-Nol™ (3 to 100mg/kg) by oral gavage. Ranitidine bismuth citrate was administered as a suspension and the other test compounds as solutions. Thirty minutes after dosing with the test compound, animals received indomethacin (60mg/kg sc) as an ulcerogenic stimulus and after a further 6 hours the animals were killed and the antral region assessed macroscopically for damage.

Results are presented in the table below. Ranitidine bismuth citrate produced a dose-related inhibition of indomethacin-induced lesions and was relatively potent, an ED_{50} value of 4.5mg/kg po being calculated. Ranitidine hydrochloride and De-Nol™ were markedly less potent.

ED_{50} Values for Inhibition of Indomethacin - Induced Antral Ulceration			
Compound	Ranitidine Bismuth Citrate	Ranitidine Hydrochloride	De-Nol™
ED_{50} mg/kg p.o.	4.5	23.4	43.2
95% confidence limits	0.5 - 10.7	16.0 - 33.0	23.6 - 93.0

Claims

1. The use of (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in the manufacture of medicaments for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

2. The use of ranitidine bismuth citrate in the manufacture of medicaments to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs.

3. The use according to Claim 1 in which the compounds (i) and (ii) are presented as separate compositions for said use.

4. A product containing compounds (i) and (ii) as defined in Claim 1 as a combined preparation for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

5. A pharmaceutical composition, for oral use, which comprises both a compound (i) and a compound (ii) as defined in Claim 1, together with a pharmaceutical carrier or excipient.

6. A use, product or composition according to any preceding claim in which the non-steroidal anti-inflammatory drug is selected from aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

7. A use or product according to any preceding claim in which compounds (i) and (ii) are in forms suitable for oral administration.

8. A use or product according to any preceding claim in which compound (i) is formulated as a tablet.

9. A use or product according to Claim 8 in which compound (i) is administered at a dosage of 200-800mg per unit dose.

10. A twin-container pack for use in treating or preventing inflammatory conditions or for analgesia, one of the containers containing (i) and the other containing (ii) as defined in the preceding claims.

11. A composition according to Claim 5 or Claim 6 or a pack according to Claim 10, in association with instructions for the use of both (i) and (ii) in treating or preventing inflammatory conditions or for analgesia.

12. A method for the preparation of a composition according to Claim 5 or Claim 6 which comprises admixing (i) and (ii) together, if desired, with suitable carriers or excipients.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 3674

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	GB-A-2 105 193 (GLAXO GROUP LIMITED) * abstract * ---	1-12	A61K31/34 A61K31/54 A61K31/415
Y	EP-A-0 426 479 (MCNEIL-PPC, INC.) * abstract; claims 1-3 * ---	1-12	A61K31/40 A61K31/405 A61K31/62
Y,D	GB-A-2 220 937 (GLAXO GROUP LIMITED) * abstract * -----	1-12	A61K31/645 //(A61K31/645,31:34)(A61K31/54,31:34)(A61K31/415,31/34)(A61K31/405,31:34)(A61K31/40,31:34)(A61K31/34,31:24)(A61K31/34,31:195)(A61K31/34,31:19)

TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11 MARCH 1993	LEHERTE C.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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Remarks:
This application was filed on 18 - 04 - 2000 as a divisional application to the application mentioned under INID code 62.

(54) Use of alkaline salts of the (-)-enantiomer of omeprazole

(57) The use of an alkaline salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical preparation having improved pharmacokinetic and metabolic properties, such as improved therapeutic profile when treating gastric acid related diseases.

EP 1 020 461 A2

Description

Field of the invention

[0001] The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

Background of the invention

[0002] The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

[0003] The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralisation will create heat which will be difficult to handle in large scale production.

[0004] The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

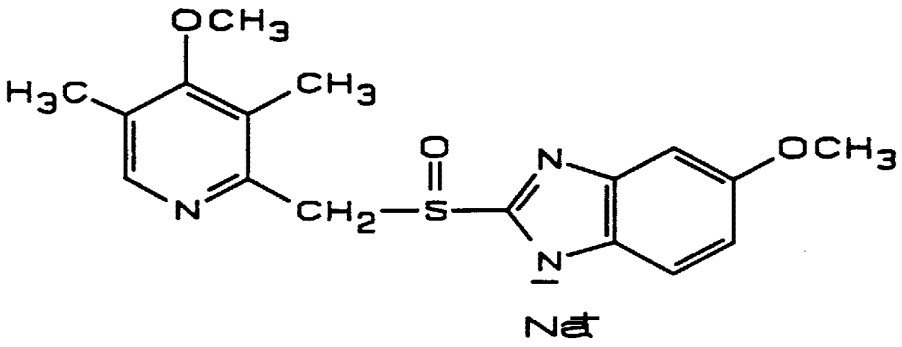
[0005] There is no example known in the prior art of any isolated or characterized salt of optically pure omeprazole, i.e. single enantiomers of omeprazole neither of any isolated or characterized salt of any optically pure omeprazole analogue.

Detailed description of the invention

[0006] The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1-4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms.

[0007] Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole calcium salt.

[0008] Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

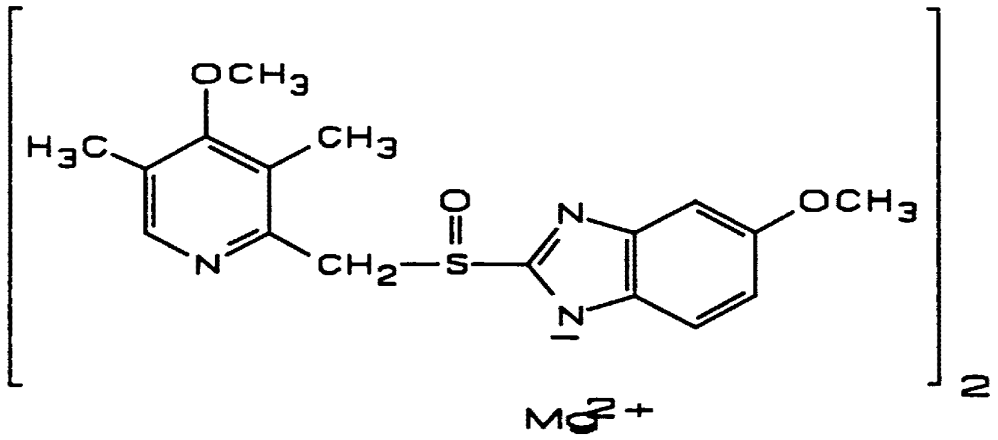


(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb



(IIa, IIb)

IIa (+)-enantiomer

IIb (-)-enantiomer

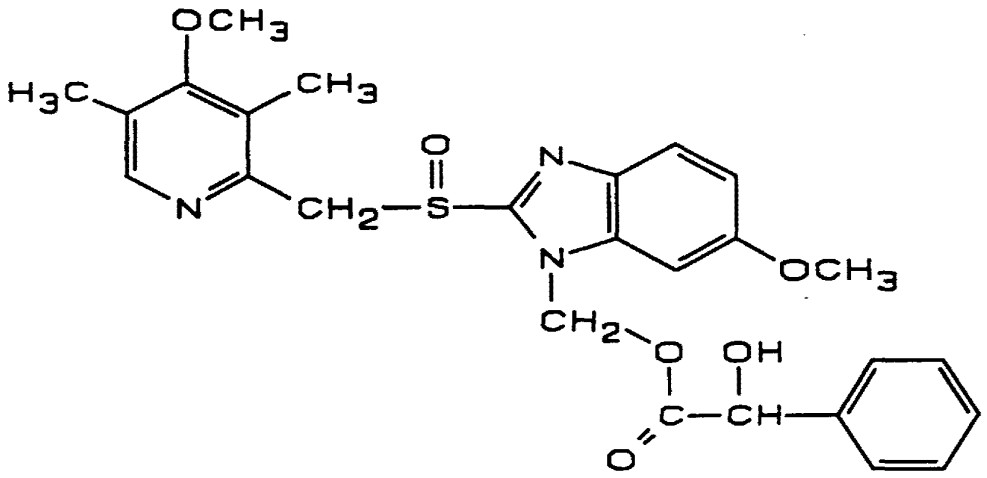
[0009] With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole, the salts defined by the present invention are easy to obtain. In addition, the salts, however not the neutral forms, are obtained as crystalline products. Because it is possible to purify optically impure salts of the enantiomers of omeprazole by crystallisation, they can be obtained in very high optical purity, namely ≥99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable towards racemization both in neutral pH and basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was expected to cause racemization under alkaline conditions. This high stability towards racemization makes it possible to use a single enantiomeric salt of the invention

in therapy.

[0010] The specific method of preparation of the single enantiomers of omeprazole is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomers of omeprazole in neutral from as well as the salts thereof.

[0011] The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with accute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

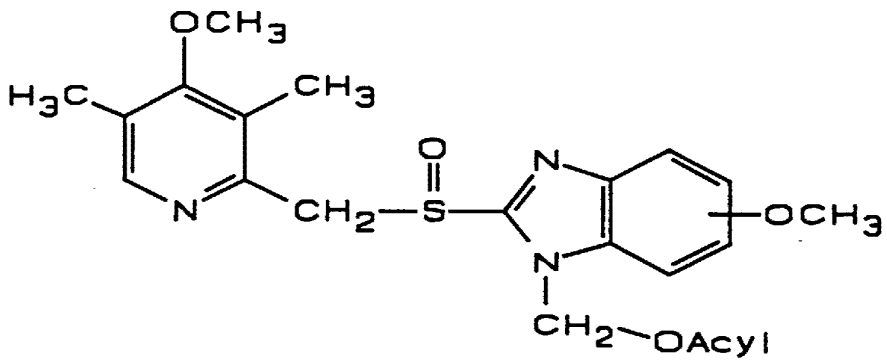
[0012] Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.



(III)

Preparation

[0013] The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



(IV)

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

[0014] The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

[0015] The diastereomeric esters can be separated either by chromatography or fractional crystallization.

[0016] The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

[0017] To obtain the optically pure Na^+ salts of the invention, i.e. the single enantiomers of omeprazole Na^+ salts, the resulting compound is treated with a base, such as NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with $NaNH_2$. Also alkaline salts wherein the cation is Li^+ or K^+ may be prepared using Lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

[0018] To obtain the optically pure Mg^{2+} salts of the invention, optically pure Na^+ salts are treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

[0019] Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compound IIa and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+R)_4$, where R is an alkyl with 1-4 C-atoms.

[0020] For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration.

[0021] In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active

compound present.

[0022] Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

[0023] Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

[0024] Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

[0025] Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

[0026] Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight These soultions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

[0027] The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

[0028] The invention is illustrated by the following examples.

Example 1. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

[0029] 100 mg (0.3 mmol) of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The tesultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$ = +42,80° (c=0.5%, water).

[0030] NMR data are given below.

Example 2. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

[0031] 100 mg (0.3 mmol) of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247-249°C.

[0032] The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[a]_D^{20}$ = -44.1° (c=0.5%, water).

[0033] NMR data are given below.

Example 3. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0034] 2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-

dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$ = +101.2° (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

Example 4. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0035] (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2xH_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$ = +129.9° (c=1%, methanol).

Example 5. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0036] (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2xH_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$ = -128.2° (c=1%, methanol).

Table I

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d. 1H), 6.54 (dd. 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
2.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

[0037] Preparation of the synthetic intermediates according to the invention will be described in the following examples.

Example 6. Preparation of 6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

[0038] A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimerhyl-2-pyridinyl)methyl]-sulfinyl]-l-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the tide compound (38%) as a diastereomeric mixture.

[0039] NMR data are given below.

Example 7. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3.5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

[0040] The diastereomers of the tide compound in Example 6 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected

to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

[0041] NMR data are given below.

Example 8. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

[0042] The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 6. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

[0043] NMR data are given below.

Example 9. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

[0044] The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 7. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colourless syrup.

[0045] NMR data are given below.

Example 10. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

[0046] 0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the tide compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$ = -155° (c=0.5%, chloroform).

[0047] NMR data are given below

Example 11. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

[0048] 0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxid in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 µl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}$ = +157° (c=0.5%, chloroform).

[0049] NMR data are given below

Table 2

Ex.	Solvent	NMR data δ ppm
6.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
7.	$CHCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
8.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
9.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
10.	$CDCl_3$ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).
11.	$CDCl_3$	2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b. 1H), 8.20 (s, 1H).

[0050] The best mode of carrying out the invention known at present is to use the sodium salts of the optically pure compounds of the invention, thus the compounds described in Example 1 and Example 2.

[0051] Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

[0052] A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 2	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

[0053] Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

[0054] An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 3 as Mg salt	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to Example 3, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcolhol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^{R}, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

[0055] A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

[0056] The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

[0057] Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to Example 1	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g

(continued)

Disodium hydrogen phosphate	2 g
Purified water	q.s.

[0058] The active compound was mixed with the dry ingredients and granulated wit a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

[0059] 500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated wit a second coating as given below:

[0060] Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

[0061] The final coated pellets were filled into capsules.

Suppositories

[0062] Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 2	4 g
Witepsol H-15	180 g

[0063] The active compound was homogenously mixed with Witepsol H- 15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Stability towards racemization at different pH:es

[0064] The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations in refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

[0065] In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ($c=10^{-5}$M) was warmed for 26 hours at 37°C without any racemization at all being observed.

[0066] The following pages 22 - 26 of the description relate to preferred embodiments of the invention, wherein "embt. / embts." means embodiment / embodiments.

1. Optically pure compounds **characterized** in that the compounds are Na^+, Mg^{2+}, Li^+, K^+ Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, wherein R is an alkyl with 1-4 carbon atoms.

2. Compounds according to embt. 1 **characterized** in that the compounds are (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium Salt.

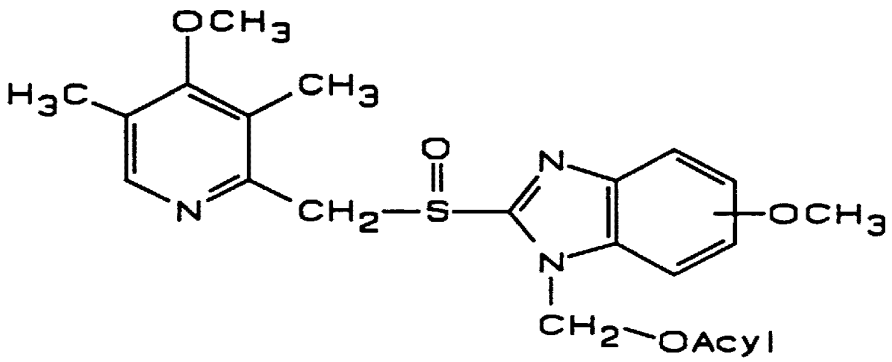
3. Compounds according to embts. 1 and 2 **characterized** in that the compounds are (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

4. Compounds according to embts. 1 and 2 **characterized** in that the compounds are (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt in their crystalline forms.

5. Compounds according to embts. 1 and 2 **characterized** in that the compound is (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form.

6. Compounds according to embts. 1 and 2 **characterized** in that the compound is (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form.

7. Process for the preparation of a compound according to embt. 1 **characterized** in that a diastereomeric ester of formula IV



(IV)

wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is dissolved in an alkaline solution where the acyloxymethyl group is hydrolyzed to give the optically pure compound.

8. Process according to embt.7 **characterized** in that the diastereomers are separated by chromatography or fractional crystallization.

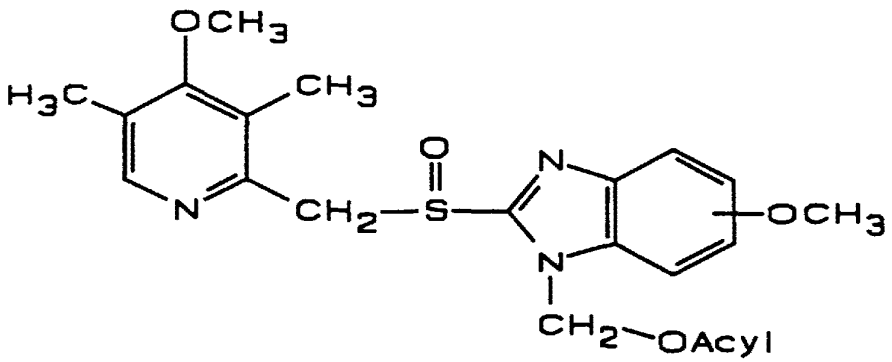
9. Process according to embt. 7 **characterized** in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide.

10. Process for the preparation of a compound according to embt. 1 in crystalline form **characterized** in that a product from the process in embt. 7 is neutralized with a neutralizing agent which can be an acid or an ester such as methyl formate, followed by treatment with a base in non-aqueous solution.

11. Process for preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimi-

dazole sodium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt in their crystalline forms **characterized** in that (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl-1H-benzimidazole sodium salt crude product respectively is neutralized followed by treatment with NaOH in a non-aqueous medium.

12. Process for the preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole **characterized** in that a diastereomeric ester of formula IV



(IV)

wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is dissolved in an alkaline solution where the acyloxymethyl group is hydrolyzed off to give the optically pure compound after neutralization with a neutralizing agent which can be an acid or an ester.

13. Process according to embt. 12 **characterized** in that the diastereomers are separated by chromatography or fractional crystallization.

14. Process according to embt. 12 **characterized** in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide.

15. The compound (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in embt. 12.

16. The compound (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in embt. 12.

17. Pharmaceutical preparation containing an optically pure compound according to any of embts. 1-6 as active ingredient.

18. Optically pure compounds according to any of embts. 1-6 for use in therapy.

19. Use of an optically pure compound according to any of embts. 1-6 in the preparation of a pharmaceutical formulation for inhibiting gastric acid secretion.

20. Use of an optically pure compound according to any of embts. 1-6 for the preparation of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.

21. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound according to any of embts. 1-6.

22. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound according to any of embts. 1-6.

23. The compound 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-1 -[mandeloyloxymethyl]-1H-benzimidazole.

Claims

1. The use of an alkaline salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical preparation having improved pharmacokinetic and metabolic properties.

2. The use of claim 1, wherein said improved pharmacokinetic and metabolic properties comprise an improved therapeutic profile when treating gastric acid related diseases.

3. The use of claim 1 or 2, wherein said improvement comprises a lower degree of interindividual variation in plasma levels.

4. The use of any of claims 1 to 3, wherein said alkaline salt is selected from the Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+}, and $N^+(R)_4$ salts, wherein R is an alkyl with 1-4 carbon atoms.

5. The use of claim 4, wherein said salt is selected from the Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts.

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(54) Use of alkaline salts of the (-)-enantiomer of omeprazole

(57) The use of an alkaline salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical preparation having improved pharmacokinetic and metabolic properties, such as improved therapeutic profile when treating gastric acid related diseases.

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EUROPEAN SEARCH REPORT

Application Number
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TECHNICAL FIELDS SEARCHED (IPC)

C07D
A61K
A61P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	28 August 2006	Wolf, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 10 8480

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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(54) Pharmaceutical tablet comprising an NSAID and misoprostol

(57) A pharmaceutical tablet comprising a core and a film coating wherein the core comprises an NSAID and the film coating comprises a polymer and misoprostol.

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Description

BACKGROUND OF THE INVENTION

[0001] The invention herein is directed to a pharmaceutical tablet which comprises both an NSAID and misoprostol.

[0002] Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis and rheumatoid arthritis. While the NSAIDs present a beneficial therapeutic value, they also exhibit an undesirable ulcerogenic effect generally associated with chronic use. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit few or no symptoms and may cause bleeding when undetected. In some instances, bleeding ulcers can prove fatal.

[0003] Certain prostaglandins have been shown to prevent NSAID induced ulcers. Misoprostol is a prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States.

[0004] It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side effects attendant to NSAID administration.

[0005] This can be achieved by combining an NSAID and misoprostol in a single pharmaceutical tablet. However, this is not easy to do, because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol.

[0006] One solution to this problem, which is disclosed in U.S. Patent 5601843, is to produce a composition in the form of a tablet comprising within it a smaller tablet. Such a composition is known in the art as a "compression coated" tablet or "mantle" tablet. The portion of the larger tablet (i.e. the whole composition) that surrounds the smaller inner or "core" tablet is known as the "mantle". In the compositions of U.S. patent 5601843, the misoprostol and NSAID are separated from each other by having the core tablet comprise the NSAID and the mantle comprise the misoprostol.

[0007] It is also disclosed that, in order to prevent contact between the misoprostol and the NSAID at the surface of the inner core, the inner core may be coated with an inert film coating. Such coating may be an enteric film coating, which also serves to reduce the likelihood of the NSAID dissolving in the stomach and thereby prevent exposing the stomach to the NSAID.

[0008] While the invention of U.S. Patent 5601843 accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages.

[0009] One disadvantage is that the process of making the mantle tablet is complicated, and the machinery needed is specialized and relatively expensive. In the process of manufacture of the mantle tablet, it is necessary to first make the smaller core tablet, which is done on a conventional tablet press, and then to use a compression coating press to make the final tablet. Such a press makes the final tablet much the same as a conventional tablet is made, but must have the added feature of being able to insert the core tablet along with the mantle powder mix into each die for compression into the final tablet.

[0010] Another disadvantage is that the final tablet must be substantially larger than the inner core tablet to have an adequate quantity of compressible mantle material completely surrounding the inner core. In the compositions of U.S. patent 5601843, the substantial mass of the mantle is in any event necessary to comprise the misoprostol. This is because misoprostol is unstable in pure form, and the only way known in the art to stabilize misoprostol is to process it into a dispersion comprising 1 part misoprostol in from about 50 to about 500 parts of a polymer, as disclosed in U.S. patent 4301146. The examples of U.S. patent 5601843 all use a dispersion of 1 part misoprostol in 100 parts hydroxypropyl methylcellulose ("HPMC"). Also this dispersion must be mixed with a binder, lubricant and other ingredients to make a mixture which can be compressed into the mantle. Thus it follows that the mass of the mantle must be large relative to the core.

[0011] In all nine examples of U.S. patent 5601843, the core tablet has a mass of 90 mg and the mantle has a mass of 265 mg. The nine examples differ from each other only in details of film coatings applied to the core tablet before it is inserted into the final tablet. Hence, in all nine examples, the total mass of the final tablet is at least 355 mg, despite the fact that the mass of the core tablet is only 90 mg.

[0012] The object of the present invention is to enable a pharmaceutical tablet that incorporates both an NSAID and misoprostol, but overcomes these disadvantages.

BRIEF SUMMARY OF THE INVENTION

[0013] The present invention is a pharmaceutical composition in the form of a tablet comprising a core and a film coating applied over the core, wherein the core comprises an NSAID and the film coating comprises misoprostol.

[0014] As aforesaid, the misoprostol must be stabilized by processing it into a dispersion in a polymer. However, a film coating also must comprise a polymer. The essence of the invention is to film-coat the core tablet with a coating comprised of both the misoprostol and a polymer, so that the polymer simultaneously serves the two purposes of stabilizing the misoprostol and forming a polymeric film coating around the core.

[0015] The procedure of applying the film coating

comprising misoprostol is to dissolve the misoprostol and polymer in solvent, optionally along with other ingredients such as plasticizers and surfactants, and to spray the solution onto the tablets in conventional tablet coating equipment. As the solvent is evaporated, the film coating comprising the misoprostol and polymer is formed around the tablet.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The NSAID contained within the core tablet will preferably be piroxicam, or diclofenac, or a salt of diclofenac, such as diclofenac sodium or diclofenac potassium. Most preferably, the NSAID will be diclofenac sodium.

[0017] Where diclofenac or a salt thereof is used, the amount per tablet will preferably be from about 25 to about 75 mg. The core tablet containing diclofenac or salt thereof will contain, along with the diclofenac or salt thereof, usual tablet excipients such as binders, lubricants, fillers and the like. Preferably, the tablet containing the diclofenac or salt thereof will be coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the small intestine. The enteric coating can be formulated with any suitable enteric coating polymer, many of which are known to those skilled in the art.

[0018] Where piroxicam is used as the NSAID, the amount per tablet will preferably be from about 10 to about 20 mg. Again, the tablet containing piroxicam will also comprise usual tablet excipients.

[0019] It will be understood that the film coating comprising misoprostol may be sprayed directly on the core tablet containing the NSAID. Optionally, the core tablet may first be coated with an enteric film coating, and the film coating comprising the misoprostol applied as an overcoat.

[0020] Also optionally, the core tablet may first be coated with an enteric film coating and then overcoated with another inert film coating, and then overcoated again with the film coating comprising misoprostol.

[0021] Also optionally, another inert film coating may be applied on top of the film coating which comprises the misoprostol, in order to protect the misoprostol from the effects of light and air.

[0022] The polymer used in the film coating which comprises the misoprostol may be any water-soluble polymer which will form a film coating when sprayed onto a tablet and which will also stabilize misoprostol. The polymer will preferably be selected from povidone and water-soluble cellulose derivatives, and most preferably will be hydroxypropyl methylcellulose. The ratio of polymer to misoprostol by weight will preferably be from about 10 to about 100 parts polymer to 1 part misoprostol, and more preferably from about 15 to about 50 parts polymer to 1 part misoprostol.

[0023] The solvent system used to dissolve the misoprostol and polymer may be comprised of water or organic solvents and will preferably be a mixture of a chlorinated hydrocarbon and an alcohol, and most preferably be a mixture of methylene chloride and an alcohol. The solution will optionally also comprise other ingredients, such as a plasticizer or surfactant.

[0024] The invention will be further understood from the following example, which is intended to be illustrative and not limiting of the invention.

EXAMPLE 1

[0025] Core tablets are made with ingredients per tablet as follows:

	mg per tablet
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
corn starch	8.4
povidone	4.8
magnesium stearate	0.9
	90.0

[0026] The process of production of these core tablets is to mix all of the ingredients except the magnesium stearate, granulate by adding water and mixing, dry the granules, add the magnesium stearate, mix again, and compress this final mixture into tablets on a tablet press.

[0027] These core tablets are then enteric coated by applying a coating with ingredients per tablet as follows:

	mg per tablet
cellulose acetate phthalate	5.4
diethyl phthalate	1.5
	6.9

[0028] The process of application of this film coating is to dissolve the cellulose acetate phthalate and the diethyl phthalate in acetone, and to spray the solution onto the tablets in a coating pan and evaporate the acetone.

[0029] These enteric film coated tablets are then overcoated with a film coating comprising hydroxypropyl methylcellulose, polyethylene glycol as plasticizer, and misoprostol, with the following ingredients per tablet:

	mg per tablet
hydroxypropyl methylcellulose	4.0
polyethylene glycol	0.2
misoprostol	0.2
	4.4

[0030] The process of application of this film coating is to dissolve the hydroxypropyl methylcellulose, poly-

ethylene glycol, and misoprostol in a mixture of methylene chloride and methanol, and to spray the solution onto the enteric coated tablets in a coating pan and evaporate the methylene chloride and methanol.

Claims

1. A pharmaceutical composition in the form of a tablet comprising a core and a film coating applied over the core, wherein the core comprises an NSAID and the film coating comprises a polymer and misoprostol.

2. A pharmaceutical composition as in claim 1 further comprising an enteric coating applied between the core and the film coating comprising a polymer and misoprostol.

3. A composition as in claim 1 or 2 wherein the NSAID is piroxicam or diclofenac or a salt thereof.

4. A composition as in claim 1 or 2 wherein the NSAID is diclofenac sodium.

5. A composition as in any of claims 1 to 4, wherein the polymer is povidone or a water-soluble cellulose derivative.

6. A composition as in any of claims 1 to 4, wherein the polymer is hydroxypropyl methylcellulose.

7. A composition as in any of claims 1 to 6 wherein the ratio of polymer to misoprostol by weight is from about 10 to about 100.

8. A composition as in any of claims 1 to 6 wherein the ratio of polymer to misoprostol by weight is from about 15 to about 50.

9. The process of making a composition according to any of claims 1 and 3 to 8 which comprises the steps of making the core tablet comprising the NSAID, and applying around the core a film coating comprising the polymer and misoprostol by dissolving the polymer and misoprostol in solvent, spraying the solution, and evaporating the solvent.

10. The process of making a composition according to any of claims 2 to 8 which comprises the steps of making the core tablet comprising the NSAID, applying an enteric coating around the core, and applying an overcoating around the enteric coating comprising the polymer and misoprostol by dissolving the polymer and misoprostol in solvent, spraying the solution, and evaporating the solvent.

11. A process of claim 9 or 10 wherein the solvent comprises a chlorinated hydrocarbon and an alcohol.

12. A process of claim 9 or 10 wherein the chlorinated hydrocarbon is methylene chloride.

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(54) Pharmaceutical tablet comprising an NSAID and misoprostol

(57) A pharmaceutical tablet comprising a core and a film coating wherein the core comprises an NSAID and the film coating comprises a polymer and misoprostol.

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EUROPEAN SEARCH REPORT

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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	1 March 2001	Epskamp, S

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 30 5965

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01-03-2001

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(54) Oral pharmaceutical formulation for the prevention and/or the treatment of cardiovascular and inflammatory diseases

(57) The invention relates to oral pharmaceutical formulations for the prevention and/or the treatment of cardiovascular and inflammatory diseases. This invention also addresses methods of prevention and/or treatment of these diseases, using these oral formulations. Cardiovascular diseases of particular concern for the invention are the diseases resulting from excessive and uncontrolled platelet aggregations (platelet disorders). More particularly, these diseases are those caused by an excess of thromboxane and against which antithrombotic treatments can be proposed to the patients.

EP 1 726 300 A1

Description

[0001] The invention relates to oral pharmaceutical formulations for the prevention and/or the treatment of cardiovascular and inflammatory diseases. This invention also addresses methods of prevention and/or treatment of these diseases, using these oral formulations. Cardiovascular diseases of particular concern for the invention are the diseases resulting from excessive and uncontrolled platelet aggregations (platelet disorders). More particularly, these diseases are those caused by an excess of thromboxane and against which antithrombotic treatments can be proposed to the patients.

[0002] In the present exposure, the "thrombotic" troubles denotes, notably, the thrombotic cardiovascular events such as such as stroke, myocardial ischemia, myocardial infarction, angina pectoris, transient ischemic attack, reversible ischemic neurological deficits, and any similar thrombotic event in any vascular bed (splanchnic, renal, aortic, peripheral, etc.).

[0003] One of the medical problems supporting the instant invention is the enhancement of the safety of these antithrombotic treatments.

[0004] Indeed, to inhibit platelet aggregation and limit the inherent cardiovascular risks, it is known to administrate to the patients two major anti-platelets drugs, namely low dose aspirin and PLAVIX®.

[0005] PLAVIX® (clopidogrel bisulfate) is an inhibitor of platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent A.P. mediated activation of the glycoprotein GPIIb/ IIIa complex. Chemically, it is methyl (+)-(S)-a -(2- chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5 (4H)-acetate sulfate (1:1). The side effects of the PLAVIX® are notably: gastrointestinal hemorrhaging; Neutropenia/agranulocytosis; gastrointestinal events (e. g. abdominal pain, dyspepsia, gastritis and constipation, peptic, gastric or duodenal ulcers, diarrhea); Rash and Other Skin Disorders, etc.

[0006] Aspirin, or acetylsalicylic acid, acts to prevent platelet aggregation by irreversibly inhibiting cyclooxygenase (COX-1 & COX-2, collectively known as COX). COX converts arachodonic acid to thromboxane, a potent vasoconstrictor and a platelet aggregation stimulator. Aspirin inhibits COX by acetylating it. The inhibition of COX activity by aspirin is generally irreversible. This is an important distinction for aspirin because the duration of the effects of aspirin is related to the turnover of COX in different tissue targets. Platelets are especially susceptible to aspirin mediated irreversible inactivation of COX because platelets have little or no capacity for protein biosynthesis and, thus, cannot regenerate the COX enzyme. In practical terms, this means that a single dose of aspirin will inhibit the platelet COX for the life of the platelet, 8-11 days.

[0007] When aspirin is absorbed from the digestive tract, it is collected by the portal vein. The portal vein then goes to the liver where the aspirin is deacetylated. Once deacetylated, aspirin no longer has the ability to aceytelate COX. However, the mechanism in the liver can rapidly reach saturation causing the aspirin overflow to enter the systemic blood circulation. In the systemic circulation, aspirin that has not been deacetylated by the liver can further inhibit COX in other tissues and cells. For instance, in the endothelial cells that line the vasculature, aspirin-induced COX inhibition results in a decrease of prostacyclin, which is a potent vasodilator, a platelet aggregation inhibitor and a cytoprotector. Therefore, aspirin that enters the systemic blood circulation results in inhibition of the prostacyclin and other prostaglandins, which runs counter to the desired effect on platelet aggregation. This phenomenon of blind inhibition of the different prostaglandins in the organism is commonly referred to as the dilemma of aspirin. It is well known to scientists and has been widely described in the literature.

[0008] Aspirin is a very useful medication for the prevention of cardiovascular thrombotic events in patients with or those at risk for cardiovascular disease. However, there are serious side effects of aspirin administration. For example, the most common side effect is a propensity to induce gastric or intestinal ulceration, which may result in hemorrhaging. This effect occurs when acetylated aspirin allows back diffusion of acid into the gastric mucosa and induces tissue damage and bleeding, correlated with inhibition of the biosynthesis of gastric prostaglandins that ordinarily serve as cytoprotective mucous in the intestines. The gastrointestinal effects of aspirin may be caused by its lack of selectivity between antiplatelet COX-1 inhibition and endothelial COX-1 inhibition leading to gastric mucosal effects.

[0009] In patients with established cardiovascular disease, aspirin use has been documented to decrease the risk of a primary myocardial infarction, stroke and vascular death. Secondary prevention refers to the use of aspirin to prevent cardiovascular events in patients with established cardiovascular disease such as a myocardial infarction, stroke, or angina. The use of aspirin in these individuals is recommended based on a documented decrease in future cardiovascular events and mortality. The risk for gastrointestinal injury is observed in patients being treated with aspirin, even at dosages as low as 81 mg/day for cardio protection.

[0010] In patients with established cardiovascular disease, aspirin may have further side effects. For example, aspirin may decrease renal blood flow and the rate of glomerular filtration in patients with congestive heart failure. Therefore, acute renal failure may be precipitated. Aspirin may also promote the retention of salt and water by reducing the prostaglandin induced inhibition of both the reabsorption of chloride and the action of anti-diuretic hormone. This may cause edema in some patients who are treated with aspirin and may reduce the effectiveness of anti-hypertensive regimens. Aspirin and other COX-2 inhibitors may also increase the risk of heart disease. Metabolism of arachodonic acid by COX-2 results in the production of prostaglandins, which promotes inflamma-

tion. Therefore inhibition of COX-2 results in decreased inflammation. However, COX-2 inhibition also promotes arachodonic acid to be converted to pro-inflammatory agents such as leukotriene B4 and thromboxane A2. The resulting increase in these pro-inflammatory agents may lead to increased atherosclerosis and platelet aggregation, and other complications such as stroke and heart attack.

[0011] Aspirin that is not metabolized by the liver may induce serious side effects. Since aspirin may be taken by the patient for a substantial portion of his life, it is important to improve the safety profile of the treatment for the tens of millions of patients today who regularly take anti-platelet drugs. Thus, it appears that there is a need in a therapeutic solution for treating the pathologies linked to platelet aggregation, optionally the inflammatory disorders, without causing the serious side effects to the patients.

[0012] US-B-6,599,529 relates to an oral pharmaceutical modified release multiple-units composition for the administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance - e.g., aspirin - (in the following abbreviated "an NSAID substance") to obtain both a relatively fast or quick onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. The modified release multiple-units composition comprises at least two fractions of multiple units such as a first and a second fraction. The first fraction is an immediate release form of NSAIDs, which comprises individual units that are designed to quickly release the drug substance. The second fraction is a delayed release sustained release form, which comprises individual units that are designed to slowly release the drug substance to enable a delayed and extended release of the drug substance. Typically, the second fraction comprises multiple units which are coated with a sustained release coating designed to release the drug substance in such a manner that the maintenance of a therapeutically active plasma concentration for a relatively long period of time are obtained (once- or twice-a-day administration)- [Pellet cores: Polysorbate 20/Cellulose microcrystalline/Lactose/Carmellose sodium/Maltodextrin/Pregelatinized starch -Inner coat: Hypromellose (Methocel E prem) /Magnesium stearate / Talc / Eudragit NE 30 D - Outer coat: Hypromellose (Methocel E5 prem) / Talc].The composition can comprise a further active drug substance selected from the group consisting of an antidepressant, an opioid, a prostaglandin analog, a glucocorticosteroid, a cytostaticum, a H_2 receptor antagonist, a proton pump inhibitor and an antacid. The immediate release fraction of NSAIDs (aspirin) in this composition is still creating all gastric side effects mentioned before. The problem of aspirin dilemma is not solved.

[0013] US-A-2004/0121004 & US-A-2004/0131676 disclose a non-enterically coated dosage form comprising: a) a proton pump inhibitor(lansoprazole); b) a buffer; and c) a non-steroidal anti-inflammatory drug (aspirin at an amount between 50 mg and 100 mg) and a method of treating a condition selected from the group consisting of angina, aorto-pulmonary shunt occlusion, colorectal cancer, esophageal cancer, colon cancer, coronary artery disease, dementia, dysmenorrhea, myocardial infarction, rheumatoid arthritis, osteoarthritis, pain, headache, migraine headache, stroke, thrombocythemia, post-operative thromboembolism, ischemia, bursitis, cognitive decline, fever, gout, musculoskeletal disorders, soft tissue injury, and pericarditis; wherein the method comprises administering to a patient having one or more of the above conditions said non-enterically coated dosage form. This form is an immediate release form of acetylsalicylic acid at basic pH. Granulates of NSAIDs are prepared from Magnesium Hydroxide- buffer-; Calcium Carbonate; Mannitol; Avicel (micro-crystalline Cellulose); PVPP (Cross- povidone). These granulates are tabletted.

[0014] The immediate release aspirin included in this dosage and the immediate release fraction of NSAIDs (aspirin) in this composition still creates many of the gastric side effects mentioned before. The problem of aspirin dilemma is not solved.

[0015] Finally, the prior art discloses how treating the side effects in terms of bleeding and pitichia induced by acetylsalicylic acid entering the systemic circulation. This prior art proposes to co-administrate large amounts of proton pump inhibitor to increase the gastric pH to reduce the pain. The drawbacks of this approach are as follows:

1. damages of the gastric mucosa are very high and permanent;
2. the large dose of proton pump inhibitor results in a constant high pH, so which is deleterious for chronic use.

[0016] US-B-5,603,957 belonging to the applicant, and incorporated in its entirety by reference discloses and claims a pharmaceutical form comprising microcapsules for the controlled release of acetylsalicylic acid in the gastrointestinal environment, said microcapsules consisting of particles of acetylsalicylic acid with a size of between 100 and 1000 μm. These microcapsules are coated and designed so that, when ingested orally in a single administration of a dose of between 50 and 325 mg of acetylsalicylic acid, they induce moderate acetylsalicylic acid absorption kinetics in vivo in man, extending over at least 24 hours, said acetylsalicylic acid absorption being less than or equal to 10% by weight of the absorbed fraction of the dose at a time t after ingestion of 0.4 hour, less than or equal to 50% by weight of the absorbed fraction of the dose at t=3.9 hours, and less than or equal to 90% by weight of the absorbed fraction of the dose at t=23 hours, t being given to within +/-10%. It is also possible to create microcapsules of even smaller size, such as 50μm or less. One method to create such smaller microcapsules is disclosed in USPN 6,022,562 to Durant et al. , which is incorporated by reference in its entirety.

[0017] We find it surprising that we can use the pharmaceutical form of microcapsules to selectively inhibit COX in platelets, and thus reduce the production of thromboxane, while minimizing COX inhibition in the circulation. It is therefore possible to optimize the inhibition of platelet aggregation, in order to prevent and/or treat cardiovascular diseases and risks, while minimizing the side effects.

[0018] While not wishing to be constrained by any mode of action, we believe that by coating the acetylsalicylic acid to form microcapsules, we promote the direct action of aspirin on only the COX of the blood platelets in the portal circulation. Our pharmaceutical formulation results in a low, constant release rate of aspirin being released from the microcapsules and absorbed by the portal vein. This low release rate of aspirin is sufficient to inhibit COX in the portal vein, and therefore prevent thromboxane formation and platelet aggregation. Once aspirin is deacetylated, it is no longer active in that it can no longer inhibit COX. The liver can quickly be saturated with aspirin, and any aspirin that is not deacetylated will overflow into the systemic blood stream. We find it surprising that our use of microcapsules results in a release rate of aspirin low enough such that the liver is not saturated. Therefore, once the low release rate of aspirin inhibits the COX in the platelets of the portal vein, any remaining active aspirin is then deacetylated by the liver. This results in minimal aspirin overflow into the systemic circulation to inhibit prostaglandin and prostacyclin production, thus preventing damage of the gastroendothelium and other side effects of aspirin. Thus, the method permits the rapid saturation of the liver without the normal deleterious side effects, a result that we find unexpected.

[0019] We also propose combining a controlled release form of aspirin that releases a low, constant release rate of aspirin such that very little aspirin reaches the systemic circulation, and a minimal release rate of a gastric acid suppressing agent to decrease the gastric damages by increasing the gastric pH.

[0020] While not wishing to be constrained to low dose of gastric acid suppressing agent, we fmd it surprising that we can greatly minimize gastric damage with only a minimal dose of gastric acid suppressing agent. The low dose of gastric acid suppressing agent in our invention increases the gastric pH only a small amount. Further, the low, constant dose of aspirin released in the intestinal tract would sufficiently inhibit COX in the platelets while having minimal effects on the systemic prostaglandins. Therefore, the applicant takes credit for demonstrating that the combination of a controlled release aspirin microcapsules with at least one gastric acid suppressing agent makes it possible to increase the safety of the antiplatelet drug while decreasing the side effects.

[0021] The present invention concerns an oral pharmaceutical formulation for enhancing notably the safety of antithrombotic treatments,

- comprising a combination of microcapsules for the controlled release of acetylsalicylic acid (acetylsalicylic acid), in the gastrointestinal environment and at least one gastric acid suppressing agent,
- said microcapsules:
  - having an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that 70% of the acetylsalicylic acid is released over a period of time of between 2 and 20 hours, preferably between 4 and 18 hours, and even more preferably between 6 and 15 hours, and
  - inhibiting COX-1 in portal vein which limits the production of thromboxane while maintaining COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin production to decrease the side effects and to maintain its vasodilatation properties;
- said gastric acid suppressing agent increasing the pH of the stomach just enough to decrease the dissolving of aspirin while minimizing the damage from any residual of non-deacetylated acetylsalicylic acid coming from the liver and the portal blood circulation and entering the systemic blood circulation.

[0022] The term "controlled release" denotes, in the present disclosure, a prolonged or sustained release and/or a delayed release and/or a pulsed release of active principle by an oral pharmaceutical formulation. Such a controlled-release oral pharmaceutical formulation may, for example, comprise an immediate-release phase and a slow-release phase. Modified-release medicinal products are well known in this field; see, for example, Remington: The Science and practice of pharmacy", 19th edition, Mack Publishing Co. Pennsylvania, USA. The modified release may in particular be a prolonged and/or delayed release.

[0023] Preferably, the microcapsules can be orally ingestible in a dose and can comprise particles of acetylsalicylic acid with a size of less than about 1000 μm, preferably between about 50 μm or 100 μm to 1000 μm, which are coated and designed so that, when ingested orally in a single administration of a dose of between 50 and 325 mg of acetylsalicylic acid, they induce moderate acetylsalicylic acid absorption kinetics in vivo in man, extending over at least 24 hours, said acetylsalicylic acid absorption being less than or equal to 10% by weight of the absorbed fraction of the dose at a time t after ingestion of 0.4 hour, less than or equal to 50% by weight of the absorbed fraction of the dose at t=3.9 hours, and less than or equal to 90% by weight of the absorbed fraction of the dose at t=23 hours, t being given to within +/-10%.

[0024] According to another of its features, the present invention also concerns a method for treating the thrombotic diseases, said method comprising the administration to a patient an oral pharmaceutical formulation ac-

cording to the above definition. Said method is a method of preventing and/or treating pathological disorders associated with excesses of thromboxane, particularly cardiovascular diseases and risks. This method consists in the oral administration of the pharmaceutical formulation according to the invention, preferably in a once or twice-a-day administration.

[0025] It is apparent from the foregoing text that the microcapsules of the invention are very effective in pharmacological terms, perfectly tolerated by the organism, especially as regards gastric tolerance, capable of being presented in various appropriate galenical forms and, finally, easy and inexpensive to obtain.

[0026] The controlled release-acetylsalicylic acid microcapsules have high selectivity for the thromboxane inhibition, which makes it possible to maintain the production of prostacyclin, in order to protect the gastrointestinal tract.

[0027] Furthermore, the gastric acid suppressing agent maintains the pH of the stomach high enough to reduce the acidic erosion of the surface of the stomach and even to facilitate the healing process when some ulceration occurs.

[0028] In a preferred embodiment of the invention, the absorption takes place over a period of between 24 and hours in the following manner:

- 10% of the absorbed fraction of the dose at t=0.4 to 5 hours,
- 50% of the absorbed fraction of the dose at t=3.9 to 25 hours,
- and 90% of the absorbed fraction of the dose at t=23 to 45 hours.

[0029] The curve of FIG. 1 of US-B-5,603,957 shows the kinetic profile of the in vivo absorption of acetylsalicylic acid, and more precisely the upper limit of the acetylsalicylic acid in vivo absorption profile induced by the controlled release-acetylsalicylic acid microcapsules according to US-B-5,603,957, as a function of time, at a dose of 320 mg. This absorption is expressed in % absorbed relative to the absorbed fraction of the initial dose D. This curve is obtained by conventional deconvolution analysis (Milo GIBALDI and D. PERRIER, Pharmacokinetics, 2nd ed., New York, Marcel Dekker Inc., 1983, p. 145-167) from the mean curves of the plasma concentrations as a function of time after the oral administration of 350 mg of acetylsalicylic acid equivalents of ASPEGIC. (control form) and 320 mg of acetylsalicylic acid equivalents of microcapsules according to the invention in the form of gelatin capsules. In this case, the tracer molecule chosen for the plasma concentrations as a function of time is necessarily salicylic acid (SA), a metabolite of acetylsalicylic acid. The plasma concentrations of SA are determined by HPLC. The critical points at 0.4, 3.9 and 23 h, given above in the definition of the microcapsules of the invention, are of course to be found on this curve. Beyond this curve, the hepatic acetylsalicylic acid deacetylation mechanism is saturated. It must be considered that all the acetylsalicylic acid in vivo absorption profiles contained in the area under the curve are controlled release-acetylsalicylic acid microcapsules according to US-B-5,603,957.

[0030] To solve the technical problem on which the invention is based, it is highly preferable that the formulation according to the invention be free or almost free of immediate release acetylsalicylic acid form. The term "almost free" means that the formulation can include negligible amount of immediate release acetylsalicylic acid form, namely a insufficient amount so that there is remaining non-deacetylated acetylsalicylic acid in the systemic blood stream after the liver, said non-deacetylated acetylsalicylic acid being in a sufficient amount to inhibit COX-1 of the systemic blood compartment.

[0031] "Immediate release acetylsalicylic acid form" is intended to denote, in the present disclosure, a form in which the acetylsalicylic acid is released, at pH 6.8 and under sink conditions in a in vitro dissolution test, most of the amount of acetylsalicylic acid contained in the immediate release acetylsalicylic acid form, in a relatively brief period of time; for example at least 70% of the acetylsalicylic acid is preferably released in forty five minutes and more preferably in thirty minutes.

[0032] All the dissolution profiles to which reference is made in the present disclosure are determined according to the indications of the European Pharmacopoeia, 4th edition, entitled: "Dissolution test for solid oral forms": type II dissolutest performed under SINK conditions, at 37°C, at a test dose of 10 mg of active, and with agitation of 100 rpm.

[0033] In a preferred embodiment of the invention, the oral pharmaceutical formulation according to the invention, contains a dose of acetylsalicylic acid in the controlled release-acetylsalicylic acid microcapsules, said dose being comprised between 60 and 320 mg. In a more preferred embodiment of the invention, the oral pharmaceutical formulation according to the invention, contains a dose of acetylsalicylic acid in the controlled release-acetylsalicylic acid microcapsules, said dose being comprised between 75 and 310 mg. In another preferred modality of the invention, the oral pharmaceutical formulation according to the invention, contains a dose of gastric acid suppressing agent comprised between 1 and 130 mg.

[0034] In a more preferred modality of the invention, the oral pharmaceutical formulation according to the invention, contains a dose of gastric acid suppressing agent comprised between 2 and 120 mg.

[0035] According to a first embodiment, the oral pharmaceutical formulation according to the invention has the following characteristics, among others:

a) the dose of acetylsalicylic acid in the controlled release-acetylsalicylic acid microcapsules is comprised between 50 and 325 mg;

b) the dose of gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)- is comprised between 5 and 120 mg;

c) it is a once-a-day administration form.

[0036] The oral pharmaceutical formulation comprising a), b), c) features, can include at least one immediate release acetylsalicylic acid form.

[0037] The oral pharmaceutical formulation comprising a), b), c) features, can include at least one immediate release gastric acid suppressing agent.

[0038] The oral pharmaceutical formulation comprising a), b), c) features, can include at least one controlled release gastric acid suppressing agent.

[0039] According to a second embodiment, the oral pharmaceutical formulation according the invention has the following characteristics, among others:

i. wherein the dose of acetylsalicylic acid in the microcapsules is comprised between 50 and 325 mg;
ii. wherein the dose of gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)- is comprised between 5 and 120 mg;
iii. which is a twice-a-day administration form.

[0040] The oral pharmaceutical formulation comprising i, ii, iii features, can include at least one immediate release acetylsalicylic acid form.

[0041] The oral pharmaceutical formulation comprising i, ii, iii features, can include at least one immediate release gastric acid suppressing agent. The oral pharmaceutical formulation comprising i, ii, iii features, can include at least one controlled release gastric acid suppressing agent.

[0042] It is remarkable that the oral pharmaceutical formulation according to the invention, is designed so that it induces reduction of bleeding and pitichia, notably, in the stomach during the treatment.

[0043] We find it surprising that we can selectively inhibit COX and platelets in the portal vein permitting minimal aspirin to enter the systemic circulation. This significantly increases the comfort of the patients and the safety of the drug. Patients will be no longer compelled either to interrupt the treatment with aspirin or to switch to another drug. This also permits a method of quickly inhibiting COX in platelets with less side effects than previously known. Finally, we have a method that permits the unexpected precise titration of the effects of aspirin on the liver, the circulatory system, and the stomach.

[0044] This remarkable feature can give rise to a method for reducing the side effects during the treatment of diseases at least partially caused by an inhibition of Cox-1 in systemic circulation, said treatment comprising the administration to a patient an oral pharmaceutical formulation including acetylsalicylic acid, wherein the oral pharmaceutical formulation is a formulation for enhancing, notably, the safety of antithrombotic treatments, said formulation comprising a combination of at least one gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)- and microcapsules for the controlled release of acetylsalicylic acid (acetylsalicylic acid) in the gastrointestinal environment,

- wherein said microcapsules:
  - having an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that 70% of the acetylsalicylic acid is released over a period of time of between 2 and 20 hours, preferably between 4 and 18 hours, and even more preferably between 6 and 15 hours, and
  - inhibiting COX-1 in portal vein which limits the production of thromboxane while maintaining COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin, to protect the gastric endothelium and to maintain its vasodilatation properties;
- said gastric acid suppressing agent increasing the pH of the stomach just enough to minimize the damage resulting from the residual amount of non-deacetylated acetylsalicylic acid coming from the liver and the portal blood circulation and entering the systemic blood circulation.

[0045] The side effects of the oral pharmaceutical formulation according to the invention is also very interesting in that it is designed so that it improves the healing process, notably, in the stomach during the treatment. The oral pharmaceutical formulation is also designed to decrease other side effects of antithrombotic treatments, such as gastric or intestinal ulceration and hemorrhaging, renal failure, edema, atherosclerosis, and any resulting cardiovascular disease.

[0046] This interesting feature can give rise to a method according to another aspect of the present invention, namely a method for improving the healing process, notably, in the stomach, during the treatment of diseases at least partially caused by an inhibition of Cox-1 in systemic circulation, said treatment comprising the administration to a patient an oral pharmaceutical formulation including acetylsalicylic acid, wherein the oral pharmaceutical formulation is a formulation for enhancing, notably, the safety of antithrombotic treatments, said formulation comprising a combination of at least one gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)- and microcapsules for the controlled release of acetylsalicylic acid (acetylsalicylic acid) in the gastrointestinal environment,

- wherein said microcapsules:
  - having an in vitro release profile, in 0.05M

potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that 70% of the acetylsalicylic acid is released over a period of time of between 2 and 20 hours, preferably between 4 and 18 hours, and even more preferably between 6 and 15 hours, and

➢ inhibiting COX-1 in portal vein which limits the production of thromboxane while maintaining COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin, to protect the gastric endothelium and to maintain its vasodilatation properties;

■ said gastric acid suppressing agent increasing the pH of the stomach just enough to minimize the damage resulting from the residual amount of non-deacetylated acetylsalicylic acid coming from the liver and the portal blood circulation and entering the systemic blood circulation.

[0047] In the two above mentioned methods, the implemented microcapsules being orally ingestible in a dose and comprising particles of acetylsalicylic acid with a size of less than 1000 μm which are coated and designed so that, when ingested orally in a single administration of a dose of acetylsalicylic acid, it induces acetylsalicylic acid absorption kinetics in vivo in man, extending over at least 24 hours, said acetylsalicylic acid absorption being less than or equal to 10% by weight of the absorbed fraction of the dose at about 0.4 hour post ingestion, less than or equal to 50% by weight of the absorbed fraction of the dose at about 3.9 hours post ingestion, and less than or equal to 90% by weight of the absorbed fraction of the dose at about 23 hours post ingestion.

[0048] Unless otherwise indicated, use of the term "about" in this invention description is intended to mean plus or minus 10% of the designated amount; thus, "about 5 to 80%" would mean a range of 4.5-5.5% to 76-84%.

[0049] The gastric acid suppressing agent is preferably a proton pump inhibitor (proton pump inhibitor) or a proton pump inhibitor is a substituted benzimidazole which inhibits gastric acid secretions by specific inhibition of the H^+, K^+-ATPase enzymatic system (proton pump) of the secretory surface of parietal gastric cells. A proton pump inhibitor is an advantageous substitute for histamine H2 receptor antagonists (blocking of gastric acid secretion) or for antacids, which are not fully effective in the treatment of ulcers, associated or not with *Helicobacter pylori* infection or of other gastric disorders, and which in addition lead to many side effects.

[0050] A proton pump inhibitor is a lipophilic weak base that is poorly soluble in water. It undergoes rapid degradation under acidic conditions but, on the other hand, it is relatively stable at neutral or basic pH.

[0051] The proton pump inhibitor more particularly concerned by the present invention are derivates of benzimidazole. These latter are substituted or non substituted benzimidazoles, one or several salts of benzimidazoles, any enantiomer of these benzimidazoles, one or several salts of enantiomer (s), any isomer of these benzimidazoles, any derivate of benzimidazole, any free base of benzimidazole or any mixing of these active principles.

[0052] The proton pump inhibitor used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg++, Ca++, Na++, K++ or Li++ salts, preferably the Mg++ salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

[0053] For example, the proton pump inhibitor concerned by the invention, are notably the proton pump inhibitor described pages 7 to 11 ofWO-A-97/25066, this extract being incorporated by reference in the present text.

[0054] The WO-A-2004/035020 patent application gives also a general formula of the class of benziimidazoles: pages 35-48. This extract of WO-A-2004/035020 is incorporated by reference in its entirety in the present text.

[0055] Examples of proton pump inhibitor are: esomeprazole, leminoprazole, omeprazole, pantoprazole, pariprazole, rabeprazole, timoprazole, picoprazole and tenatoprazole.

[0056] Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and WO094/27988.

[0057] The gastric acid suppressing agent is preferably a proton pump inhibitor, but H_2 receptor antagonists such as ranitidine, cimetidine or famotidine may be used in the pharmaceutical compositions with an alginate as proposed in WO 95/017080 or together with antacid agent(s). A wide variety of antacid agent(s) and/or alginates may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antacid agents include for example aluminium hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate and aluminium magnesium hydroxide carbonate (hydrotalcit) taken alone or in combinations with each other. The alginates may be an alginate selected from alginic acid or sodium alginate or other pharmaceutically acceptable alginate salts, hydrates, esters etc. Especially preferred antacid agents are magnesium or calcium based antacid agents and aluminium hydroxide/magnesium carbonate complex. Suitable antacid agents are for instance described in U.S. Pat. No. 5,409,709.

[0058] The preferred proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers, optionally in combination with antacid agent(s), can be a immediate release form and/or a controlled re-

lease (controlled release) form.

[0059] For example, the gastric releasing agent can be made to individually enteric or non enteric coating layered individual units (small beads, granules, microcapsules or pellets).

[0060] For example, the gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)- can be designed in the form of controlled release/MR microcapsules, notably of the type of the controlled release/MR acetylsalicylic acid microcapsules, as described herein.

[0061] It could be very useful that the oral pharmaceutical formulation according to the invention, comprises at least one active principle different from acetylsalicylic acid and gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)-.

[0062] According to one embodiment, the active principle different from acetylsalicylic acid and gastric acid suppressing agent is selected in the group comprising: anti-platelet drugs, beta adrenergic receptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, diuretics, anti-arrhythmic drugs, anti-ischemic drugs, anti-hypertensive drugs, beta adrenergic agonists, cardiac glycosides, nitrates, sodium channel blockers, central nervous system acting anti-hypertensive drugs, potassium channel activators, vasodilatory drugs, and vasoconstrictive drugs.

[0063] Examples of anti-platelet drugs include non-steroidal anti-inflammatory drugs, dipyridamole, and ticlopidine.

[0064] Examples of diuretics include acetazolamide, dichlorphenamide, methazolamide, glycerin, isosorbide, mannitol, urea, furosemide, bumetanide, ethacrynic acid, torsemide, azosemide, muzolimine, piretanide, tripamide, bendroflumethiazide (naturetin), benzthiazide (exna), chlorothiazide (diuril), hydrochlorothiazide (hydrodiuril), hydroflumethiazide (saluron), methyclothiazide (enduron), polythiazide (renese), trichlormethiazide, chlorthalidone (hygroton), indapamide (lozol), metolazone (mykrox, zaroxolyn), quinethazone (hydromox), amiloride, triamterene, spironolactone, canrenone, potassium canrenoate.

[0065] Examples of angiotensin converting enzyme inhibitors include benazepril, captopril, enalapril, fosinopril sodium, lisinopril, quinapril, ramipril, spirapril.

[0066] Examples of nitrates include amyl nitrite (isoamyl nitrite), nitroglycerin (glyceryl trinitrate, nitro-bid, nitrostat, nitrol, nitro-dur, others), isosorbide dinitrate (isordil, sorbitrate, dilatrate, others), isosorbide-5-mononitrate (imdur, ismo, others), erythrityl tetranitrate (cardilate).

[0067] Examples of calcium channel blockers include amlodipine (norvasc), bepridil (vascor), diltiazem (cardizem, dilacor), felodipine (plendil), isradipine (dynacirc), nicardipine (cardene), nifedipine (adalat, procardia), nimodipine (nimotop), verapamil (calan, isoptin, verelan).

[0068] Examples of vasodilator drugs include nitrovasodilators such as nitroglycerin, isosorbide dinitrate, sodium nitroprusside; angiotensin receptor antagonist such as losartan (cozaar), phosphodiesterase inhibitors such as amrinone (inocor), milrinone (primacor), and vesnarinone; "direct" vasodilators such as hydralazine (apresoline), nicorandil, adrenergic receptor antagonists such as prazosin (minipress, and other quinazoline derivatives), phentolamine (regitine), labetalol (normodyne, trandate), carvedilol, and bucindolol; Ca^{2+} channel blocking drugs such as nifedipine (adalat, procardia), amlodipine (norvasc), and sympathomimetics such as dobutamine (dobutrex).

[0069] Examples of anti-arrhythmic drugs include adenosine, amiodarone, bretylium, digoxin, digitoxin, diltiazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide (N-acetyl procainamide), propafenone, propranolol, quinidine, sotalol, tocainide, verapamil.

[0070] According to another embodiment, the active principle different from acetylsalicylic acid and gastric acid suppressing agent is selected in the group of the anti-inflammatory drugs.

[0071] According to another embodiment, the active principle different from acetylsalicylic acid and gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)-, is selected in the group of the Non Steroidal Anti Inflammatory Drugs (NSAIDs).

[0072] Regarding NSAIDs, very large number of patients who are treated with common NSAIDs or with more specific NSAIDs such as COX-2 inhibitors, have severe side effects, including life threatening ulcers and thrombotic cardiovascular events, that limit their therapeutic potential. In addition, there is evidence that patients with chronic inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythematosis are at increased risk for thrombotic cardiovascular events. Thus, it is desirable that these patients receive antiplatelet therapy, with only minimal side effects. This need is reinforced by the fact that many patients treating with NSAIDs or suffering from chronic COX-2 mediated disease or condition, are elderly and thus are at increased risk for thrombotic cardiovascular events.

[0073] There is a need to associate anti-platelet aggregation drugs to NSAIDs, particularly COX-2 inhibitor anti-inflammatory drugs, without inducing gastric side effects.

[0074] Then, it has been proposed to associate low dose aspirin with COX-2 inhibitors. But due to the aspirin dilemma, the gastro-protection activity of the prostacyclin and of the prostaglandins, is affected and thus it induces severe gastric disorders.

[0075] The last mentioned embodiment according to the invention, offers an advantageous solution to this problem.

[0076] Preferably, the NSAID(s) is (are) selected in the group comprising:

- aminoarylcarboxylic acid and its derivates such as: enfenamic acid, flufenamic acid, isonixin,

meclofenamic acid, mefenamic acid, morniflumate, niflumic acid & tolfenamic acid,

- arylacetic acid and its derivates such as: aceclofenac, acemetacin, amfenac, bromfenac, cimmetacin, diclofenac, etodolac, fentiazac, glucametacin, indomethacin, lonazolac, l'acid metiavinic, oxametacine, pirazolaque, proglumetacin, sulindac, tiaramide, tolmetin et zomepirac,
- arylcarboxylic acids such as ketorolac & tinoridine,
- arylpropionic acid and its derivates such as: alminoprofen, bermoprofen, carprofen, dexibuprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, ketoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, protizinic acid & tiaprofenic acid,
- pyrazoles, *e.g.*: epirizole,
- pyrazolones such as: benzpiperylon, mofebutazone, oxyphenbutazone, phenylbutazone & ramifenazone,
- salicylic acid derivates such as : acetaminosalol, benorylate, eterisalate, fendosal, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, parsalmide, l'acid salamidacetic & le salsalate,
- thiazinecarboxamides such as : ampiroxicam, droxicam, lornoxicam, meloxicam, piroxicam & tenoxicam,
- others such as: bucillamine, bucolome, bumadizon, diferenpiramide, ditazol, emorfazone, nabumetone, nimesulide, proquazone et piroxicam (in the form of the betacyclodextrin complex).
- alclofenac, azapropazone, benoxaprofen, acid bucloxic, choline magnesium trisalicylate, clidanaque, clopinaque, dapsone, diflunisal, fenclofenec, floctafenine, flufenisal, (r)-flurbiprofen, (s)-flurbiprofen, furofenaque, feprazone, fluprofen, ibufenaque, indoprofen, isoxepac, isoxicam, miroprofen, mefenamic, meclofen, acid niflumic, nitroflurbiprofen, oxipinaque, podophyllotoxin derivates, piprofen, pirprofen, prapoprofen, sudoxicam, suprofen, acid tiaprofenic, tiopinaque, tioxaprofen, zidometacin, acid 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic, a 4-(nitrooxy)butyl ester, ketoporfen, ketrolac.

[0077] More preferably, the NSAID(s) is (are) selected in the group comprising: lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, acid tiaprofenic, proglumetacin, acid mefenamic, fenbufen, etodolaque, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen and/or the pharmaceutical salts and/or the complexes and/or the prodrugs and/or the mixtures thereof.

[0078] The examples of cyclooxygenase-2 selective inhibitors include: rofecoxib (VIOXX® cf. US-B- 5 474 995), etoricoxib (ARCOXIA™ cf. US-B- 5 861 419), celecoxib (CELEBREX® cf. US-B- 5 466 823), valdecoxib (cf. US —B-6 633 272), parecoxib (cf. brevet US —B-5 932 598), COX-189 (Novartis), BMS347070 (Bristol Myers Squibb), tiracoxib ou JTE522 (Japan Tobacco), ABT963 (Abott), CS502 (Sankyo), and GW406381 (GlaxoSmithKline).

[0079] According to another embodiment, the active principle different from acetylsalicylic acid and gastric acid suppressing agent - preferably a proton pump inhibitor (proton pump inhibitor)-, is selected in the group of the anti-diabetic drugs comprising: Acarbose, Acetohexamide, Buformin, 1-Butyl-3-metanilylurea, Carbutamide, Chlorpropamide, Ciglitazone, Glibornuride, Gliclazide, Glimepiride, Glipizide, Gliquidone, Glisoxepid, Glyburide, Glybuthiazole, Glybuzole, Glyhexamide, Glymidine, Glypinamide, Metformin, Miglitol, Nateglinide, Phenbutamide, Phenformin, Pioglitazone, Proinsulin, Repaglinide, Rosiglitazone, Tolazamide, Tolbutamde, Tolcyclamide, Troglitazone and/or the pharmaceutical salts and/or the complexes and/or the prodrugs and/or the mixtures thereof.

[0080] Advantageously, the controlled release-acetylsalicylic acid microcapsules are so designed that the absorption takes place over a period of between 24 and 48 hours in the following manner: 10% of the absorbed fraction of the dose at t=0.4 to 5 hours, 50% of the absorbed fraction of the dose at t=3.9 to 25 hours, and 90% of the absorbed fraction of the dose at t=23 to 45 hours.

[0081] In the disclosure of the invention, the term "controlled release-acetylsalicylic acid microcapsules" denotes microparticles of acetylsalicylic acid that are film-coated with at least one coating for modified/controlled release of acetylsalicylic acid. The non-film-coated microparticles of acetylsalicylic acid may, for example, be neutral cores coated with at least one layer containing acetylsalicylic acid, or microparticles of pure acetylsalicylic acid or alternatively granules formed by a matrix of support excipients including lansoprazole.

[0082] Advantageously, the film-coating (or coating) covering(s) has(have) sufficient mechanical strength to prevent it(them) tearing and/or it(them) breaking up in the organism, until the end of the release of the active principle. These controlled release-acetylsalicylic acid microcapsules can be compared to vehicles for the transport and the release of acetylsalicylic acid and, optionally, of one or more other active principles in the stomach and in the small intestine.

[0083] The pharmaceutical formulation according to the invention can also be characterized in that the controlled release-acetylsalicylic acid microcapsules have an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that:

- 70% of the acetylsalicylic acid is released over a period of time of between 1 and 10 hours, preferably between 2 and 8 hours, and even more preferably between 2 and 6 hours, and
- 40% of the acetylsalicylic acid is released over a pe-

riod of time of between 0.5 and 5 hours, preferably between 1 and 4 hours, and even more preferably between 1 and 3 hours.

[0084] Advantageously, the controlled release-acetylsalicylic acid microcapsules have an in vitro release profile, in a 0.04M hydrochloric acid medium pH 1.4, such that 40% of the acetylsalicylic acid is released over a period of time of less than or equal to 3h, preferably less than or equal to 2h, and even more preferably less than or equal to 0.75h.

[0085] According to another pharmacokinetic defmition of the pharmaceutical formulation according to the invention, the controlled release-acetylsalicylic acid microcapsules have an in vitro release profile in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that, for any value of time t of between 2h and t(70%), preferably for any value of time t of between 1h and t(70%), the % of dissolved (released) acetylsalicylic acid is greater than or equal to 35 t / t(70%).

[0086] For example, the coating of the controlled release-acetylsalicylic acid microcapsules represents 5 to 50% by weight, based on the total mass of said microcapsules.

[0087] Preferably, the coating of the controlled release-acetylsalicylic acid microcapsules comprises at least one layer, which controls the modified release of agent, the composition of said layer is as follows:

A) at least one film-forming (co)polymer (A) that is insoluble in the fluids of the gastrointestinal tract;
B) optionally, at least one water-insoluble hydrophilic film-forming (co)polymer (B) that is insoluble in the fluids of the gastrointestinal tract, carrying groups that are ionized in the fluids of the gastrointestinal tract,
C) at least one (co)polymer (C) that is soluble in the fluids of the gastrointestinal tract;
D) at least one plasticizer (D);
E) optionally, at least one surfactant and/or lubricant (E).

[0088] According to a preferred embodiment of the invention:

* (A) is selected from the group of following products:

- non-water-soluble derivatives of cellulose, preferably ethylcellulose and/or cellulose acetate,
- polyvinyl acetates,
- and mixtures thereof.

* (B) is chosen from water-insoluble charged acrylic derivatives, preferably from (co)polymers of acrylic and methacrylic acid ester carrying at least one quaternary ammonium group, (B) even more preferably comprising at least one copolymer of alkyl (meth) acrylate and of trimethylammonioethyl methacrylate chloride, and more precisely the products sold under the trade marks EUDRAGIT ® RS and/or RL, e.g. the powders EUDRAGIT ® RL PO and/or EUDRAGIT ® RS PO and/or the granules EUDRAGIT ® RL 100 and/or EUDRAGIT ® RS 100 and/or the suspensions and/or solutions of these EUDRAGIT ® RL and RS, namely, respectively, EUDRAGIT® RL 30D and/or EUDRAGIT® RS 30D and/or EUDRAGIT® RL 12.5 and/or EUDRAGIT® RS 12.5;

* (C) is chosen from

- nitrogenous (co)polymers, preferably from the group comprising polyacrylamides, poly-N-vinylamides, polyvinylpyrrolidones (PVP) and poly-N-vinyllactams;
- water-soluble derivatives of cellulose,
- polyvinyl alcohols (PVAs),
- polyoxyethylenes (POEs),
- and mixtures thereof;
  polyvinylpyrrolidone being particularly preferred.

* (D) is chosen from the group comprising:

- cetyl alcohol esters,
- glycerol and its esters, preferably from the following subgroup: acetylated glycerides, glyceryl monostearate, glyceryl triacetate, glyceryl tributyrate,
- phthalates, preferably from the following subgroup: dibutyl phthalate, diethyl phthalate, dimethyl phthalate, dioctyl phthalate,
- citrates, preferably from the following subgroup: acetyl tributyl citrate, acetyltriethyl citrate, tributyl citrate, triethyl citrate,
- sebacates, preferably from the following subgroup: diethyl sebacate, dibutyl sebacate,
- adipates,
- azelates,
- benzoates,
- plant oils,
- fumarates, preferably diethyl fumarate,
- malates, preferably diethyl malate,
- oxalates, preferably diethyl oxalate,
- succinates, preferably dibutyl succinate,
- butyrates,
- salicylic acid,
- triacetin,
- malonates, preferably diethyl malonate,
- castor oil (this being particularly preferred),
- and mixtures thereof.

* (E) is chosen from the group comprising:

- anionic surfactants, preferably from the subgroup of alkali metal or alkaline-earth metal salts of fatty acids, stearic acid and/or oleic acid being

preferred,

- and/or nonionic surfactants, preferably from the following subgroup:

  - o polyoxyethylenated oils, preferably polyoxyethylenated hydrogenated castor oil,
  - o polyoxyethylene-polyoxypropylene copolymers,
  - o polyoxyethylenated esters of sorbitan,
  - o polyoxyethylenated derivatives of castor oil,
  - o stearates, preferably calcium stearate, magnesium stearate, aluminium stearate or zinc stearate,
  - o stearyl fumarates, preferably sodium stearyl fumarate,
  - o glyceryl behenates,
  - o and mixtures thereof.

[0089] According to a particularly advantageous embodiment, the composition of the modified-release layer is as follows:

A. the film-forming polymer(s) (A) is (are) present in a proportion of 10 to 90%, preferably 20 to 40% by weight on a dry basis relative to the total mass of the coating composition;
B. the water-insoluble hydrophilic film-forming polymer(s) (B) is (are) present in a proportion of 10 to 90%, preferably 20 to 40% by weight on a dry basis relative to the total mass of the coating composition;
C. the polymer(s) (C) that is (are) soluble in the fluids of the gastrointestinal tract is (are) present in a proportion of 2 to 25, preferably 5 to 15% by weight on a dry basis relative to the total mass of the coating composition;
D. the plasticizer(s) (D) is (are) present in a proportion of 2 to 20, preferably of 4 to 15% by weight on a dry basis relative to the total mass of the coating composition;
E. the optional surfactant(s) and/or lubricant(s) (E) is (are) present in a proportion of 2 to 20, preferably of 4 to 15% by weight on a dry basis relative to the total mass of the coating composition.

[0090] For further details, in particular qualitative and quantitative details, regarding at least some of the constituents of this coating composition, reference will be made, for example, to European patent EP-B-0 709 087 or to PCT applications WO-A-2004/010983 and WO-A-2004/010984, the content of which is incorporated into the present disclosure in their entirety by way of reference.

[0091] The monolayer or multilayer coating may comprise various other additional adjuvants conventionally used in the coating field. They may be, for example, pigments or coloring agents, fillers, anti-foaming agents...

[0092] To prevent the problems of caking of the coated particles constituting the controlled release-acetylasalicylic acid microcapsules used in the invention, provision is advantageously made for adding thereto at least one anticaking agent preferably formed of talc, colloidal silica or a mixture of the two.

[0093] According to a particular embodiment of the invention, the controlled release-acetylasalicylic acid microcapsule coating responsible for the modified release of acetylasalicylic acid consists of a single coating layer or a single coating film. This simplifies their preparation and limits the degree of coating.

[0094] Moreover, the pharmaceutical formulation according to the invention has the particularity that the coating of each controlled release-acetylasalicylic acid microcapsule is nonenteric and does not desintegrate whatever the pH be, and in particular at any pH above 5.0.

[0095] Advantageously, the diameter of the controlled release-acetylasalicylic acid microcapsules is less than or equal to 1000 μm, preferably between 50 and 800 μm, and even more preferably between 100 and 600 μm. The microparticle diameters to which the present disclosure refers are, unless otherwise indicated, mean diameters by volume.

[0096] This size makes it possible to cross the stomach independently of the opening of the pylorus. The gastric transit time is thus shorter and more uniform.

[0097] Advantageously, the controlled release-acetylasalicylic acid microcapsules are obtained from particles of acetylasalicylic acid having a size of between 250 and 800 μm before the coating operation.

[0098] According to the invention, practical implementations in which the proportion of acetylasalicylic acid in the microcapsules (expressed as % by weight on a dry basis relative to the total mass of the microcapsules) is between 5 and 80, preferably between 10 and 60, and even more preferably between 20 and 50, are preferred.

[0099] As regards the monolayer or multilayer coating (or film) responsible for the modified release of acetylasalicylic acid, it represents, for example, at most 40%, preferably at most 15%, by weight of the microcapsules.

[0100] The controlled release-acetylasalicylic acid microcapsules are obtained from particles of acetylasalicylic acid which are coated by being sprayed with the intimate combination forming the coating, suspended in an organic solvent or mixture of organic solvents. The coating process, which constitutes a further subject of the invention, fits into the general pattern of microencapsulation techniques, of which the main ones are summarized in the article by C. DUVERNEY and J. P. BENOIT in "L'actualité chimique", December 1966. More precisely, the technique in question is microencapsulation by film coating. Preferably, this process consists essentially in: a) preparing the coating composition by mixing ABCDE in a solvent system, b) applying the composition/solvent system mixture to particles of acetylsalicylic acid, c) drying the resulting microcapsules, and d) if appropriate, mixing the latter with at least one anticaking agent. Examples of solvents which are suitable for forming part

of the composition of the solvent system are ketones, esters, chlorinated solvents, alcohols, preferably aliphatic alcohols, alkanes or mixtures thereof. These solvents are advantageously C_1-C_6 compounds and particularly preferably acetone, methyl ethyl ketone, methanol, ethanol, isopropanol, cyclohexane and methylene chloride. If the coating methodology which can be used according to the invention is considered in greater detail, it can be stated that the coating composition/solvent system mixture is applied by being sprayed onto the moving particles of acetylasalicylic acid, said movement preferably being created by mechanical agitation or by blowing (fluidization). To obtain microcapsules according to the invention possessing the desired absorption kinetics, it is necessary to encapsulate particles of acetylasalicylic acid with a mean size of between 75 and 500 μm, preferably of between 300 and 500 μm, for a dose of between 75 and 320 mg.

[0101] The controlled release-acetylasalicylic acid microcapsules described above, which may have been obtained by the process also explained above, can be used for the preparation of novel galenical forms of aspirin having a biochemical selectivity for the inhibition of thromboxane relative to the other prostaglandins, in particular for the preparation of novel galenical forms useful as platelet aggregation inhibitors, and/or, more precisely, for the preparation of novel galenical forms active in the prevention and/or treatment of cardiovascular diseases and risks.

[0102] The present invention further relates to these novel galenical units as such, and comprising the pharmaceutical formulation according to the invention.

[0103] Advantageously, these galenical, novel in their structure, their presentation and their composition, are presented in the form of a sachet of powder, a sachet of a powder for multidose suspension to be reconstituted, a tablet or a gelatin capsule. They can contain, for instance, a dose of acetylasalicylic acid of 20 to 500 mg, preferably 50 to 400 mg and particularly preferably 50 to 325 mg of acetylasalicylic acid and a dose of proton pump inhibitor of 1 to 300 mg, preferably 2 to 200 mg and particularly preferably 5 to 120 mg. Such galenical forms are preferably administered per or in single or twice daily doses D,D'.

[0104] It should be noted that it can be of value to mix, in one and the same gelatin capsule, tablet or powder, at least two types of microcapsules whose absorption kinetics are different but within the framework characteristic of the controlled release-acetylasalicylic acid microcapsules according to US-B-5,603,957 (profile of curve of FIG. 1).

[0105] The invention will be understood more clearly from the following Examples, which are given solely by way of illustration and serve to provide a clear understanding of the invention and to illustrate its different embodiments and/or modes of implementation, as well as its various advantages.

EXAMPLES

Description of the figures:

[0106]

Figure 1: In vitro release profiles for the controlled release-acetylasalicylic acid-based Microcapsules prepared according to Example 1.

Figure 2: In vitro release profiles for the controlled release-omeprazole based Microcapsules prepared according to Example 2.

Example 1 Preparation of CR-ASA-based Microcapsules

[0107] 66 g of ethyl cellulose (Ethocel 7 Premium / Dow), 7 g of Plasdone K29/32® (Povidone/ISP), 8 g of castor oil, 9 g of magnesium stearate and 10 g tartaric acid are dispersed in 1200 g of a mixture made of 60% of isopropanol & 40% of acetone. The suspension is sprayed on 900 g of acetylsalicylic acid (aspirin) crystals, previously sieved between 200 and 500 μm.

These microparticles have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37°C and stirred with a paddle speed of 100 rpm (USP II apparatus). See Figure 1.

Example 2 Preparation of CR- omeprazole- based Microcapsules

step 1 :

[0108] 700 g of omeprazole and 100 g de Klucel EF® (Hydroxypropyl cellulose / Aqualon) are dispersed in 3000 g of isopropanol. The suspension is sprayed on 200 g of neutral microspheres (Asahi-Kasei) in a spray coater Glatt GPCG1.

step 2 :

[0109] 50 g of ethyl cellulose (Ethocel 20 Premium / Dow), 20 g of Plasdone K29/32® (Povidone/ISP), 20 g of Lutrol F-68 (Poloxamer 188 / BASF) and 10 g of castor oil are dispersed in mixture made of 60% of isopropanol and 40% of acetone. This solution is sprayed on 900 g of omeprazole granules (prepared at step 1).

The obtained microparticles are filled into a gelatine size 3 capsule. The dose of omeprazole per capsule is, in this test, 80 mg i.e 127 mg of microcapsules.

These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37°C and stirred with a paddle speed of 100 rpm (USP II apparatus).

See Figure 2.

Example 3: Preparation of IR- lansoprazole based Microcapsules

[0110] 900 g of lansoprazole & 100 g of Klucel EF® (Hydroxypropyl cellulose / Aqualon) are previously dry-mixed in a high shear granulator (Aeromatic PMA1) for 5 minutes. This mixture is then granulated with water (180 g). The granules are dried at 40 °C in ventilated oven, and calibrated on 500 μm sieve. The fraction 200-500 μm is selected by sieving.
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37 °C and stirred with a paddle speed of 100 rpm (USP II apparatus) Their release is immediate.

Example 4: Preparation of enteric coated- lansoprazole based Microcapsules

Step 1:

[0111] 900 g of lansoprazole & 100 g of Klucel EF® (Hydroxypropyl cellulose / Aqualon) are previously dry-mixed in a high shear granulator (Aeromatic PMA1) for 5 minutes. This mixture is then granulated with water (180 g). The granules are dried at 40 °C in ventilated oven, and calibrated on 500 μm sieve. The fraction 200-500 μm is selected by sieving.

Step 2:

[0112] 50 g of Eudragit L100-55® (Rohm) and 10 g of triethyl citrate are dispersed in isopropanol. This solution is sprayed on 450 g of lansoprazole granules (prepared at step 1).
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37 °C and stirred with a paddle speed of 100 rpm (USP II apparatus) Their release is immediate.

Example 5: Preparation of IR- celecoxib based Microcapsules

[0113] 860 g of celecoxib, 70 g of Klucel EF® (Hydroxypropyl cellulose / Aqualon) & 70 of Lutrol F-68 (Poloxamer 188 / BASF) are previously dry-mixed in a high shear granulator (Aeromatic PMA1) for 5 minutes. This mixture is then granulated with water (180 g). The granules are dried at 40 °C in ventilated oven, and calibrated on 500 μm sieve. The fraction 200-500 μm is selected by sieving.
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37 °C and stirred with a paddle speed of 100 rpm (USP II apparatus) Their release is immediate.

Example 6: Capsule containing CR-aspirin and CR-omeprazole

[0114] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e.162.5 mg of acetylsalicylic acid) and 15.4 mg of microcapsules of omeprazole (i.e. 10 mg of omeprazole) prepared at example 2 are filled in size 2 capsule.
This capsule is the final form of the drug for preventing cardiovascular diseases (by means of aspirin), while hindering gastric damages due to the presence of a ppi and CR-ASA microcapsules.

Example 7: Capsule containing CR-aspirin and IR-lansoprazole

[0115] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e.162.5 mg of acetylsalicylic acid) and 5.5 mg of microcapsules of lansoprazole (i.e. 5 mg of lansoprazole) prepared at example 3 are filled in size 2 capsule.
This capsule is the final form of the drug for preventing cardiovascular diseases (by means of aspirin), while hindering gastric damages due to the presence of a ppi and CR-ASA microcapsules.

Example 8: Capsule containing CR-aspirin and enteric coated-lansoprazole

[0116] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e.162.5 mg of acetylsalicylic acid) and 6.2 mg of microcapsules of lansoprazole (i.e. 5 mg of lansoprazole) prepared at example 4 are filled in size 2 capsule.
This capsule is the final form of the drug for preventing cardiovascular diseases (by means of aspirin), while hindering gastric damages due to the presence of a ppi and CR-ASA microcapsules.

Example 9: Capsule containing CR-aspirin and enteric coated-lansoprazole and celecoxib

[0117] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e.162.5 mg of acetylsalicylic acid), 6.2 mg of microcapsules of lansoprazole (i.e.5 mg of lansoprazole) prepared at example 4 and 233 mg of microcapsules of celecoxib (i.e.200 mg of celecoxib) prepared at example 5 are filled in size 0 capsule.
This capsule is the final dosage form for preventing cardiovascular diseases (by means of aspirin), said diseases being caused by repeated administration of anti-inflammatory drugs, such as COX-2 inhibitors (celecoxib), while hindering gastric damages due to the presence of a ppi and CR-ASA microcapsules. The combination of a ppi with the CR-ASA microcapsules makes it possible to prevent gastric damages due to aspirin.

Comparative example 10 showing that the known CR-ASA microcapsules could be improved, by means of the combination according to the invention:

[0118] Controlled release microcapsules of aspirin according to example 1 were compared to aspirin at a dose of 325 mg in double blind, randomized cross-over study, on 24 healthy non smoking volunteers. Endoscopic damage was assessed on days 0, 7, 14, 21 on each treatment period. The primary end point was the total number of gastrioduodenal erosions and petechiae assessed endoscopically. The study performed by a group led by Professor Hawkey of Gastroenterology Division of University Hospital, Nottingham (UK) indicated that Controlled released aspirin cause less endoscopic damage than conventional aspirin.

[0119] The study indicated that significantly fewer gastric lesions were observed in patients taking controlled released aspirin 325 mg than in patients taking entero-coated aspirin at the same dose. In particular, gastric erosion per patient were 1.57 with Controlled released aspirin 325 compared to 5.48 with entero-coated aspirin product, or a reduction of 70% ($p<0.001$). Concerning haemorrhagic event, 0.3 events per patient were observed with controlled released aspirin 325 compared to 2.96 with conventional aspirin ($p<0.001$). In addition, a 3.09 petechia per patient were observed with controlled released aspirin compared to 7.35 with the comparator ($p<0.001$).

[0120] These very positive results for controlled released aspirin could be explained by the biochemical selectivity of the product which inhibits platelets COX-1 and consequently thromboxan (TXB2), the platelet aggregant prostanoids, which sparing prostacyclin (PGI2), the systemic cytoproctective prostaglandin generated by endothelial COX-1.

[0121] Although, this result is very positive for GI tract safety, it open the door to an improvement of the controlled released aspirin directed toward a decrease of the level of safety events especially those observed in gastro intestinal tract. It is worthwhile noticing that if the number of adverse events is significantly decreased using Controlled released aspirin compared to conventional aspirin, the GI tact events (i.e. erosion and petechia) are still measurable and could led to some safety concerns for chronic use.

[0122] The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. Modifications and variations of the above-described embodiments of the invention are possible without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described, which merely illustrate preferred embodiments.

Claims

1. An oral pharmaceutical formulation for enhancing notably the safety of antithrombotic treatments,

   - comprising a combination of microcapsules for the controlled release of acetylsalicylic acid (ASA), in the gastrointestinal environment and at least one gastric acid suppressing agent,
   - said microcapsules:

     - having an in vitro release profile, in 0.05M potassium dihydrogenophosphate/ sodium hydroxide buffer medium pH 6.8, such that 70% of the ASA is released over a period of time of between 2 and 20 hours, preferably between 4 and 18 hours, and even more preferably between 6 and 15 hours, and
     - inhibiting COX-1 in portal vein which limits the production of thromboxane while maintaining COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin, to protect the gastric endothelium and to maintain its vasodilatation properties;

   - said gastric acid suppressing agent increasing the pH of the stomach just enough to minimize the damage resulting from the residual amount of non-deacetylated ASA coming from the liver and the portal blood circulation and entering the systemic blood circulation.

2. An oral pharmaceutical formulation according to claim 1, wherein the microcapsules being orally ingestible in a dose D and comprising particles of acetylsalicylic acid with a mean diameter below or equal to 1000 μm, preferably between 50 and 800 μm, and even more preferably between 100 and 600 μm which are coated and designed so that, when ingested orally in a single administration of a dose D of between 50 and 325 mg of ASA, they induce moderate ASA absorption kinetics in vivo in man, extending over at least 24 hours, said ASA absorption being less than or equal to 10% by weight of the absorbed fraction of D at a time t after ingestion of 0.4 hour, less than or equal to 50% by weight of the absorbed fraction of D at t=3.9 hours, and less than or equal to 90% by weight of the absorbed fraction of D at t=23 hours, t being given to within +/-10%.

3. An oral pharmaceutical formulation according to

claim 1 or 2, wherein the gastric acid suppressing agent is a proton pump inhibitor (ppi).

4. An oral pharmaceutical formulation according to any of the preceding claims, wherein the dose D of ASA in the microcapsules is comprised between 60 and 320 mg, preferably between 75 and 310 mg.

5. An oral pharmaceutical formulation according to any of the preceding claims, wherein the dose D' of gastric acid suppressing agent is comprised between 1 and 130 mg, preferably between 2 and 120 mg.

6. An oral pharmaceutical formulation according to any of the preceding claims:

a) the dose D of ASA in the CR-ASA microcapsules is comprised between 50 and 325 mg;
b) the dose D' of gastric acid suppressing agent is comprised between 5 and 120 mg;
c) it is a once-a-day administration form.

7. An oral pharmaceutical formulation according to claim 6 including at least one immediate release gastric acid suppressing agent form.

8. An oral pharmaceutical formulation according to claim 6 including at least one controlled release gastric acid suppressing agent form.

9. An oral pharmaceutical formulation according to any of claims 1 to 5:

i. wherein the dose D of ASA in the microcapsules is comprised between 50 and 325 mg;
ii. wherein the dose D' of gastric acid suppressing agent is comprised between 5 and 120 mg;
iii. which is a twice-a-day administration form.

10. An oral pharmaceutical formulation according to claim 9 including at least one immediate release ASA form.

11. An oral pharmaceutical formulation according to claim 9 including at least one immediate release gastric acid suppressing agent form.

12. An oral pharmaceutical formulation according to claim 9 including at least one controlled release gastric acid suppressing agent form.

13. An oral pharmaceutical formulation according to any of the preceding claims, which is designed so that it induces reduction of bleeding and pitichia, notably, in the stomach during the treatment.

14. An oral pharmaceutical formulation according to any of the preceding claims, which is designed so that it improves the healing process, notably, in the stomach during the treatment.

15. An oral pharmaceutical formulation according to any of the preceding claims, comprising at least one active principle different from ASA and gastric acid suppressing agent.

16. An oral pharmaceutical formulation according to claim 15, wherein the active principle different from ASA and gastric acid suppressing agent - preferably a proton pump inhibitor (ppi)-, is selected in the group comprising:

- the cardiovascular drugs acting as anti-platelets;
- the cardiovascular drugs acting as beta-blockers;
- the cardiovascular drugs acting as ACE inhibitors;
- and any of their associations.

17. An oral pharmaceutical formulation according to claim 15, wherein the active principle different from ASA and gastric acid suppressing agent is selected in the group of the anti-inflammatory drugs.

18. An oral pharmaceutical formulation according to claim 17, wherein the active principle different from ASA and gastric acid suppressing agent is selected in the group of the Non Steroidal Anti Inflammatory Drugs (NSAIDs).

19. An oral pharmaceutical formulation according to claim 15, wherein the active principle different from ASA and gastric acid suppressing agent, is selected in the group of the anti-diabetic drugs.

20. An oral pharmaceutical formulation according to claim 2, wherein the ASA microcapsules are so designed that the absorption takes place over a period of between 24 and 48 hours in the following manner: 10% of the absorbed fraction of D at t=0.4 to 5 hours, 50% of the absorbed fraction of D at t=3.9 to 25 hours, and 90% of the absorbed fraction of D at t=23 to 45 hours.

21. An oral pharmaceutical formulation according to any of the preceding claims, wherein the coating agent of the ASA microcapsules represents 5 to 50% by weight, based on the total mass of said microcapsules.

22. An oral pharmaceutical formulation according to any of the preceding claims, wherein the coating of the ASA microcapsules comprises at least one layer which controls the modified release of agent, the composition of said layer is as follows:

A) at least one film-forming (co)polymer (A) that is insoluble in the fluids of the gastrointestinal tract;
B) optionally, at least one water-insoluble hydrophilic film-forming (co)polymer (B) that is insoluble in the fluids of the gastrointestinal tract, carrying groups that are ionized in the fluids of the gastrointestinal tract,
C) at least one (co)polymer (C) that is soluble in the fluids of the gastrointestinal tract;
D) at least one plasticizer (D);
E) optionally, at least one surfactant and/or lubricant (E).

23. An oral pharmaceutical formulation according to claim 22, wherein:

* (A) is selected from the group of following products:

  • non-water-soluble derivatives of cellulose,
  • polyvinyl acetates,
  • mixtures thereof;

* (B), when it is present, is chosen from water-insoluble charged acrylic derivatives;
* (C) is chosen from

  • nitrogenous (co)polymers;
  • water-soluble derivatives of cellulose,
  • polyvinyl alcohols (PVAs),
  • polyoxyethylenes (POEs),
  • and mixtures thereof;

* (D) is chosen from the group comprising:

  • cetyl alcohol esters,
  • glycerol and its esters,
  • phthalates, citrates, sebacates, adipates,
  • azelates,
  • benzoates,
  • plant oils,
  • fumarates, malates, oxalates, succinates,
  • butyrates,
  • salicylic acid,
  • triacetin,
  • malonates,
  • castor oil ,
  • and mixtures thereof;

* (E) is chosen from the group comprising:

  • anionic surfactants,
  • and/or nonionic surfactants.

24. An oral pharmaceutical formulation according to claim 22, wherein the composition of the modified-release layer is as follows:

A. the film-forming polymer(s) (A) is (are) present in a proportion of 10 to 90%, by weight on a dry basis relative to the total mass of the coating composition;
B. the hydrophilic water-insoluble film-forming polymer(s) (B) is (are) present in a proportion of 0 to 90%, by weight on a dry basis relative to the total mass of the coating composition;
C. the soluble polymer(s) (C) is (are) present in a proportion of 2 to 25, by weight on a dry basis relative to the total mass of the coating composition;
D. at least one plasticizer (D) is (are) present in a proportion of 2 to 20, by weight on a dry basis relative to the total mass of the coating composition;
E. the optional surfactant(s) and/or lubricant(s) (E) is (are) present in a proportion of 2 to 20, by weight on a dry basis relative to the total mass of the coating composition.

25. An oral pharmaceutical formulation according to any of the preceding claims, wherein the diameter of the ASA microcapsules is less than or equal to 1000 μm.

26. An oral pharmaceutical formulation according to any of the preceding claims, wherein the ASA microcapsules are obtained from particles of ASA having a size of between 250 and 800 μm before the coating operation.

27. An oral pharmaceutical formulation according to any of the preceding claims, wherein the proportion of ASA in the microcapsules (expressed as % by weight on a dry basis relative to the total mass of the microcapsules) is between 5 and 80.

28. An oral pharmaceutical formulation according to any of the preceding claims, provided in the form a galenical unit selected in the group comprising: a sachet of powder, a sachet of a powder for multidose suspension to be reconstitued, a tablet or a gelatin capsule.

29. An oral pharmaceutical formulation comprising:

  • at least one gastric acid suppressing agent, and
  • acetylsalicylic acid that is coated to form microcapsules, said microcapsules having a release profile such that 70% of the acetylsalicylic acid in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium at a pH of 6.8 is released between about 2 and 20 hours, preferably between about 4 and 18 hours and even more preferably between 6 and 15 hours.

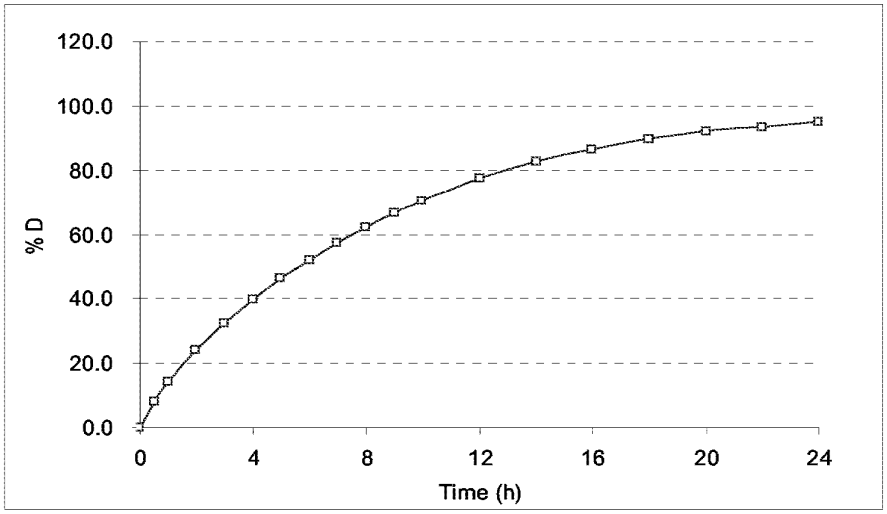

Figure 1

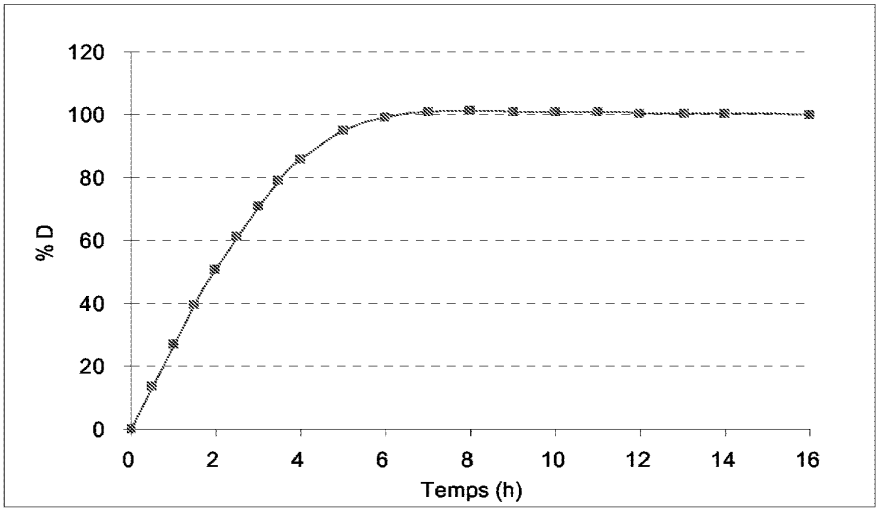

Figure 2

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 05 30 0406

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	28 November 2005	Hedegaard, A

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X : particularly relevant if taken alone
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(54) Oral pharmaceutical composition for treating a COX-2 mediated condition

(57) The invention relates to oral pharmaceutical formulations for the prevention and/or the treatment of chronic cyclooxygenase (COX)-2 mediated diseases or conditions, ie the inflammatory diseases or conditions, while reducing the risk of thrombotic cardiovascular and. This invention also addresses methods of prevention and/or treatment of these diseases, using these oral pharmaceutical formulations.

The oral pharmaceutical formulation comprises a combination of at least one active principle for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition and of microcapsules for the controlled release of acetylsalicylic acid (ASA), in the gastrointestinal environment.

EP 1 726 301 A1

Description

[0001] The invention relates to oral pharmaceutical formulations for the prevention and/or the treatment of chronic cyclooxygenase (COX)-2 mediated diseases or conditions, ie the inflammatory diseases or conditions, while reducing the risk of thrombotic cardiovascular and. This invention also addresses methods of prevention and/or treatment of these diseases, using these oral pharmaceutical formulations.

[0002] COX-2 mediated diseases of particular concern for the invention include inflammatory diseases.

Chronic cyclooxygenase (COX)-2 mediated diseases such as rheumatoid arthritis and systemic lupus erythematosis are often treated with Non Steroidal Anti Inflammatory Drugs (NSAIDs). A large number of patients, who are treated with common NSAIDs, or with more specific NSAIDs such as COX-2 inhibitors, have severe side effects. These severe side effects may include life threatening ulcers and thrombotic cardiovascular events that limit the therapeutic potential of said NSAIDs.

In addition, there is evidence that patients with chronic inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythematosis, are at increased risk for thrombotic cardiovascular events.

Furthermore, many patients treated with NSAIDs or suffering from chronic COX-2 mediated disease or condition are elderly and thus are at increased risk for thrombotic cardiovascular events. Thus, it is desirable to treat such patients with appropriate antiplatelet therapy, such as low dose aspirin.

[0003] Thus, there is a need that the patients treated with NSAIDs receive antiplatelet aggregation drugs therapy, without gastric side effects.

In sum, there is a need for a therapeutic solution that combines NSAIDs, particularly COX-2 inhibitor anti-inflammatory drugs with anti-platelet aggregation drugs , without inducing gastric side effects.

[0004] In the present exposure, the "thrombotic cardiovascular events" include stroke, myocardial ischemia, myocardial infarction, angina pectoris, transient ischemic attack (TIA; amaurisis fugax), reversible ischemic neurologic deficits, and any similar thrombotic event in any vascular bed (splanchnic, renal, aortic, peripherical, etc.)

[0005] Aspirin, or AcetylSalicylic Acid (ASA), acts to prevent platelet aggregation by irreversibly inhibiting cyclooxygenase (COX-1 & COX-2, collectively known as COX). COX converts arachidonic acid to thromboxane, a potent vasoconstrictor and a platelet aggregation stimulator. Aspirin inhibits COX by acetylating it. The inhibition of COX activity by aspirin is generally irreversible.

[0006] When aspirin is absorbed from the digestive tract, it is collected by the portal vein. The portal vein then goes to the liver where the aspirin is deacetylated. Once deacetylated, aspirin no longer has the ability to acetylate COX. However, the mechanism in the liver can rapidly reach saturation causing the aspirin overflow to enter the systemic blood circulation. In the systemic circulation, aspirin that has not been deacetylated by the liver can further inhibit COX in other tissues and cells. For instance, outside the portal system, ie notably in the endothelial cells that line the vasculature and in the gastric endothelium, aspirin-induced COX-1 inhibition results in a decrease of prostacyclin, which, contrary to thromboxane, is a potent vasodilator, a platelet aggregation inhibitor and a cytoprotector. Therefore, aspirin that enters the systemic blood circulation results in inhibition of the prostacyclin and other prostaglandins, which runs counter to the desired effect on platelet aggregation, and which induces gastric side effects. This phenomenon of blind inhibition of the different prostaglandins in the organism is commonly referred to as the dilemma of aspirin. It is well known to scientists and has been widely described in the literature.

[0007] Aspirin is a very useful medication for the prevention of cardiovascular thrombotic events in patients with or those at risk for cardiovascular disease. However, there are serious side effects of aspirin administration. For example, the most common side effect is a propensity to induce gastric or intestinal ulceration, which may result in hemorrhaging. This effect occurs when acetylated aspirin inhibits COX-1 in the systemic circulation. Now, COX-1 in the systemic circulation catalyzes the biosynthesis of gastric prostaglandins that ordinarily serve as cytoprotective mucous in the intestines. So, the gastric mucosa is no longer protected by these gastric prostaglandins and it is atta.cked by gastric acid, which induces tissue damage and bleeding... The gastrointestinal effects of aspirin may be caused by its lack of selectivity between antiplatelet COX-1 inhibition and endothelial COX-1 inhibition leading to gastric mucosal effects.

[0008] In patients with established cardiovascular disease, aspirin use has been documented to decrease the risk of a primary myocardial infarction, stroke and vascular death. Secondary prevention refers to the use of aspirin to prevent cardiovascular events in patients with established cardiovascular disease such as a myocardial infarction, stroke, or angina. The use of aspirin in these individuals is recommended based on a documented decrease in future cardiovascular events and mortality. The risk for gastrointestinal injury is observed in patients being treated with aspirin, even at dosages as low as 81 mg/day for cardioprotection.

[0009] In patients with established cardiovascular disease, aspirin may have further side effects. For example, aspirin may decrease renal blood flow and the rate of glomerular filtration in patients with congestive heart failure. Therefore, acute renal failure may be precipitated. Aspirin may also promote the retention of salt and water by reducing the prostaglandin induced inhibition of both the reabsorption of chloride and the action of anti-diuretic hormone. This may cause edema in some patients who are treated with aspirin and may reduce the effectiveness of anti-hypertensive regimens. Aspirin and other COX-2 inhibitors may also increase the risk of heart disease. Metabolism of arachidonic acid by COX-2 results in the

production of prostaglandins, which promotes inflammation. Therefore inhibition of COX-2 results in decreased inflammation. However, COX-2 inhibition also promotes arachidonic acid to be converted to pro-inflammatory agents such as leukotriene B4 and thromboxane A2. The resulting increase in these pro-inflammatory agents may lead to increased atherosclerosis and platelet aggregation, and other complications such as stroke and heart attack.

[0010] So, it appears that aspirin that is not metabolized by the liver may induce serious side effects.

[0011] Since the NSAIDs, and especially the COX-2 specific inhibitors, possibly combined with aspirin, may be taken by the patient for a substantial portion of his life, it is important to improve the safety profile of the treatment for the tens of millions of patients concerned today who regularly take these drugs.

[0012] Thus, it appears that there is a need in a therapeutic solution for treating the inflammatory disorders and the associated pathologies linked to platelet aggregation, , without causing the serious side effects to the patients.

[0013] In this respect, it has been previously proposed to associate low dose aspirin, with COX-2 inhibitors to make an anti-inflammatory therapeutic for decreasing the risk of a thrombotic cardiovascular event while decreasing the side effects (notably gastric) of such treatment.

[0014] For instance, WO-A-03/094924 suggests replacing low dose aspirin with nitric oxide releasing aspirin. WO-A-03/094924 discloses a method for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event comprising orally concomitantly or sequentially administering to said patient a cyclooxygenase-2 selective inhibitor in an amount effective to treat the cyclooxygenase-2 mediated disease or condition and nitric oxide releasing aspirin in an amount effective to reduce the risk of the thrombotic cardiovascular event while maintaining a high level of upper gastrointestinal safety and tolerability. The invention also encompasses a method for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event. This treatment comprises orally concomitantly or sequentially administering to the patient a nitric oxide releasing cyclooxygenase-2 selective inhibitor in an amount effective to treat the cyclooxygenase-2 mediated disease or condition and aspirin in an amount effective to reduce the risk of the thrombotic cardiovascular event, while maintaining a high level of upper gastrointestinal safety and tolerability. WO-A-03/033001 further proposes to use aspirin in lower dosages as those previously implemented, namely 75-325 mg per day. The particularly preferred COX-2 inhibitor is 5-alkyl-2-aminophenylacetic acid derivative.

[0015] However the immediate release aspirin included in this composition may still create many of the gastric side effects mentioned before. The problem of aspirin dilemma is not solved.

[0016] US-B-6,599,529 relates to an oral pharmaceutical modified-release multiple-units composition for the administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance - e.g. aspirin - (in the following abbreviated "an NSAID substance") to obtain both a relatively fast or quick onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. The modified release multiple-units composition comprises at least two fractions of multiple units such as a first and a second fraction. The first fraction is an immediate release immediate release form of NSAIDs, which comprises individual units that are designed to quickly release the drug substance. The second fraction is a delayed release DR / sustained release SR form, which comprises individual units that are designed to slowly release the drug substance to enable a delayed and extended release of the drug substance. Typically, the second fraction comprises multiple units which are coated with a sustained release coating designed to release the drug substance in such a manner that the maintenance of a therapeutically active plasma concentration for a relatively long period of time are obtained (once- or twice-a-day administration)- [Pellet cores: Polysorbate 20/Cellulose microcrystalline/Lactose/Carmellose sodium/Maltodextrin/Pregelatinized starch - Inner coat: Hypromellose(Methocel E prem) / Magnesium stearate / Talc / Eudragit NE 30 D - Outer coat: Hypromellose (Methocel E5 prem) / Talc].The composition can comprise a further active drug substance selected from the group consisting of an antidepressant, an opioid, a prostaglandin analog, a glucocorticosteroid, a cytostaticum, a H2 receptor antagonist, a proton pump inhibitor and an antacid.

[0017] The immediate release fraction of NSAIDs (aspirin) in this composition is still creating all gastric side effects mentioned before. The problem of aspirin dilemma is not solved.

[0018] US-A-2004/0121004 and US-A-20040131676 disclose a non-enterically coated dosage form comprising: a) a proton pump inhibitor(lansoprazole); b) a buffer; and c) a non-steroidal anti-inflammatory drug (aspirin at an amount between 50 mg and 100 mg) and a method of treating a condition selected from the group consisting of angina, aorto-pulmonary shunt occlusion, colorectal cancer, esophageal cancer, colon cancer, coronary artery disease, dementia, dysmenorrhea, myocardial infarction, rheumatoid arthritis, osteoarthritis, pain, headache, migraine headache, stroke, thrombocythemia, post-operative thromboembolism, ischemia, bursitis, cognitive decline, fever, gout, musculoskeletal disorders, soft tissue injury, and pericarditis; wherein the method comprises administering to a patient having one or more of the above conditions said non-enterically coated dos-

age form. This form is an immediate release form of acetylsalicylic acid at basic pH. Granulates of NSAIDs are prepared from Magnesium Hydroxide- buffer-; Calcium Carbonate; Mannitol; Avicel (micro-crystalline Cellulose); PVPP (Cross- povidone). These granulates are tabletted.

[0019] The immediate release of NSAIDs (aspirin) in this composition is still creating all gastric side effects mentioned before. The problem of aspirin dilemma is not solved.

[0020] US-B-5,603,957 belonging to the applicant, and incorporated in its entirety by reference, discloses a pharmaceutical form comprising microcapsules for the controlled release of acetylsalicylic acid in the gastrointestinal environment, said microcapsules consisting of particles of acetylsalicylic acid with a size of between 100 and 1000 μm. These microcapsules are coated and designed so that, when ingested orally in a single administration of a dose of between 50 and 325 mg of ASA, they induce moderate acetylsalicylic acid absorption kinetics in vivo in man, extending over at least 24 hours, said acetylsalicylic acid absorption being less than or equal to 10% by weight of the absorbed fraction of D at a time t after ingestion of 0.4 hour, less than or equal to 50% by weight of the absorbed fraction of D at t=3.9 hours, and less than or equal to 90% by weight of the absorbed fraction of D at t=23 hours, t being given to within +/-10%. One method to create such smaller microcapsules is disclosed in U.S. Patent No. 6,022,562 to Autant et al., which is incorporated in its entirety by reference.

[0021] We find it surprising that we can use the pharmaceutical of microcapsules to selectively inhibit the cyclooxygenase COX-1 in the portal vein and/or in the liver, and thus reduce the production of thromboxane, while minimizing cyclooxygenase COX-1 inhibition in the systemic circulation, in order to to optimize the inhibition of platelet aggregation, and subsequently to prevent and/or treat cardiovascular diseases and risks associated with anti-inflammatory drugs used in the treatment of chronic cyclooxygenase (COX)-2 mediate diseases or conditions and consisting of NSAIDs, more particularly of COX-2 specific inhibitors, while minimizing the side effects (notably the gastric ones).

[0022] While not wishing to be constrained by any mode of action, we believe that by coating the acetylsalicylic acid to form microcapsules, we promote the direct action of aspirin on only the COX-1 of the portal circulation. Our pharmaceutical formulation results in a low, constant release rate of aspirin being released from the microcapsules and absorbed by the portal vein. This low release rate of aspirin is sufficient to inhibit COX-1 in the portal circulation, and therefore prevent thromboxane formation. Once aspirin is deacetylated, it is no longer active in that it can no longer inhibit COX. The liver can quickly be saturated with aspirin, and any aspirin that is not deacetylated will overflow into the systemic blood stream. We find it surprising that our use of microcapsules results in a release rate of aspirin low enough such that the liver is not saturated. Therefore, once the low release rate of aspirin inhibits COX-1 in the portal circulation, the liver then deacetylates any remaining active aspirin. This results in minimal aspirin overflow into the systemic circulation to inhibit prostaglandin and prostacyclin production, thus preventing damage of the gastroendothelium and other side effects of aspirin. Thus, the method permits the rapid saturation of the liver without the normal deleterious side effects, a result that we fmd unexpected.

[0023] Optionally, we also propose to add a minimal dose of a gastric acid suppressing agent to the above mentioned combination of NSAIDs with a controlled release form of aspirin that releases aspirin at a low release rate such that very little aspirin reaches the systemic circulation. This gastric acid suppressing agent is intended to decrease or suppress any residual gastric damage by increasing gastric pH

[0024] While not wishing to be constrained to low doses of gastric acid suppressing agent, we fmd it surprising that we can greatly minimize gastric damage with only a minimal dose of gastric acid suppressing agent. The low dose of gastric acid suppressing agent in our invention increases the gastric pH only a small amount. Further, the low, constant dose of aspirin released in the intestinal tract would sufficiently inhibit COX in the portal circulation, while having minimal effects on the systemic prostaglandins. Therefore, the applicant takes credit for demonstrating that the combination of NSAIDs with a controlled release aspirin microcapsules and with at least one gastric acid suppressing agent makes it possible to increase the safety of the anti-platelet drug while decreasing the side effects.

[0025] According to the invention, we propose the combination of:

- at least one NSAIDs, preferably a COX-2 specific inhibitor,
- a controlled release dosage form of aspirin releasing slowly acetylsalicylic acid in such manner that a few amount of acetylsalicylic acid reaches the systemic circulation and, hence, induces very limited gastric damage, and,
- and optionally minimal amounts of gastric acid suppressing agent to completely suppress the gastric damage without important increase of the gastric pH.

[0026] The present invention concerns an oral pharmaceutical formulation for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition while reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event,

- comprising a combination of at least one active principle for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition and of microcapsules for the controlled release of acetylsalicylic acid

(ASA), in the gastrointestinal environment,

- said microcapsules:
  - having an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that 70% of the acetylsalicylic acid is released over a period of time of between 2 and 20 hours, , and
  - inhibiting cyclooxygenase COX-1 in portal vein which limits the production of thromboxane while maintaining cyclooxygenase COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin, to protect the gastric endothelium and to maintain its vasodilatation properties.

[0027] The term "controlled release" denotes, in the present disclosure, a prolonged or sustained release and/or a delayed release and/or a pulsed release of active principle by an oral pharmaceutical formulation. Such a controlled-release oral pharmaceutical formulation may, for example, comprise an immediate-release phase and a slow-release phase. Modified-release medicinal products are well known in this field; see, for example, Remington: The Science and practice of pharmacy", 19th edition, Mack Publishing Co. Pennsylvania, USA. The modified release may in particular be a prolonged and/or delayed release.

[0028] The oral pharmaceutical formulation according to the invention can be, e.g., a once-α-day or a twice-α-day form.

[0029] Preferably, the active principle for treating a chronic cyclooxygenase-2 mediated disease or condition in the oral pharmaceutical formulation according to the invention is an anti-inflammatory drug. More preferably, the active principle for treating a chronic cyclooxygenase-2 mediated disease or condition in the oral pharmaceutical formulation according to the invention is selected from the Non Steroidal Anti Inflammatory Drugs (NSAIDs).

[0030] For instance, the NSAID(s) is (are) selected in the group comprising:

- aminoarylcarboxylic acid and its derivates such as: enfenamic acid, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, morniflumate, niflumic acid and tolfenamic acid,
- arylacetic acid and its derivates such as: aceclofenac, acemetacin, amfenac, bromfenac, cimmetacin, diclofenac, etodolac, fentiazac, glucametacin, indomethacin, lonazolac, l'acid metiavinic, oxametacine, pirazolaque, proglumetacin, sulindac, tiaramide, tolmetin and zomepirac,
- arylcarboxylic acids such as ketorolac and tinoridine,
- arylpropionic acid and its derivates such as: alminoprofen, bermoprofen, carprofen, dexibuprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, ketoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, protizinic acid and tiaprofenic acid,
- pyrazoles e.g.: epirizole,
- pyrazolones such as: benzpiperylon, mofebutazone, oxyphenbutazone, phenylbutazone and ramifenazone,
- salicylic acid derivates comme : acetaminosalol, benorylate, eterisalate, fendosal, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, parsalmide, l'acid salamidacetic and le salsalate,
- thiazinecarboxamides such as : ampiroxicam, droxicam, lornoxicam, meloxicam, piroxicam and tenoxicam,
- others such as: bucillamine, bucolome, bumadizon, diferenpiramide, ditazol, emorfazone, nabumetone, nimesulide, proquazone and piroxicam (in the form of the betacyclodextrin complex).
- alclofenac, azapropazone, benoxaprofen, acid bucloxic, choline magnesium trisalicylate, clidanaque, clopinaque, dapsone, diflunisal, fenclofenec, floctafenine, flufenisal, (r)-flurbiprofen, (s)-flurbiprofen, furofenaque, feprazone, fluprofen, ibufenaque, indoprofen, isoxepac, isoxicam, miroprofen, mefenamic, meclofen, acid niflumic, nitroflurbiprofen, oxipinaque, podophyllotoxin derivates, piprofen, pirprofen, prapoprofen, sudoxicam, suprofen, acid tiaprofenic, tiopinaque, tioxaprofen, zidometacin, acid 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic, a 4-(nitrooxy)butyl ester, ketoporfen, ketrolac.

[0031] More particularly: the NSAID(s) is (are) selected in the group comprising:

lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, acid tiaprofenic, proglumetacin, acid mefenamic, fenbufen, etodolaque, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen and/or the pharmaceutical salts and/or the complexes and/or the prodrugs and/or the mixtures thereof.

[0032] More preferably, in the oral pharmaceutical formulation according to the invention, the active principle for treating a chronic cyclooxygenase-2 mediated disease or condition, is selected in the sub-class of the class of NSAIDs comprising the specific inhibitors of COX-2.

[0033] The examples of cyclooxygenase-2 specific or selective inhibitors include: rofecoxib (VIOXX® cf. US-B- 5 474 995), etoricoxib (ARCOXIA™ cf. US-B- 5 861 419), celecoxib (CELEBREX® cf. US-B- 5 466 823), valdecoxib (cf. US -B-6 633 272), parecoxib (cf. brevet US -B-5 932 598), COX-189 (Novartis), BMS347070 (Bristol Myers Squibb), tiracoxib ou JTE522 (Japan Tobacco), ABT963 (Abott), CS502 (Sankyo), and GW406381 (GlaxoSmithKline).

[0034] With respect to therapeutic agents, it is expected that the skilled practitioner will adjust dosages on a case by case basis using methods well established in clinical medicine. The daily dosage may be provided in either a single or multiple regimen with the latter being generally preferred. These are simply guidelines since the actual dose must be carefully selected and titrated by the attending physician based upon clinical factors unique to each patient. The optimal daily dose will be determined by methods known in the art and will be influenced by factors such as the age of the patient, the disease state, side effects associated with the particular agent being administered and other clinically relevant factors.

[0035] Generally, the COX-2 inhibitor may be present between about 1 to about 1000mg , preferably about 5 to about 500mg. For example, the recommended dosage for one particular COX-2 inhibitor, Celecoxib (Celebrex), is typically 100 mg twice per day or 200 mg once per day. Celecoxib is a preferred COX-2 inhibitor in the compositions and methods of the present invention and may typically be present at 50-500 mg per unit dose. Especially preferred are methods and compositions utilizing 100 to 400 mg celecoxib. As another example, Rofecoxib (Vioxx) for oral administration is available in tablets of 12. 5, 25 or 50 mg and in an oral suspension containing either 12.5 mg or 25 mg rofecoxib per 5 ml. The recommended initial daily dosage for the management of acute pain is 50 mg. Peak plasma concentrations of rofecoxib typically occur about 2-3 hours after oral administration and the drug has a half life of about 17 hours.

[0036] Advantageously, the oral pharmaceutical COX-2 inhibitor formulations, can include:

→ at least one immediate COX-2 inhibitor form;
→ and/or at least one controlled release COX-2 inhibitor form.

[0037] According to an aspect of the invention, the oral pharmaceutical formulation comprises at least one gastric acid suppressing agent to increase the pH of the stomach just enough to minimize the damage resulting from the residual amount of non-deacetylated acetylsalicylic acid coming from the liver and the portal blood circulation and entering the systemic blood circulation. Preferably, said gastric acid suppressing agent is a proton pump inhibitor (ppi).

[0038] Preferably, the microcapsules can be orally ingestible in a dose and can comprise particles of acetylsalicylic acid with a size of less than about 1000 μm, preferably between about 50 μm or 100 μm to 1000 μm, which are coated and designed so that, when ingested orally in a single administration they induce acetylsalicylic acid absorption kinetics in vivo in man, extending over at least 24 hours, said acetylsalicylic acid absorption being less than or equal to 10% by weight of the absorbed fraction of the dose at about 0.4 hour post ingestion, less than or equal to 50% by weight of the absorbed fraction of the dose at about 3.9 hours post ingestion, and less than or equal to 90% by weight of the absorbed fraction of the dose at about 23 hours post ingestion.

[0039] According to another of its features, the present invention also concerns a method for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event, said method comprising the administration to a patient an oral pharmaceutical formulation according to the above definition. This method is a method of preventing and/or treating pathological disorders associated with excesses of thromboxane, particularly cardiovascular diseases and risks. This method consists in the oral administration of the pharmaceutical formulation according to the invention, preferably in a once or twice-a-day administration.

[0040] It is apparent from the foregoing text that the microcapsules of the invention are very effective in pharmacological terms, perfectly tolerated by the organism, especially as regards gastric tolerance, capable of being presented in various appropriate galenical forms and, finally, easy and inexpensive to obtain.

[0041] The controlled release acetylsalicylic acid microcapsules have high selectivity for the thromboxane inhibition, which makes it possible to maintain the production of prostacyclin, in order to protect the gastrointestinal tract.

[0042] Furthermore, the gastric acid suppressing agent maintains the pH of the stomach high enough to reduce the acidic erosion of the surface of the stomach and even to facilitate the healing process when some ulceration occurs.

[0043] In a preferred embodiment of the invention, the absorption takes place over a period of between 24 and hours in the following manner:

- 10% of the absorbed fraction of the dose at t=0.4 to 5 hours,
- 50% of the absorbed fraction of the dose at t=3.9 to 25 hours,
- and 90% of the absorbed fraction of the dose at t=23 to 45 hours.

[0044] The curve of FIG. 1 of US-B-5,603,957 shows the kinetic profile of the in vivo absorption of ASA, and more precisely the upper limit of the acetylsalicylic acid in vivo absorption profile induced by the controlled release acetylsalicylic acid microcapsules according to US-B-5,603,957, as a function of time, at a dose of 320 mg. This absorption is expressed in % absorbed relative to the absorbed fraction of the initial dose D. This curve is obtained by conventional deconvolution analysis (Milo GIBALDI and D. PERRIER, Pharmacokinetics, 2nd ed., New York, Marcel Dekker Inc., 1983, p. 145-167) from the mean curves of the plasma concentrations as a function of time after the oral administration of 350 mg of acetylsalicylic acid equivalents of ASPEGIC. (control

form) and 320 mg of acetylsalicylic acid equivalents of microcapsules according to the invention in the form of gelatin capsules. In this case, the tracer molecule chosen for the plasma concentrations as a function of time is necessarily salicylic acid (SA), a metabolite of ASA. The plasma concentrations of SA are determined by HPLC. The critical points at 0.4, 3.9 and 23 h, given above in the defmition of the microcapsules of the invention, are of course to be found on this curve. Beyond this curve, the hepatic acetylsalicylic acid deacetylation mechanism is saturated. It must be considered that all the acetylsalicylic acid in vivo absorption profiles contained in the area under the curve are controlled release acetylsalicylic acid microcapsules according to US-B-5,603,957.

[0045] To solve the technical problem on which the invention is based, it highly preferable that the formulation according to the invention be free or almost free of immediate release acetylsalicylic acid form. The term "almost free" means that the formulation can include negligible amount of immediate release acetylsalicylic acid form, namely a insufficient amount so that there is remaining non-deacetylated acetylsalicylic acid in the systemic blood stream after the liver, said non-deacetylated acetylsalicylic acid being in a sufficient amount to inhibit COX-1 of the systemic blood compartment.

[0046] "Immediate release acetylsalicylic acid form" is intended to denote, in the present disclosure, a form in which the acetylsalicylic acid is released, at pH 6.8 and under sink conditions in an in vitro dissolution test, most of the amount of acetylsalicylic acid contained in the immediate release acetylsalicylic acid form, in a relatively brief period of time; for example at least 70% of the acetylsalicylic acid is preferably released in forty five minutes and more preferably in thirty minutes.

[0047] All the dissolution profiles to which reference is made in the present disclosure are determined according to the indications of the European Pharmacopoeia, 4th edition, entitled: "Dissolution test for solid oral forms": type II dissolutest performed under SINK conditions, at 37°C, at a test dose of 10 mg of active, and with agitation of 100 rpm.

[0048] In a preferred embodiment of the invention, the oral pharmaceutical formulation according to the invention contains a dose of acetylsalicylic acid in the controlled release acetylsalicylic acid microcapsules, said dose being comprised between 60 and 320 mg.

[0049] In another preferred embodiment of the invention, the oral pharmaceutical formulation according to the invention contains a dose of acetylsalicylic acid in the controlled release acetylsalicylic acid microcapsules, said dose being comprised between 50 and 325 mg.

[0050] In a more preferred embodiment of the invention, the oral pharmaceutical formulation according to the invention contains a dose of acetylsalicylic acid in the controlled release acetylsalicylic acid microcapsules, said dose being comprised between 75 and 310 mg.

[0051] In a preferred embodiment of the invention, the oral pharmaceutical formulation according to the invention, contains a dose of gastric acid suppressing agent comprised between 1 and 130 mg.

[0052] In a more preferred modality of the invention, the oral pharmaceutical formulation according to the invention, contains a dose of gastric acid suppressing agent comprised between 2 and 120 mg.

[0053] According to a first embodiment, the oral pharmaceutical formulation according to the invention has the following characteristics, among others:

a) the dose of NSAID(s) is comprised between 1 and 1000 mg;
b) the dose of acetylsalicylic acid in the controlled release acetylsalicylic acid microcapsules is comprised between 50 and 325 mg;
c) optionally, the dose of gastric acid suppressing agent is comprised between 5 and 120 mg;
d) it is a once-a-day administration form.

[0054] The oral pharmaceutical formulation comprising a), b), optional c), d) features, can include:

- at least one immediate release NSAID(s) form
- and/or at least one controled release NSAID(s) form
- and/or at least one immediate release gastric acid suppressing agent form
- and/or at least one controlled release gastric acid suppressing agent form.

[0055] According to a second embodiment, the oral pharmaceutical formulation according the invention has the following characteristics, among others:

i. the dose of NSAID(s) is comprised between 1 and 1000 mg;
ii. wherein the dose of acetylsalicylic acid in the microcapsules is comprised between 50 and 325 mg;
iii. wherein the optional dose of gastric acid suppressing agent is comprised between 5 and 120 mg;
iv. which is a twice-a-day administration form.

[0056] The oral pharmaceutical formulation comprising i, ii, optional iii, iv features, can include:

- at least one immediate release NSAID(s) form
- and/or at least one controled release NSAID(s) form
- and/or at least one immediate release gastric acid suppressing agent form
- and/or at least one controlled release gastric acid suppressing agent form.

[0057] It is remarkable that the oral pharmaceutical formulation according to the invention, is designed so that it induces reduction of bleeding and pitichia, or ulceration, in the stomach during the treatment.

[0058] We find it surprising that we can selectively in-

hibit COX-1 in the portal vein, permitting minimal aspirin to enter the systemic circulation. This significantly increases the comfort of the patients and the safety of the drug. Patients will be no longer compelled either to interrupt the treatment with aspirin or to switch to another drug. This also permits a method of quickly inhibiting COX in the portal vein, with less side effects than previously known. Finally, we have a method that permits the unexpected precise titration of the effects of aspirin on the liver, the circulatory system, and the stomach.

[0059] This remarkable feature can give rise to a method for reducing the side effects during the treatment of diseases at least partially caused by an inhibition of COX-1 in systemic circulation, said treatment comprising the administration to a patient of an oral pharmaceutical formulation for treating chronic cyclooxygenase(COX)-2 mediated diseases or conditions and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event, said formulation comprising a combination of at least one active principle for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition and of microcapsules for the controlled release of acetylsalicylic acid (ASA), in the gastrointestinal environment,
said microcapsules:

- having an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that 70% of the acetylsalicylic acid is released over a period of time of between 2 and 20 hours, and
- inhibiting cyclooxygenase COX-1 in portal vein which limits the production of thromboxane while maintaining cyclooxygenase COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin, to protect the gastric endothelium and to maintain its vasodilatation properties.

[0060] According to a preferred embodiment, said formulation comprises at least one gastric acid suppressing agent increasing the pH of the stomach just enough to minimize the damage resulting from the residual amount of non-deacetylated acetylsalicylic acid coming from the liver and the portal blood circulation and entering the systemic blood circulation.

[0061] The side effects of the oral pharmaceutical formulation according to the invention is also very interesting in that it is designed so that it improves the healing process, notably, in the stomach during the treatment. The oral pharmaceutical formulation is also designed to decrease other side effects of antithrombotic treatments, such as gastric or intestinal ulceration and hemorrhaging, renal failure, edema, atherosclerosis, and any resulting cardiovascular disease.

[0062] This interesting feature can give rise to a method according to another aspect of the present invention, namely a method for improving the healing process, notably, in the stomach, during the treatment of diseases at least partially caused by an inhibition of COX-1 in systemic circulation, said treatment comprising the administration to a patient of an oral pharmaceutical formulation including ASA, wherein the oral pharmaceutical formulation is a formulation for treating chronic cyclooxygenase (COX)-2 mediated diseases or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event,
said formulation comprising a combination of at least one active principle for treating a chronic cyclooxygenase (COX)-2 mediated disease or condition and of microcapsules for the controlled release of acetylsalicylic acid (ASA), in the gastrointestinal environment, said microcapsules:

- having an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that 70% of the acetylsalicylic acid is released over a period of time of between 2 and 20 hours, , and
- inhibiting cyclooxygenase COX-1 in portal vein which limits the production of thromboxane while maintaining cyclooxygenase COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin, to protect the gastric endothelium and to maintain its vasodilatation properties.

[0063] According to a variant which makes it possible to decrease the possible residual gastric damage resulting from the passage of possible remaining small amounts of non deacetylated ASA from the portal and/or the liver into the systemic circulation, said formulation comprises at least one gastric acid suppressing agent increasing the pH of the stomach just enough to minimize the damage resulting from the residual amount of non-deacetylated acetylsalicylic acid coming from the liver and the portal blood circulation and entering the systemic blood circulation.

[0064] In the two above mentioned methods, the implemented microcapsules being orally ingestible in a dose and comprising particles of acetylsalicylic acid with a size of less than 1000 μm which are coated and designed so that, when ingested orally in a single administration of a dose of acetylsalicylic acid, it induces acetylsalicylic acid absorption kinetics in vivo in man, extending over at least 24 hours, said acetylsalicylic acid absorption being less than or equal to 10% by weight of the absorbed fraction of the dose at about 0.4 hour post ingestion, less than or equal to 50% by weight of the absorbed fraction of the dose at about 3.9 hours post ingestion, and less than or equal to 90% by weight of the absorbed fraction of the dose at about 23 hours post ingestion.

[0065] Unless otherwise indicated, use of the term "about" in this invention description is intended to mean

plus or minus 10% of the designated amount; thus, "about 5 to 80%" would mean a range of 4.5-5.5% to 76-84%.

[0066] The gastric acid suppressing agent is preferably a proton pump inhibitor (ppi). According to the terminology of the present text, the acronym "ppi" used in the singular will designate indifferently one or several ppi, e.g. the lansoprazole, and /or at least one of its metabolites.

[0067] A ppi is a substituted benzimidazole which inhibits gastric acid secretions by specific inhibition of the H^+, K^+-ATPase enzymatic system (proton pump) of the secretory surface of parietal gastric cells. A ppi is an advantageous substitute for histamine H2 receptor antagonists (blocking of gastric acid secretion) or for antacids, which are not fully effective in the treatment of ulcers, associated or not with *Helicobacter pylori* infection or of other gastric disorders, and which in addition lead to many side effects.

[0068] A ppi is a lipophilic weak base that is poorly soluble in water. It undergoes rapid degradation under acidic conditions but, on the other hand, it is relatively stable at neutral or basic pH.

[0069] The ppi more particularly concerned by the present invention are derivates of benzimidazole. These latter are substituted or non substituted benzimidazoles, one or several salts of benzimidazoles, any enantiomer of these benzimidazoles, one or several salts of enantiomer (s), any isomer of these benzimidazoles, any derivate of benzimidazole, any free base of benzimidazole ou any mixing of these active principles.

[0070] The ppi used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg++, Ca++, Na++, K++ or Li++ salts, preferably the Mg++ salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

[0071] For example, the ppi concerned by the invention, are notably the ppi described pages 7 to 11 of WO-A-97/25066, this extract being incorporated by reference in the present text.

[0072] The WO-A-2004/035020 patent application gives also a general formula of the class of benziimidazoles: pages 35-48. This extract of WO-A-2004/035020 is incorporated by reference in the present text.

[0073] Examples of ppi are: esomeprazole, leminoprazole, omeprazole, pantoprazole, pariprazole, rabeprazole, timoprazole, picoprazole and tenatoprazole.

[0074] Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and W0094/27988.

[0075] The gastric acid suppressing agent is preferably a proton pump inhibitor, but H_2 receptor antagonists such as ranitidine, cimetidine or famotidine may be used in the pharmaceutical compositions with an alginate as proposed in WO 95/017080 or together with antacid agent(s). A wide variety of antacid agent(s) and/or alginates may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antacid agents include for example aluminium hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate and aluminium magnesium hydroxide carbonate (hydrotalcit) taken alone or in combinations with each other. The alginates may be an alginate selected from alginic acid or sodium alginate or other pharmaceutically acceptable alginate salts, hydrates, esters etc. Especially preferred antacid agents are magnesium or calcium based antacid agents and aluminium hydroxide/magnesium carbonate complex. Suitable antacid agents are for instance described in U.S. Pat. No. 5,409,709.

[0076] The preferred ppi in the form of a racemate, an alkaline salt or one of its single enantiomers, optionally in combination with antacid agent(s), can be an immediate release form and/or a controlled release (CR) form.

[0077] As examples of CR/MR, reference can be made to individually enteric or non enteric coating layered individual units (small beads, granules, microcapsules or pellets).

[0078] For example, the gastric acid suppressing agent can be designed in the form of CR/MR microcapsules, notably of the type of the CR/MR acetylsalicylic acid microcapsules, as described herein.

[0079] It could be very useful that the oral pharmaceutical formulation according to the invention, comprises at least one active principle different from acetylsalicylic acid and from gastric acid suppressing agent - preferably a proton pump inhibitor (ppi).

[0080] According to one embodiment, the oral pharmaceutical formulation further comprises a cardiovascular selected from the group comprising: anti-platelet drugs, beta adrenergic receptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, diuretics, anti-arrhythmic drugs, anti-ischemic drugs, anti-hypertensive drugs, beta adrenergic agonists, cardiac glycosides, nitrates, sodium channel blockers, central nervous system acting anti-hypertensive drugs, potassium channel activators, vasodilatory drugs, vasoconstrictive drugs, and mixtures thereof.

[0081] Examples of anti-platelet drugs include non-steroidal anti-inflammatory drugs, dipyridamole, and ticlopidine.

[0082] Examples of diuretics include acetazolamide, dichlorphenamide, methazolamide, glycerin, isosorbide, mannitol, urea, furosemide, bumetanide, ethacrynic acid, torsemide, azosemide, muzolimine, piretanide, tripamide, bendroflumethiazide (naturetin), benzthiazide (exna), chlorothiazide (diuril), hydrochlorothiazide (hydrodiuril), hydroflumethiazide (saluron), methyclothiazide (enduron), polythiazide (renese), trichlormethiazide, chlorthalidone (hygroton), indapamide (lozol), metolazone (mykrox, zaroxolyn), quinethazone (hydromox), amilo-

ride, triamterene, spironolactone, canrenone, potassium canrenoate.

[0083] Examples of angiotensin converting enzyme inhibitors include benazepril, captopril, enalapril, fosinopril sodium, lisinopril, quinapril, ramipril, spirapril.

[0084] Examples of nitrates include amyl nitrite (isoamyl nitrite), nitroglycerin (glyceryl trinitrate, nitro-bid, nitrostat, nitrol, nitro-dur, others), isosorbide dinitrate (isordil, sorbitrate, dilatrate, others), isosorbide-5-mononitrate (imdur, ismo, others), erythrityl tetranitrate (cardilate).

[0085] Examples of calcium channel blockers include amlodipine (norvasc), bepridil (vascor), diltiazem (cardizem, dilacor), felodipine (plendil), isradipine (dynacirc), nicardipine (cardene), nifedipine (adalat, procardia), nimodipine (nimotop), verapamil (calan, isoptin, verelan).

[0086] Examples of vasodilator drugs include nitrovasodilators such as nitroglycerin, isosorbide dinitrate, sodium nitroprusside; angiotensin receptor antagonist such as losartan (cozaar), phosphodiesterase inhibitors such as amrinone (inocor), milrinone (primacor), and vesnarinone; "direct" vasodilators such as hydralazine (apresoline), nicorandil, adrenergic receptor antagonists such as prazosin (minipress, and other quinazoline derivatives), phentolamine (regitine), labetalol (normodyne, trandate), carvedilol, and bucindolol; Ca^{2+} channel blocking drugs such as nifedipine (adalat, procardia), amlodipine (norvasc), and sympathomimetics such as dobutamine (dobutrex).

[0087] Examples of anti-arrhythmic drugs include adenosine, amiodarone, bretylium, digoxin, digitoxin, diltiazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide (N-acetyl procainamide), propafenone, propranolol, quinidine, sotalol, tocainide, verapamil.

[0088] According to another embodiment, the oral pharmaceutical formulation comprises an anti-diabetic drug. Examples of anti-diabetic drugs include: Acarbose, Acetohexamide, Buformin, 1-Butyl-3-metanilylurea, Carbutamide, Chlorpropamide, Ciglitazone, Glibornuride, Gliclazide, Glimepiride, Glipizide, Gliquidone, Glisoxepid, Glyburide, Glybuthiazole, Glybuzole, Glyhexamide, Glymidine, Glypinamide, Metformin, Miglitol, Nateglinide, Phenbutamide, Phenformin, Pioglitazone, Proinsulin, Repaglinide, Rosiglitazone, Tolazamide, Tolbutamde, Tolcyclamide, Troglitazone and/or the pharmaceutical salts and/or the complexes and/or the prodrugs and/or the mixtures thereof.

[0089] Advantageously, the controlled release acetylsalicylic acid microcapsules are so designed that the absorption takes place over a period of between 24 and 48 hours in the following manner: 10% of the absorbed fraction of the dose at t=0.4 to 5 hours, 50% of the absorbed fraction of the dose at t=3.9 to 25 hours, and 90% of the absorbed fraction of the dose at t=23 to 45 hours.

[0090] In the disclosure of the invention, the term "controlled release acetylsalicylic acid microcapsules" denotes microparticles of acetylsalicylic acid that are film-coated with at least one coating for modified/controlled release of ASA. The non-film-coated microparticles of acetylsalicylic acid may, for example, be neutral cores coated with at least one layer containing ASA, or microparticles of pure acetylsalicylic acid or alternatively granules formed by a matrix of support excipients including lansoprazole.

[0091] Advantageously, the film-coating (or coating) covering(s) has(have) sufficient mechanical strength to prevent it(them) tearing and/or it(them) breaking up in the organism, until the end of the release of the active principle.

[0092] These controlled release acetylsalicylic acid microcapsules can be compared to vehicles for the transport and the release of acetylsalicylic acid and, optionally, of one or more other active principles in the stomach and in the small intestine.

[0093] The pharmaceutical formulation according to the invention can also be characterized in that the controlled release acetylsalicylic acid microcapsules have an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that:

- 70% of the acetylsalicylic acid is released over a period of time of between 1 and 10 hours, preferably between 2 and 8 hours, and even more preferably between 2 and 6 hours, and
- 40% of the acetylsalicylic acid is released over a period of time of between 0.5 and 5 hours, preferably between 1 and 4 hours, and even more preferably between 1 and 3 hours.

[0094] Advantageously, the controlled release acetylsalicylic acid microcapsules have an in vitro release profile, in a 0.04M hydrochloric acid medium pH 1.4, such that 40% of the acetylsalicylic acid is released over a period of time of less than or equal to 3h, preferably less than or equal to 2h, and even more preferably less than or equal to 0.75h.

[0095] According to another pharmacokinetic definition of the pharmaceutical formulation according to the invention, the controlled release acetylsalicylic acid microcapsules have an in vitro release profile in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that, for any value of time t of between 2h and t(70%), preferably for any value of time t of between 1h and t(70%), the % of dissolved (released) acetylsalicylic acid is greater than or equal to 35 t / t(70%).

[0096] For example, the coating of the controlled release acetylsalicylic acid microcapsules represents 5 to 50% by weight, based on the total mass of said microcapsules.

[0097] Preferably, the coating of the controlled release acetylsalicylic acid microcapsules comprises at least one layer which controls the modified release of agent, the composition of said layer is as follows:

A) at least one film-forming (co)polymer (A) that is insoluble in the fluids of the gastrointestinal tract;
B) optionally, at least one water-insoluble hydrophilic film-forming (co)polymer (B) that is insoluble in the fluids of the gastrointestinal tract, carrying groups that are ionized in the fluids of the gastrointestinal tract,
C) at least one (co)polymer (C) that is soluble in the fluids of the gastrointestinal tract;
D) at least one plasticizer (D);
E) optionally, at least one surfactant and/or lubricant (E).

[0098] According to a preferred embodiment of the invention:

* (A) is selected from the group of following products:

- non-water-soluble derivatives of cellulose, preferably ethylcellulose and/or cellulose acetate,
- polyvinyl acetates,
- and mixtures thereof.

* (B) is chosen from water-insoluble charged acrylic derivatives, preferably from (co)polymers of acrylic and methacrylic acid ester carrying at least one quaternary ammonium group, (B) even more preferably comprising at least one copolymer of alkyl (meth) acrylate and of trimethylammonioethyl methacrylate chloride, and more precisely the products sold under the trade marks EUDRAGIT ® RS and/or RL, e.g. the powders EUDRAGIT ® RL PO and/or EUDRAGIT ® RS PO and/or the granules EUDRAGIT ® RL 100 and/or EUDRAGIT ® RS 100 and/or the suspensions and/or solutions of these EUDRAGIT ® RL and RS, namely, respectively, EUDRAGIT® RL 30D and/or EUDRAGIT® RS 30D and/or EUDRAGIT® RL 12.5 and/or EUDRAGIT® RS 12.5;

* (C) is chosen from

- nitrogenous (co)polymers, preferably from the group comprising polyacrylamides, poly-N-vinylamides, polyvinylpyrrolidones (PVP) and poly-N-vinyllactams;
- water-soluble derivatives of cellulose,
- polyvinyl alcohols (PVAs),
- polyoxyethylenes (POEs),
- and mixtures thereof;

polyvinylpyrrolidone being particularly preferred.

* (D) is chosen from the group comprising:

- cetyl alcohol esters,
- glycerol and its esters, preferably from the following subgroup: acetylated glycerides, glyceryl monostearate, glyceryl triacetate, glyceryl tributyrate,
- phthalates, preferably from the following subgroup: dibutyl phthalate, diethyl phthalate, dimethyl phthalate, dioctyl phthalate,
- citrates, preferably from the following subgroup: acetyl tributyl citrate, acetyltriethyl citrate, tributyl citrate, triethyl citrate,
- sebacates, preferably from the following subgroup: diethyl sebacate, dibutyl sebacate,
- adipates,
- azelates,
- benzoates,
- plant oils,
- fumarates, preferably diethyl fumarate,
- malates, preferably diethyl malate,
- oxalates, preferably diethyl oxalate,
- succinates, preferably dibutyl succinate,
- butyrates,
- salicylic acid,
- triacetin,
- malonates, preferably diethyl malonate,
- castor oil (this being particularly preferred),
- and mixtures thereof.

* (E) is chosen from the group comprising:

- anionic surfactants, preferably from the subgroup of alkali metal or alkaline-earth metal salts of fatty acids, stearic acid and/or oleic acid being preferred,
- and/or nonionic surfactants, preferably from the following subgroup:

  - polyoxyethylenated oils, preferably polyoxyethylenated hydrogenated castor oil,
  - polyoxyethylene-polyoxypropylene copolymers,
  - polyoxyethylenated esters of sorbitan,
  - polyoxyethylenated derivatives of castor oil,
  - stearates, preferably calcium stearate, magnesium stearate, aluminium stearate or zinc stearate,
  - stearyl fumarates, preferably sodium stearyl fumarate,
  - glyceryl behenates,
  - and mixtures thereof.

[0099] According to a particularly advantageous embodiment, the composition of the modified-release layer is as follows:

A. the film-forming polymer(s) (A) is (are) present in a proportion of 10 to 90%, preferably 20 to 40% by weight on a dry basis relative to the total mass of the coating composition;
B. the water-insoluble hydrophilic film-forming polymer(s) (B) is (are) present in a proportion of 10 to

90%, preferably 20 to 40% by weight on a dry basis relative to the total mass of the coating composition;
C. the polymer(s) (C) that is (are) soluble in the fluids of the gastrointestinal tract is (are) present in a proportion of 2 to 25, preferably 5 to 15% by weight on a dry basis relative to the total mass of the coating composition;
D. the plasticizer(s) (D) is (are) present in a proportion of 2 to 20, preferably of 4 to 15% by weight on a dry basis relative to the total mass of the coating composition;
E. the optional surfactant(s) and/or lubricant(s) (E) is (are) present in a proportion of 2 to 20, preferably of 4 to 15% by weight on a dry basis relative to the total mass of the coating composition.

[0100] For further details, in particular qualitative and quantitative details, regarding at least some of the constituents of this coating composition, reference will be made, for example, to European patent EP-B-0 709 087 or to PCT applications WO-A-2004/010983 and WO-A-2004/010984, the content of which are incorporated into the present disclosure, in their entirety, by reference.

[0101] The monolayer or multilayer coating may comprise various other additional adjuvants conventionally used in the coating field. They may be, for example, pigments or coloring agents, fillers, or anti-foaming agents.

[0102] To prevent the problems of caking of the coated particles constituting the controlled release acetylsalicylic acid microcapsules used in the invention, provision is advantageously made for adding thereto at least one anticaking agent preferably formed of talc, colloidal silica or a mixture of the two.

[0103] According to a particular embodiment of the invention, the controlled release acetylsalicylic acid microcapsule coating responsible for the modified release of acetylsalicylic acid consists of a single coating layer or a single coating film. This simplifies their preparation and limits the degree of coating.

[0104] Moreover, the pharmaceutical formulation according to the invention has the particularity that the coating of each controlled release acetylsalicylic acid microcapsule is nonenteric and does not desintegrate whatever the pH be, and in particular at any pH above 5.0.

[0105] Advantageously, the diameter of the controlled release acetylsalicylic acid microcapsules is less than or equal to 1000 μm, preferably between 50 and 800 μm, and even more preferably between 100 and 600 μm. The microparticle diameters to which the present disclosure refers are, unless otherwise indicated, mean diameters by volume.

[0106] This size makes it possible to cross the stomach independently of the opening of the pylorus. The gastric transit time is thus shorter and more uniform.

[0107] Advantageously, the controlled release acetylsalicylic acid microcapsules are obtained from particles of acetylsalicylic acid having a size of between 250 and 800 μm before the coating operation.

[0108] According to the invention, practical implementations in which the proportion of acetylsalicylic acid in the microcapsules (expressed as % by weight on a dry basis relative to the total mass of the microcapsules) is between 5 and 80, preferably between 10 and 60, and even more preferably between 20 and 50, are preferred.

[0109] As regards the monolayer or multilayer coating (or film) responsible for the modified release of ASA, it represents, for example, at most 40%, preferably at most 15%, by weight of the microcapsules.

[0110] The controlled release acetylsalicylic acid microcapsules are obtained from particles of acetylsalicylic acid which are coated by being sprayed with the intimate combination forming the coating, suspended in an organic solvent or mixture of organic solvents. The coating process, which constitutes a further subject of the invention, fits into the general pattern of microencapsulation techniques, of which the main ones are summarized in the article by C. DUVERNEY and J. P. BENOIT in "L'actualite chimique", December 1966. More precisely, the technique in question is microencapsulation by film coating. Preferably, this process consists essentially in: a) preparing the coating composition by mixing ABCDE in a solvent system, b) applying the composition/solvent system mixture to particles of acetylsalicylic acid, c) drying the resulting microcapsules, and d) if appropriate, mixing the latter with at least one anticaking agent. Examples of solvents which are suitable for forming part of the composition of the solvent system are ketones, esters, chlorinated solvents, alcohols, preferably aliphatic alcohols, alkanes or mixtures thereof. These solvents are advantageously C_1-C_6 compounds and particularly preferably acetone, methyl ethyl ketone, methanol, ethanol, isopropanol, cyclohexane and methylene chloride. If the coating methodology which can be used according to the invention is considered in greater detail, it can be stated that the coating composition/solvent system mixture is applied by being sprayed onto the moving particles of ASA, said movement preferably being created by mechanical agitation or by blowing (fluidization). To obtain microcapsules according to the invention possessing the desired absorption kinetics, it is necessary to encapsulate particles of acetylsalicylic acid with a mean size of between 75 and 500 μm, preferably of between 300 and 500 μm, for a dose of between 75 and 320 mg.

[0111] The controlled release acetylsalicylic acid microcapsules described above, which may have been obtained by the process also explained above, can be used for the preparation of novel galenical forms of aspirin having a biochemical selectivity for the inhibition of thromboxane relative to the other prostaglandins, in particular for the preparation of novel galenical forms useful as platelet aggregation inhibitors, and/or, more precisely, for the preparation of novel galenical forms active in the prevention and/or treatment of cardiovascular diseases and risks.

[0112] The present invention further relates to these novel galenical units as such, and comprising the phar-

maceutical formulation according to the invention.

[0113] Advantageously, these galenical, novel in their structure, their presentation and their composition, are presented in the form of a sachet of powder, a sachet of a powder for multidose suspension to be reconstituted, a tablet or a gelatin capsule. They can contain, for instance, a dose of acetylsalicylic acid of 20 to 500 mg, preferably 50 to 400 mg and particularly preferably 50 to 325 mg of acetylsalicylic acid and a dose of ppi of 1 to 300 mg, preferably 2 to 200 mg and particularly preferably 5 to 120 mg. Such galenical forms are preferably administered in single or twice daily doses.

[0114] It should be noted that it can be of value to mix, in one and the same gelatin capsule, tablet or powder, at least two types of microcapsules whose absorption kinetics are different but within the framework characteristic of the controlled release acetylsalicylic acid microcapsules according to US-B-5,603,957 (profile of curve of FIG. 1).

[0115] The invention will be understood more clearly from the following Examples, which are given solely by way of illustration and serve to provide a clear understanding of the invention and to illustrate its different embodiments and/or modes of implementation, as well as its various advantages.

EXAMPLES

Description of the figure:

[0116]

Figure 1: In vitro release profiles for the CR-Aspirin-based Microcapsules prepared according to Example 1.

Example 1 Preparation of CR-Aspirin-based microcapsules

[0117] 66 g of ethyl cellulose (Ethocel 7 Premium / Dow), 7 g of Plasdone K29/32® (Povidone/ISP), 8 g of castor oil, 9 g of magnesium stearate and 10 g tartaric acid are dispersed in 1200 g of a mixture made of 60% of isopropanol & 40% of acetone. The suspension is sprayed on 900 g of acetylsalicylic acid (aspirin) crystals, previously sieved between 200 and 500 μm.
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37°C and stirred with a paddle speed of 100 rpm (USP II apparatus) (See Figure 1).

Example 2: Preparation of IR- celecoxib based microcapsules

[0118] 860 g of celecoxib, 70 g of Klucel EF® (Hydroxypropyl cellulose / Aqualon) & 70 of Lutrol F-68 (Poloxamer 188 / BASF) are previously dry-mixed in a high shear granulator (Aeromatic PMA1) for 5 minutes. This mixture is then granulated with water (180 g). The granules are dried at 40°C in ventilated oven, and calibrated on 500 μm sieve. The fraction 200-500 μm is selected by sieving.
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37°C and stirred with a paddle speed of 100 rpm (USP II apparatus) Their release is immediate.

Example 3: Preparation of IR-rofecoxib based microcapsules

[0119] 1500 g of rofecoxib, 150 g de Klucel EF® (Hydroxypropyl cellulose / Aqualon) and 150 g of Cremophor RH 40® (PEG 40-hydrogenated castor oil / BASF) are dispersed in 4000 g of water. The suspension is sprayed on 200 g of neutral microspheres (Asahi-Kasei) in a spray coater Glatt GPCG1.
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37°C and stirred with a paddle speed of 100 rpm (USP II apparatus). Their release is immediate.

Example 4: Preparation of IR-meloxicam based microcapsules

[0120] 600 g of meloxicam, 100 g de Klucel EF® (Hydroxypropyl cellulose / Aqualon) and 100 g of Lutrol F-68 (Poloxamer 188 / BASF) are dispersed in 2000 g of water. The suspension is sprayed on 200 g of neutral microspheres (Asahi-Kasei) in a spray coater Glatt GPCG1.
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37°C and stirred with a paddle speed of 100 rpm (USP II apparatus). Their release is immediate.

Example 5: Preparation of enteric coated- lansoprazole based microcapsules

Step 1:

[0121] 900 g of lansoprazole & 100 g of Klucel EF® (Hydroxypropyl cellulose / Aqualon) are previously dry-mixed in a high shear granulator (Aeromatic PMA1) for 5 minutes. This mixture is then granulated with water (180 g). The granules are dried at 40°C in ventilated oven, and calibrated on 500 μm sieve. The fraction 200-500 μm is selected by sieving.

Step 2:

[0122] 50 g of Eudragit L100-55® (Rohm) and 10 g of triethyl citrate are dispersed in isopropanol. This solution is sprayed on 450 g of lansoprazole granules (prepared at step 1).
These microcapsules have been tested in a pH 6.8 (KH_2PO_4 0.05M/ NaOH) dissolution medium maintained at 37°C and stirred with a paddle speed of 100 rpm (USP

II apparatus) Their release is immediate.

Example 6: Capsule containing CR-aspirin and IR-celecoxib

[0123] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e. 162.5 mg of acetylsalicylic acid) and 233 mg of microcapsules of celecoxib (i.e. 200 mg of celecoxib) prepared at example 2 are filled in size 0 capsule.
This capsule is the fmal dosage form for preventing cardiovascular diseases (by means of aspirin), said diseases being caused by repeated administration of anti-inflammatory drugs, such as COX-2 inhibitors (celecoxib).

Example 7: Capsule containing CR-aspirin and IR-rofecoxib

[0124] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e. 162.5 mg of acetylsalicylic acid) and 33 mg of microcapsules of rofecoxib (i.e. 25 mg of rofecoxib) prepared at example 3 are filled in size 2 capsule.
This capsule is the fmal dosage form for preventing cardiovascular diseases (by means of aspirin), said diseases being caused by repeated administration of anti-inflammatory drugs, such as COX-2 inhibitors (rofecoxib).

Example 8: Capsule containing CR-aspirin and IR-meloxicam

[0125] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e. 162.5 mg of acetylsalicylic acid) and 25 mg of microcapsules of meloxicam (i.e. 15 mg of meloxicam) prepared at example 4 are filled in size 2 capsule.
This capsule is the fmal dosage form for preventing cardiovascular diseases (by means of aspirin), said diseases being caused by repeated administration of anti-inflammatory drugs, such as COX-2 inhibitors (meloxicam).

Example 9: Capsule containing CR-aspirin, enteric coated-lansoprazole and IR-celecoxib

[0126] 180 mg of microcapsules of acetylsalicylic acid prepared in example 1 (i.e. 162.5 mg of acetylsalicylic acid), 6.2 mg of microcapsules of lansoprazole (i.e. 5 mg of lansoprazole) prepared at example 5 and 233 mg of microcapsules of celecoxib (i.e. 200 mg of celecoxib) prepared at example 2 are filled in size 0 capsule.
This capsule is the final dosage form for preventing cardiovascular diseases (by means of aspirin), said diseases being caused by repeated administration of anti-inflammatory drugs, such as COX-2 inhibitors (celecoxib), while hindering gastric damages due to the presence of a ppi and controlled release acetylsalicylic acid microcapsules. The combination of a ppi with the controlled release acetylsalicylic acid microcapsules makes it possible to prevent gastric damages due to aspirin.

Example 10 showing that the known controlled release acetylsalicylic acid microcapsules could be improved, by means of the combination according to the invention:

[0127] Controlled release microcapsules of aspirin according to example 1 were compared to aspirin at a dose of 325 mg in double blind, randomized cross-over study, on 24 healthy non smoking volunteers. Endoscopic damage was assessed on days 0, 7, 14, 21 on each treatment period. The primary end point was the total number of gastroduodenal erosions and petechiae assessed endoscopically. The study performed by a group led by Professor Hawkey of Gastroenterology Division of University Hospital, Nottingham (UK) indicated that Controlled released aspirin cause less endoscopic damage than conventional aspirin.

[0128] The study indicated that significantly fewer gastric lesions were observed in patients taking controlled released aspirin 325 mg than in patients taking entero-coated aspirin at the same dose. In particular, gastric erosion per patient were 1.57 with Controlled released aspirin 325 compared to 5.48 with entero-coated aspirin product, or a reduction of 70% ($p<0.001$). Concerning haemorrhagic event, 0.3 events per patient were observed with controlled released aspirin 325 compared to 2.96 with conventional aspirin ($p<0.001$). In addition, a 3.09 petechia per patient were observed with controlled released aspirin compared to 7.35 with the comparator ($p<0.001$).
These very positive results for controlled released aspirin could be explained by the biochemical selectivity of the product which inhibits platelets COX-1 and consequently thromboxan (TXB2), the platelet aggregant prostanoids, which sparing prostacyclin (PGI2), the systemic cytoproctective prostaglandin generated by endothelial COX-1.

[0129] Although, this result is very positive for GI tract safety, it open the door to an improvement of the controlled released aspirin directed toward a decrease of the level of safety events especially those observed in gastro intestinal tract. It is worthwhile noticing that if the number of adverse events is significantly decreased using Controlled released aspirin compared to conventional aspirin, the GI tact events (i.e. erosion and petechia) are still measurable and could led to some safety concerns for chronic use.

[0130] The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. Modifications and variations of the above-described embodiments of the invention are possible without departing from the invention, as appreciated by those skilled

in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described, which merely illustrate preferred embodiments.

Claims

1. An oral pharmaceutical formulation notably for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event,

   • comprising a combination of at least one active principle for treating a chronic cyclooxygenase (COX)-2 mediated disease or condition and of microcapsules for the controlled release of acetylsalicylic acid (ASA), in the gastrointestinal environment,
   • said microcapsules:

   - having an in vitro release profile, in 0.05M potassium dihydrogenophosphate/sodium hydroxide buffer medium pH 6.8, such that 70% of the acetylsalicylic acid is released over a period of time of between 2 and 20 hours, and
   - inhibiting cyclooxygenase COX-1 in portal vein which limits the production of thromboxane while maintaining cyclooxygenase COX-1 in systemic blood stream and hence limiting the inhibition of the production of prostaglandin and prostacyclin, to protect the gastric endothelium and to maintain its vasodilatation properties.

2. An oral pharmaceutical formulation according to claim 1, wherein the active principle for treating a chronic cyclooxygenase-2 mediated disease or condition, is selected in the class of the Non Steroidal Anti Inflammatory Drugs (NSAIDs).

3. An oral pharmaceutical formulation according to claim 1 or 2, wherein the active principle for treating a chronic cyclooxygenase-2 mediated disease or condition, is selected in the sub-class of the class of NSAIDs comprising the inhibitors of COX-2.

4. An oral pharmaceutical formulation according to claim 1, comprising at least one gastric acid suppressing agent increasing the pH of the stomach just enough to minimize the damage resulting from the residual amount of non-deacetylated acetylsalicylic acid coming from the liver and the portal blood circulation and entering the systemic blood circulation.

5. An oral pharmaceutical formulation according to claim 4, wherein the gastric acid suppressing agent is a proton pump inhibitor (ppi).

6. An oral pharmaceutical formulation according to claim 1, wherein the microcapsules being orally ingestible in a dose and comprising particles of acetylsalicylic acid with a mean diameter below or equal to 1000 μm, which are coated and designed so that, when ingested orally in a single administration of a dose of between 50 and 325 mg of ASA, they induce moderate acetylsalicylic acid absorption kinetics in vivo in man, extending over at least 24 hours, said acetylsalicylic acid absorption being less than or equal to 10% by weight of the absorbed fraction of D at a time t after ingestion of 0.4 hour, less than or equal to 50% by weight of the absorbed fraction of D at t=3.9 hours, and less than or equal to 90% by weight of the absorbed fraction of D at t=23 hours, t being given to within +/-10%.

7. An oral pharmaceutical formulation according to claim 1, wherein the dose of acetylsalicylic acid in the microcapsules is comprised between 60 and 320 mg, preferably between 75 and 310 mg.

8. An oral pharmaceutical formulation according to claim 4, wherein the dose of gastric acid suppressing agent is comprised between 1 and 130 mg, preferably between 2 and 120 mg.

9. An oral pharmaceutical formulation according to claim 1 and 4:

   a) the dose of acetylsalicylic acid in the controlled release acetylsalicylic acid microcapsules is comprised between 50 and 325 mg;
   b) the dose of gastric acid suppressing agent is comprised between 5 and 120 mg;
   c) it is a once-a-day administration form.

10. An oral pharmaceutical formulation according to claim 9 including at least one immediate release gastric acid suppressing agent form.

11. An oral pharmaceutical formulation according to claim 1 and 4:

    i. wherein the dose of acetylsalicylic acid in the microcapsules is comprised between 50 and 325 mg;
    ii. wherein the dose of gastric acid suppressing agent is comprised between 5 and 120 mg;
    iii. which is a twice-α-day administration form.

12. An oral pharmaceutical formulation according to claim 11 including at least one immediate release acetylsalicylic acid form.

13. An oral pharmaceutical formulation according to claim 11 including at least one immediate release gastric acid suppressing agent form.

14. An oral pharmaceutical formulation according to claim 1, which is designed so that it induces reduction of bleeding and pitichia, notably, in the stomach during the treatment.

15. An oral pharmaceutical formulation according to claim 1, which is designed so that it improves the healing process, notably, in the stomach during the treatment.

16. An oral pharmaceutical formulation according to claim 1, comprising at least one active principle different from ASA, gastric acid suppressing agent and active principle for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition.

17. An oral pharmaceutical formulation according to claim 16, wherein the active principle different from ASA, gastric acid suppressing agent and active principle for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition, is selected in the group comprising:

- the cardiovascular drugs acting as anti-platelets;
- the cardiovascular drugs acting as beta-blockers;
- the cardiovascular drugs acting as ACE inhibitors;
- and any of their associations.

18. An oral pharmaceutical formulation according to claim 16, wherein the active principle different from acetylsalicylic acid and gastric acid suppressing agent is selected in the group of the anti-inflammatory drugs.

19. An oral pharmaceutical formulation according to claim 16, wherein the active principle different from acetylsalicylic acid gastric acid suppressing agent and active principle for treating a chronic cyclooxygenase(COX)-2 mediated disease or condition, is selected in the group of the anti-diabetic drugs.

20. An oral pharmaceutical formulation according to claim 6, wherein the acetylsalicylic acid microcapsules are so designed that the absorption takes place over a period of between 24 and 48 hours in the following manner:
10% of the absorbed fraction of D at t=0.4 to 5 hours,
50% of the absorbed fraction of D at t=3.9 to 25 hours, and 90% of the absorbed fraction of D at t=23 to 45 hours.

21. An oral pharmaceutical formulation according to claim 1, wherein the coating agent of the acetylsalicylic acid microcapsules represents 5 to 50% by weight, based on the total mass of said microcapsules.

22. An oral pharmaceutical formulation according to claim 1, wherein the coating of the acetylsalicylic acid microcapsules comprises at least one layer which controls the modified release of agent, the composition of said layer is as follows:

A. at least one film-forming (co)polymer (A) that is insoluble in the fluids of the gastrointestinal tract;
B. optionally, at least one water-insoluble hydrophilic film-forming (co)polymer (B) that is insoluble in the fluids of the gastrointestinal tract, carrying groups that are ionized in the fluids of the gastrointestinal tract,
C. at least one (co)polymer (C) that is soluble in the fluids of the gastrointestinal tract;
D. at least one plasticizer (D);
E. optionally, at least one surfactant and/or lubricant (E).

23. An oral pharmaceutical formulation according to claim 22, wherein:

* (A) is selected from the group of following products:

- non-water-soluble derivatives of cellulose,
- polyvinyl acetates,
- mixtures thereof;

* (B), when it is present, is chosen from water-insoluble charged acrylic derivatives,;
* (C) is chosen from

- nitrogenous (co)polymers;
- water-soluble derivatives of cellulose,
- polyvinyl alcohols (PVAs),
- polyoxyethylenes (POEs),
- and mixtures thereof;

* (D) is chosen from the group comprising:

- cetyl alcohol esters,
- glycerol and its esters,
- phthalates, citrates, sebacates, adipates,
- azelates,
- benzoates,
- plant oils,
- fumarates, malates, oxalates, succinates,
- butyrates,
- salicylic acid,
- triacetin,

- malonates,
- castor oil ,
- and mixtures thereof;

* (E) is chosen from the group comprising:

- anionic surfactants,
- and/or nonionic surfactants.

24. An oral pharmaceutical formulation according to claim 33, wherein the composition of the modified-release layer is as follows:

A. the film-forming polymer(s) (A) is (are) present in a proportion of 10 to 90%, by weight on a dry basis relative to the total mass of the coating composition;
B. the hydrophilic water-insoluble film-forming polymer(s) (B) is (are) present in a proportion of 0 to 90%, by weight on a dry basis relative to the total mass of the coating composition;
C. the soluble polymer(s) (C) is (are) present in a proportion of 2 to 25, by weight on a dry basis relative to the total mass of the coating composition;
D. at least one plasticizer (D) is (are) present in a proportion of 2 to 20, by weight on a dry basis relative to the total mass of the coating composition;
E. the optional surfactant(s) and/or lubricant(s) (E) is (are) present in a proportion of 2 to 20, by weight on a dry basis relative to the total mass of the coating composition.

25. An oral pharmaceutical formulation according to claim 1, wherein the diameter of the acetylsalicylic acid microcapsules is less than or equal to 1000 μm,.

26. An oral pharmaceutical formulation according to claim 1, wherein the acetylsalicylic acid microcapsules are obtained from particles of acetylsalicylic acid having a size of between 250 and 800 μm before the coating operation.

27. An oral pharmaceutical formulation according to claim 1, wherein the proportion of acetylsalicylic acid in the microcapsules (expressed as % by weight on a dry basis relative to the total mass of the microcapsules) is between 5 and 80.

28. An oral pharmaceutical formulation according to claim 1, provided in the form a galenical unit selected in the group comprising: a sachet of powder, a sachet of a powder for multidose suspension to be reconstituted, a tablet or a gelatin capsule.

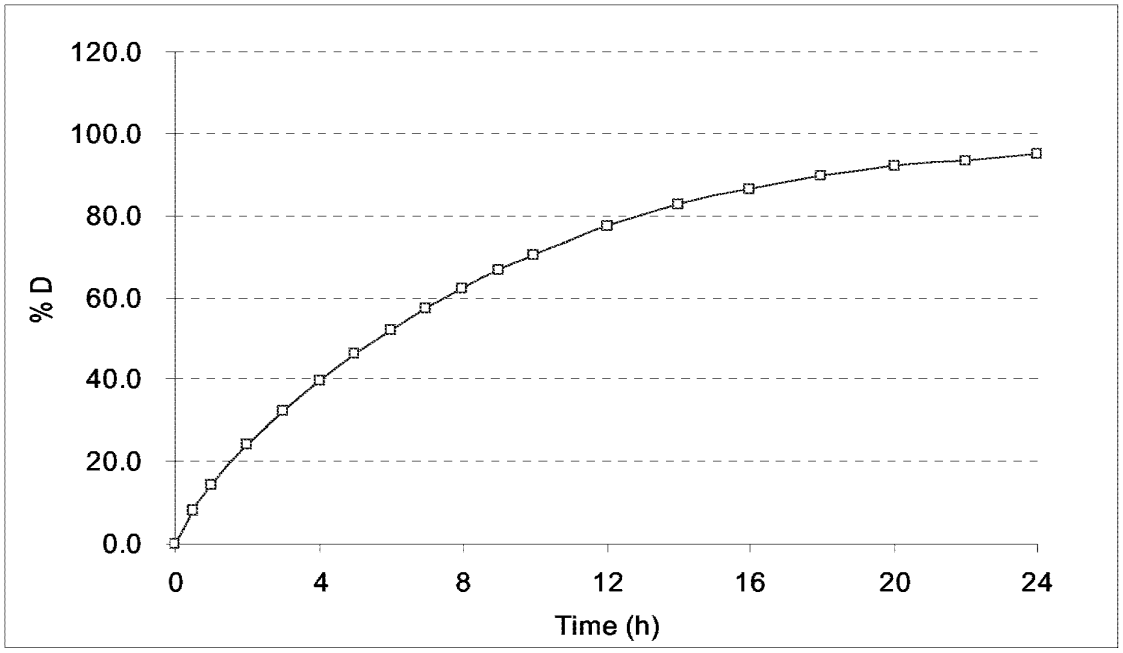

Figure 1

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 05 30 0407

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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X	EP 0 103 991 A (BRISTOL-MYERS COMPANY) 28 March 1984 (1984-03-28) * page 2, last paragraph - page 3, paragraph 1 * * examples * * claims * -----	1-4,6,7, 14-16, 20-28	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	19 October 2005	Epskamp, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 05 30 0407

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	BECKER JAN C ET AL: "Current approaches to prevent NSAID-induced gastropathy - COX selectivity and beyond" BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, vol. 58, no. 6, December 2004 (2004-12), pages 587-600, XP002349932 ISSN: 0306-5251 * abstract * * page 589, left-hand column, paragraph 3 - page 593, left-hand column, paragraph 1 * * table 3 *	1-28	
D,A	US 5 603 957 A (BURGUIERE ET AL) 18 February 1997 (1997-02-18) * column 1, line 63 - line 67 * * column 3, line 23 - line 37 * * examples * * claims *	1-28	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	19 October 2005	Epskamp, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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& : member of the same patent family, corresponding document

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19-10-2005

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(12) UK Patent Application (19) GB (11) 2 105 193 A

(21) Application No **8225177**
(22) Date of filing **3 Sep 1982**
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(43) Application published
23 Mar 1983
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392 444 446 44Y 451 453
45Y 540 54Y 565 56Y J
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(54) **Pharmaceutical compositions containing non-steroidal anti-inflammatory agents**

(57) The invention relates to a pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug together with the histamine H_2-antagonist ranitidine or a physiologically acceptable salt thereof. The histamine H_2-antagonist reduces gastric mucosal lesions caused by the anti-inflammatory drug.

GB 2 105 193 A

SPECIFICATION

Pharmaceutical compositions

This invention relates to improvements in the formulation of anti-inflammatory drugs.

Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin and ibuprofen, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric ulceration when administered orally. This side effect may be further enhanced in combination with other factors such as stress. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

Ranitidine is the approved name for N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl-N'-methyl-2-nitro-1,1-ethenediamine which is described and claimed in British Patent Specification 1,565,966. It is a potent histamine H_2-antagonist which may be used in the treatment of conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator. It has now been discovered that mucosal lesions of the gastrointestinal tract caused by systemic non-steroidal anti-inflammatory drugs can be significantly reduced by co-administering ranitidine.

The present invention provides a pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug ad ranitidine or a physiologically acceptable salt thereof.

Particularly useful pharmaceutical compositions according to the invention are those in a form suitable for oral or rectal administration.

The systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, fepra-zone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac and tolmetin. They may be used in the pharmaceutical compositions of the invention in their usual dosage amounts, e.g. 50mg - 1 g of aspirin, 10 - 100mg of indomethacin and 100 - 500mg of ibuprofen per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question.

It is preferred that ranitidine should be employed in the composition in the form of a physiologically acceptable salt. Such salts include salts of inorganic or organic acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate and fumarate salts. The hydrochloride salt is particularly preferred. The amount of ranitidine, preferably in the form a physiologically acceptable salt, employed in the pharmaceutical composition of the invention will be an amount sufficient to reduce the gastrointestinal distress caused by the anti-inflammatory drug and will preferably be in the range of 10 - 200mg per dosage unit.

The pharmaceutical compositions of the invention may be presented in a conventional manner with the aid of at least one pharmaceutical carrier or excipient. The composition may take the form of, for example, tablets, capsules, powders, granules, solutions, syrups, suspensions, or suppositories, prepared by conventional means with acceptable excipients. The composition may thus contain as excipients, for example, binding agents, compression aids, fillers, lubricants, disintegrants and wetting agents. If desired, other active ingredients may also be present in such compositions. Tablets may be coated in conventional manner, for example, with a suitable film-forming material such as methyl cellulose, ethyl cellulose and/or hydroxypropylmethyl cellulose or with sugar. Liquid preparations may also contain, for example, edible oils such as peanut oil. Suppositories may contain, for example, fat-soluble or water miscible bases.

The pharmaceutical compositions of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the anti-inflammatory drug and the ranitidine or ranitidine salt may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine.

Alternatively, the pharmaceutical compositions of the invention may be presented in a suitable controlled release form so that the ranitidine or its salt is rapidly made available for absorption and the non-steroidal anti-inflammatory drug is released more slowly. The pharmaceutical compositions may thus be presented for oral or rectal administration in a conventional manner associated with controlled release forms.

The pharmaceutical compositions of the invention maybe used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteoarthritis and ankylosing spondylitis, and for analgesia in conditions such as dysmenorrhoea, especially where the use of the anti-inflammatory drug is limited by gastro-intenstinal side-effects.

In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

Example 1 - TABLETS

(a)		mg/tablet
	Ranitidine hydrochloride	168.00*
	Ibuprofen	400.00
	Lactose	387.00
	Hydroxypropyl methylcellulose	5.00
	Sodium starch glycollate	30.00
	Magnesium stearate	10.00
	Compressive weight	1000.00

*Equivalent to 150 mg ranitidine base

The ranitidine hydrochloride and ibuprofen are sieved through a 250 μm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using 12.5mm punches.

(b)		mg/tablet
	Ranitidine hydrochloride	168.00
	Indomethacin	50.00
	Microcrystalline cellulose	79.00
	Magnesium stearate	3.00
	Compression weight	300.00

The ranitidine hydrochloride and indomethacin are blended with the microcrystalline cellulose and magnesium stearate and compressed using 9.5mm punches.

Example 2 - CAPSULES

(a)		capsule
	Ranitidine hydrochloride	168.00
	Ibuprofen	400.00
	Starch 1500**	228.00
	Magnesium stearate	4.00
	Fill weight	800.00

** A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

The ranitidine hydrochloride and ibuprofen are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

(b)		mg/capsule
	Ranitidine hydrochloride	168.00
	Indomethacin	50.00
	Starch 1500	80.50
	Magnesium stearate	1.50
	Fill weight	300.00

The ranitidine hydrochloride and indomethacin are sieved through a 250 μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 2 hard gelatin capsules using a suitable filling machine.

CLAIMS

1. A pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug and ranitidine or a physiologically acceptable salt thereof.
2. A phrarmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac or tolmetin.
3. A pharamaceutical composition as claimed in claim 1 or 2, also including at least one pharmaceutical carrier or excipient.
4. A pharmaceutical composition as claimed in any of claims 1 to 3 in a form suitable for oral or rectal administration.
5. A pharmaceutical composition as claimed in claim 4 in which the anti-inflammatory drug is indomethacin or ibuprofen.
6. A pharmaceutical composition as claimed in claim 5 which contains 10 - 100 mg of indomethacin or 100 - 500 mg of ibuprofen per dosage unit and 10 - 200 mg of ranitidine or a physiologically acceptable salt thereof per dosage unit.
7. A pharmaceutical composition as claimed in any of claims 1 to 6 in which the ranitidine is used in the form of the hydrochloride salt.

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337 338 364 366 368 36Y 397 462 551 614 620 630 660
670 680 694 697 699 802 80Y AA QL RL RM
U1S 1318 C2C

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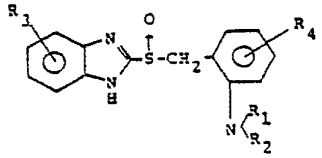
None

(58) Field of search
C2C

Reprinted front page

(54) **Benzimidazole derivatives**

(57) Benzimidazole derivatives of the formula



(where R_1 is hydrogen, C_{1-8} alkyl, cycloalkyl, phenyl or aralkyl, R_2 is hydrogen or C_{1-8} alkyl, or R_1 and R_2 together form a ring with the adjacent nitrogen atom, and R_3 and R_4 are hydrogen, halogen, trifluoromethyl, alkyl, alkoxy, alkoxycarbonyl or amino) are antiulcer agents.

GB 2 163 747 A

Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

SPECIFICATION

Benzimidazole derivatives, process for preparing the same and antiulcer agents containing the same

This invention relates to novel benzimidazole derivatives, to a process for preparing such derivatives and to antiulcer agents containing such derivatives.

As is well known in the art to which the present invention relates, $H^+ + K^+$ATPase plays a principal role in the final secretion mechanism of gastric acid in stomach cells [Scand. J. Gastroenterol., *14*, 131–135 (1979)]. Norinium bromide is known as a substance having $H^+ + K^+$ATPase inhibitory activity [Proceeding of the Society for Experimental Biology and Medicine, *172*, 308–315 (1983)].

On the other hand, 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole [Omeprazole] has been developed as an antiulcer compound having $H^+ + K^+$ATPase inhibitory activity [Am. J. of Physiol., *245*, G64–71 (1983)].

There is a keen demand for new compounds having a more enhanced effect on $H^+ + K^+$ATPase inhibition than these known compounds.

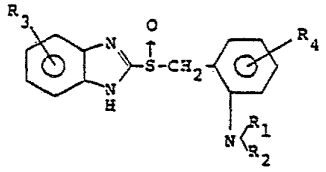
With the foregoing in view, the present Applicants have conducted extensive research and have now found that certain benzimidazole derivatives exhibit excellent suppressive effects against the secretion of gastric acid owing to their specific $H^+ + K^+$ATPase inhibitory effects, coupled with cytoprotective action.

It is an object of the present invention, therefore, to provide new benzimidazole derivates which are useful for antiulcer purposes.

Another object of the invention is to provide a novel process for preparing such benzimidazole derivatives.

Still another object of the invention is to provide antiulcer agents containing such benzimidazole derivatives as an effective component thereof.

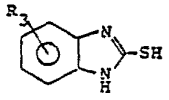
According to a first aspect of the present invention, there is provided benzimidazole derivatives represented by the formula (I),



(I)

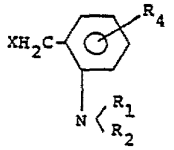
where R_1 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms, or a cycloalkyl, phenyl or aralkyl group; R_2 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms; or R_1 and R_2 together form a ring with the adjacent nitrogen atom; and R_3 and R_4 are in each case a hydrogen or halogen atom, or a trifluromethyl, lower alkyl, lower alkoxy, lower alkoxycarbonyl or amino group, and may be the same or different.

According to a second aspect of the invention there is provided a process for preparing a benzimidazole derivative as specified above, which comprises reacting a 2-mercaptobenzimidazole represented by the formula (II),



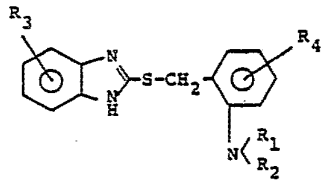
(II)

where R_3 is as defined above, with a 2-aminobenzyl compound represented by the formula (III),



(III)

where R_1, R_2 and R_4 are as defined above and X is a reactive group, thereby forming a compound represented by the formula (IV),

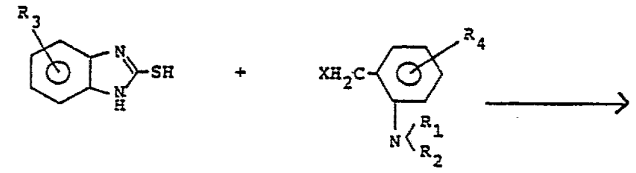


(IV)

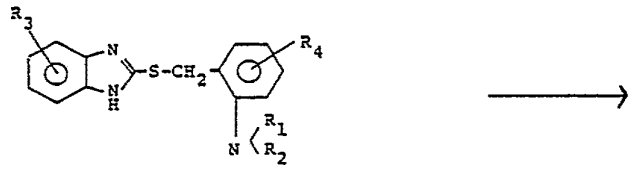
where R_1, R_2, R_3 and R_4 are as defined above, and then oxidizing the compound of the formula (IV).

According to a third aspect of the invention, there is provided an antiulcer agent comprising as an effective component thereof, a benzimidazole derivative as specified above.

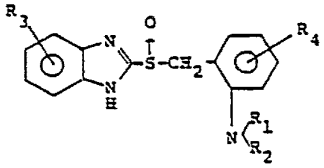
Benzimidazole derivatives of the formula (I) according to the present invention may be prepared, for example, by reacting a 2-mercaptobenzimidazole of the formula (II) with a 2-aminobenzyl compound of the formula (III) to form a compound of the formula (IV) and then oxidizing the compound (IV) in accordance with the following reaction scheme:—



(II) (III)



(IV)



(I)

where X is a reactive group and R_1 to R_4 inclusive are as defined previously.

The starting compound (II) useful for a process according to the invention is already known in the art. The compound (II) may be prepared, for example, by the process described in Org. Synth., *30*, 56. The reactive group X in the other starting compound (III) may be a halogen atom, such as chlorine or bromine, or a sulfonyloxy group such as a methylsulfonyloxy or toluenesulfonyloxy group. The compound (III) in which a chlorine atom is bonded as X may be prepared, for example, by the process disclosed in J. Chem. Soc., 98–102 (1942). Both of these starting compounds can also be in the form of salts.

The reaction between the compound (II) and the compound (III), or between their respective salts, may be effected by stirring them in an inert solvent, such as toluene, benzene, ethanol or acetone, at a temperature of from room temperature to the refluxing temperature, for 30 minutes to 24 hours. In such case, it is preferred to have an alkaline compound such as NaOH, KOH, K_2CO_3 or $NaHCO_3$ present in the reaction system, so that the resulting acid can be neutralised.

The compound (IV) may be converted to its corresponding oxo compound by any method known *per se*. For example, this conversion may be achieved by oxidizing the compound (IV) with an oxidizing agent, for example, an organic peracid such as m-chloroperbenzoic acid, hydrogen peroxide, sodium hypochlorite or sodium metaperiodate. The reaction may be effected

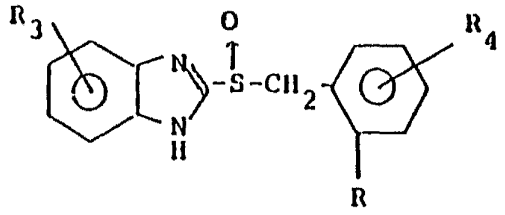
in an inert solvent such as chloroform, dichloromethane, methanol or ethyl acetate, at −30 to +50°C, preferably at −15 to +5°C.

The pharmacological effects of some compounds typical of the invention were tested. The test results are given below.

(1) $H^+ + K^+$ATPase inhibitory effects:

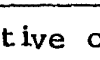
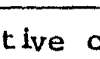
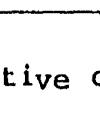
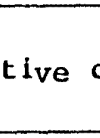
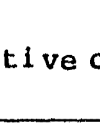
Following the method of Forte et al [J. Applied Physiol., *32*, 714–717 (1972)], gastric acid secretory cells of a rabbit gastric mucosa were isolated and vesicle containing $H^+ + K^+$ATPase was prepared by centrifuging the cells in Ficoll of discontinuous density gradient. After the enzyme was incubated at room temperature for 25 minutes in 0.5 ml of a solution which contained 5 mM of an imidazole buffer (pH 6.0) and 2×10^{-4} M of each test compound, the mixture was heated to 37°C at which it was allowed to stand for further 5 minutes. To the mixture was added 0.5 ml of a solution which contained 4 mM of magnesium chloride, 80 mM of an imidazole buffer (pH 7.4), 20 mM of potassium chloride and 4 mM of ATP. The resulting mixture was reacted at 37°C for 15 minutes and 1 ml of a 24% solution of trichloroacetic acid was then added to terminate the reaction. The inorganic phosphorus liberated was quantitatively analyzed by the method proposed by Taussky and Shorr [J. Biol. Chem., *202*, 675–685 (1953)]. The K^+-dependent activity of the ATPase was determined by subtracting its activity obtained when no potassium chloride was contained. The results are summarized in Table 1 in which Inventive compounds 1 to 19 are the compounds obtained in several of Examples 1 to 26 and Comparative compound 1 is the compound obtained in Reference Example 1, all of which examples are set out below.

Table 1



Test compound	R	R_3	R_4	$H^+ + K^+$ ATPase inhibitory effect (%)
Comparative compound 1	H	H	H	0
Inventive compound 1	NH_2	H	H	88.2
Inventive compound 2	$NHCH_3$	H	H	100
Inventive compound 3	$N(CH_3)_2$	H	H	100
Inventive compound 4	$N(CH_3)_2$	$5\text{-}OCH_3$	H	100
Inventive compound 5	$N(CH_3)_2$	$5\text{-}COOCH_3$	H	97.9
Inventive compound 6	$N(CH_3)_2$	$5\text{-}CH_3$	H	100
Inventive compound 7	$N(CH_3)_2$	5-Cl	H	100
Inventive compound 8	$N(CH_3)_2$	$5\text{-}CF_3$	H	100

Table 1 (cont'd)

Test compound	R	R_3	R_4	$H^+ + K^+$ ATPase Inhibitory effect (%)
Inventive compound 9	$N(CH_3)_2$	4-CH_3	H	100
Inventive compound 10	$N(CH_3)_2$	H	6-CH_3	100
Inventive compound 11	$N(CH_3)_2$	H	4-Cl	100
Inventive compound 12	$N(CH_3)_2$	H	5-OCH_3	100
Inventive compound 13	$N(CH_3)_2$	H	5-CH_3	100
Inventive compound 14		H	H	82.3
Inventive compound 15		H	H	100
Inventive compound 16		H	H	100
Inventive compound 17		H	H	66.7
Inventive compound 18		H	H	77.9
Inventive compound 19		H	H	100

(2) Inhibitory effects against the secretion of gastric acid:

Male Donryu rats were used which had a body weight of 200 to 250 g and fasted (while allowing free access to water) for 24 hours in accordance with the usual method [Shay, H. et al, Gastroenterology, *5*, 43–61 (1945)]. Under ether anesthesia the pylorus was ligated and each test compound was administered intraduodenally. Four hours later, each rat was killed and the stomach was removed to collect the gastric juice. The inhibitory effect was determined by comparing the acid output which was obtained by titration to pH 7.0 with 0.1–N NaOH by means of an automatic titrator, with the corresponding value of a control rat prepared in the same manner except that a vehicle alone was administered. The results are given in Table 2.

Table 2

Test compound	Dose (mg/kg)	Suppresive effect against secretion of gastirc acid (%)
Comparative compound 1	100	44
Cimetidine	100	80.3
	30	59.1
	10	25.3
Inventive compound 3	100	99.3
	30	94.3
	10	62.9
Inventive compound 7	100	77.5
Inventive compound 9	100	95.7
Inventive compound 10	100	98.7
Inventive compound 11	100	72.8
Inventive compound 13	100	97.9
Inventive compound 15	100	91.5
	30	71.7
	10	48.8

(3) Inhibitory effects against four gastric lesion models:

Four different types of gastric lesion models were induced in male Donryu rats (180 to 240 g) which had been deprived of food but allowed free access to water for 24 to 48 hours prior to experiments.

a) Shay ulcers:

Under ether anesthesia the abdomen of each rat fasted for 48 hours was incised and the pylorus ligated. Fourteen hours later, the animal was killed and the stomach was examined for any ulcer in the forestomach. Each test compound or a vehicle alone was given intraduodenally in a volume of 0.2 ml/100 g body weight immediately after pylorus ligation.

b) Water-immersion stress-induced erosions:

Rats fasted for 24 hours before experiments were placed in a restraint cage. The animals were immersed vertically to the level of the xiphoid process in a water bath (21°C) for 7 hours and then killed. The stomach of each rat was removed and inflated by injecting 10 ml of 1% formalin to fix the inner and outer layers of the gastric walls. This formalin treatment was performed in all of the following experiments. Subsequently, the stomach was incised along a greater curvature and examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 10 minutes before stressing.

c) Indomethacin-induced erosions:

Indomethacin suspended in a 0.2% CMC solution was given subcutaneously to rats in a dose of 25 mg/kg, which rats had been fasted for 24 hours before experiments. Seven hours later, each animal was killed and the stomach was examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 10 minutes before indomethacin treatment.

d) HCl-EtOH-induced erosions:

A hydrochloric acid-ethanol solution (150 mM HCl in 60% EtOH) was given orally to rats in a dose of 1 ml/200 g, which rats had been fasted for 24 hours before experiments. One hour later, each animal was killed and the stomach was examined for any erosion in the glandular portion. Each test compound or a vehicle alone was given orally 30 minutes before ethanol treatment.

The results are shown in Table 3-A to Table 3-D.

Table 3-A

a) Shay ulcers

Test compound	mg/kg id	Inhibition (%)
Inventive compound 3	3	28
	10	68
	30	69
Cimetidine	100	−29
	300	44

Table 3-B

b) Water-immersion stress-induced erosions

Test compound	mg/kg po	Inhibition (%)
Inventive compound 3	30	69
	100	97
" 4	30	27
	100	95
" 10	30	39
	100	91
" 12	30	41
	100	74
" 13	30	64
	100	88
Cimetidine	60	49
	200	87

Table 3-C

c) Indomethacin-induced erosions

Test compound	mg/kg po	Inhibition (%)
Inventive compound 3	30	7.0
	100	88
Cimetidine	30	39
	100	76

Table 3-D

d) HCl-EtOH-induced erosions

Test compound	mg/kg po	Inhibition (%)
Inventive compound 3	10	89
	30	100

(4) Acute toxicity test:

To male Wistar rats having a body weight of 80 to 90 g were intraperitoneally administered suspensions of certain inventive compounds which had been suspended in 0.2% CMC physiological saline. The rats were observed for 7 days. The results are shown in Table 4.

Table 4

Inventive compound	LD_{50}
10	600 mg/kg or more
12	500 - 600 mg/kg
13	600 mg/kg or more
18	300 mg/kg or more
19	300 mg/kg or more

Moreover, male ICR mice having a body weight of 23 to 26 g were orally administered with Inventive compound 3. The mice were then observed for 3 days. The MLD was found to be 1,000 mg/kg or more.

The compounds (I) of the present invention may be administered either orally or parenterally. Preparation forms for oral administration may include for example tablets, capsules, powder, granules, and syrup. Preparation forms for parenteral administration include injectable preparations and the like. For the formulation of these preparations, there may be used excipients, disintegrants, binders, lubricants, pigments, diluents and like materials, such as are commonly employed in the art. The excipients may include dextrose, lactose and the like. Starch, carboxymethylcellulose and the like may be used as the disintegrants. Magnesium stearate, talc and the like may be used as the lubricants. The binders may be hydroxypropylcellulose, gelatin, polyvi-

nylpyrrolidone and the like.

The dose may usually be about 1 mg/day to 50 mg/day in the case of an injectable preparation and about 10 mg/day to 500 mg/day in the case of oral administration, both for an adult. The dose may be either increased or decreased depending on the age and other conditions.

The following reference and specific examples are given to further illustrate the present invention, but it is to be noted that the invention is not limited thereto.

Reference Example 1

(1) 2-Benzylthiobenzimidazole:

To a solution containing 1.47 g of NaOH dissolved in a mixed solvent consisting of 5 ml of water and 50 ml of ethanol were added 5 g of 2-mercaptobenzimidazole and 4.2 g of benzyl chloride. The resulting solution was heated under reflux for one hour. The reaction mixture was poured into ice water and crystals precipitated were collected by filtration to give 7.7 g of crude crystals (96%). The crystals were recrystallized from ethanol to obtain 5.9 g of 2-benzylthiobenzimidazole as colorless needles. m.p. 184°C.

(2) 2-Benzylsulfinylbenzimidazole (Comparative compound 1):

In 30 ml of chloroform was dissolved 4.5 g of 2-benzylthiobenzimidazole, followed by gradual addition of 4.6 g of m-chloroperbenzoic acid (purity: 70%) at temperatures below 0°C. The mixture was stirred for 20 minutes and crystals deposited were then collected by filtration. The filtrate was washed successively with a saturated $NaHCO_3$ solution, sodium thiosulfate and saturated brine and the filtrate thus washed was dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give 4.3 g of crude crystals. The crystals were recrystallized from ethanol to obtain 2.0 g of 2-benzylsulfinylbenzimidazole as colorless crystals. m.p. 169–170°C.

Example 1

(1) 2-(2-Aminobenzylthio)benzimidazole:

In 40 ml of ethanol were dissolved 1.8 g of 2-aminobenzyl chloride hydrochloride and 1.5 g of 2-mercaptobenzimidazole. While shielding light, the resulting solution was stirred at room temperature for 23 hours. Powder precipitated was collected by filtration. After being washed successively with ethanol and ether, the powder was recrystallized from a mixed solvent of methanol and ether to obtain 1.8 g of 2-(2-aminobenzylthio)benzimidazole hydrochloride as colorless granular crystals. m.p. 207°C (decomposed).

(2) 2-(2-Aminobenzylsulfinyl)benzimidazole (Inventive compound 1):

One gram of 2-(2-aminobenzylthio)benzimidazole hydrochloride was dissolved in ice water. The solution was neutralized with 512 mg of sodium bicarbonate, followed by extraction with chloroform. The resulting chloroform solution was washed with saturated brine. After drying the chloroform solution with anhydrous sodium sulfate, the solvent was distilled off under reduced pressure at room temperature. Thereafter, 0.5 g of the thus obtained 2-(2-aminobenzylthio)benzimidazole was dissolved in a mixed solvent which consisted of 30 ml of chloroform and 3 ml of methanol. The resulting solution was chilled to −10°C and added little by little with 0.4 g of m-chloroperbenzoic acid (purity: 70%). The mixture was then stirred at the same temperature for 10 minutes. Light yellowish powder precipitated was collected by filtration. After being washed with ether, the powder was recrystallized from a mixed solvent of methanol and ether to obtain 0.33 g of 2-(2-aminobenzylsulfinyl)benzimidazole as white crystalline powder. m.p. 150°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3200, 1440, 1400, 1260, 1035

^1H–NMR ($CDCl_3$) δ:

4.40 and 4.64 (each d, 2H, J=14HZ,

–SCH_2–), 6.24–7.80 (m, 8H, aromatic protons)

Example 2

(1) 2-(2-Methylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (1.8 g) and 2-methylaminobenzyl chloride hydrochloride (2.5 g) in 10 ml of ethanol were stirred at room temperature for 30 minutes. Ten milliliters of ether was added and crystals precipitated were collected by filtration. The crystals were washed with ether to give 3.5 g of 2-(2-methylaminobenzylthio)benzimidazole hydrochloride (85%). The crystals

were suspended in ethyl acetate and then neutralized by addition of a saturated $NaHCO_3$ solution. After being washed with brine, the organic layer was dried with anhydrous sodium sulfate. After distilling off the solvent under reduced pressure, the residue was recrystallized from acetonitrile to obtain 1.87 g of 2-(2-methylaminobenzylthio)benzimidazole as colorless crystals. m.p. 107–108°C.

(2) 2-(2-Methylaminobenzylsulfinyl)benzimidazole (Inventive compound 2):

2-(2-Methylaminobenzylthio)benzimidazole (1.0 g) was dissolved in 20 ml of chloroform. After chilling the solution to −10°C, 0.87 g of m-chloroperbenzoic acid (purity: 70%) was added little by little. After being stirred at the same temperature for 10 minutes, the mixture was washed successively with a saturated $NaHCO_3$ solution and saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was recrystallized from acetonitrile to obtain 0.43 g of 2-(2-methylaminobenzylsulfinyl)benzimidazole as white crystalline powder. m.p. 122.5–124°C.

IR ν_{max}^{KBr} cm^{-1}: 3220, 1600, 1500, 1435, 1400, 1305, 1265, 1045

^1H–NMR ($CDCl_3$)δ:

2.52 (s, 3H, $-NCH_3$), 4.36 and 4.60 (each d, 2H, J=16HZ,

$-SCH_2-$), 6.30–7.80 (m, 8H, aromatic protons)

Example 3

(1) 2-(2-Dimethylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (4.73 g) was dissolved in 150 ml of ethanol, followed by addition of 6.18 g of 2-dimethylaminobenzyl chloride hydrochloride. The mixture was stirred at room temperature for 30 minutes. Crystals precipitated were collected by filtration. A saturated $NaHCO_3$ solution was added to the crystals, followed by extraction with chloroform. The chloroform layer was washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was recrystallized from a mixed solvent of chloroform and acetonitrile to obtain 5.39 g of 2-(2-dimethylaminobenzylthio)benzimidazole as colorless crystals. m.p. 164°C.

(2) 2-(2-Dimethylaminobenzylsulfinyl)benzimidazole (Inventive compound 3):

(a) 2-(2-Dimethylaminobenzylthio)benzimidazole (4.8 g) was dissolved in a mixed solvent which consisted of 40 ml of chloroform and 5 ml of methanol. After chilling the solution to 0°C, 3.86 g of m-chloroperbenzoic acid (purity: 70%) was added little by little. Ten minutes later, a saturated $NaHCO_3$ solution was added to the reaction mixture, followed by extraction with chloroform. The chloroform solution was washed with saturated brine and then dried with anhydrous sodium sulfate. The chloroform was distilled off under reduced pressure and the residue was recrystallized from a mixed solvent of chloroform and ether to obtain 2.97 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as colorless crystals. m.p. 112°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3170, 1485, 1435, 1400, 1260, 1040

^1H–NMR ($CDCl_3$)δ:

2.62 (s, 6H, $>N(CH_3)_2$), 4.47 and 4.87 (each d, 2H, J=14Hz,

$-SCH_2-$), 6.70–7.90 (m, 8H, aromatic protons), 12.16 (br., 1H, $>NH$)

(b) 2-(2-Dimethylaminobenzylthio)benzimidazole (400 g) was dissolved in methylene chloride (1.06 l)—methanol (1.06 l). Acetic acid (212 ml) was added to the solution and the mixture was stirred until the solid was dissolved completely. After cooling the resulting solution to 2 to 5°C, 182 ml of 35% hydrogen peroxide, 123 ml of water and 8.83 g of ammonium metavanadate were added. The reaction mixture was stirred at 2 to 5°C for 9 hours. The reaction was quenched with a 20% $NaHCO_3$ solution. The organic layer was separated, washed with an aqueous $Na_2S_2O_3$ solution and with saturated brine and then dried with anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure and the residue was recrystallized from acetonitrile to obtain 317 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as colorless crystals.

(c) 2-(2-Dimethylaminobenzylthio)benzimidazole (10 g) was dissolved in a 20% NaOH solution (30 ml) and ethyl acetate (120 ml). After cooling the solution with ice water, a mixture of 70 ml of 12% NaOCl and 30 ml of 20% NaOH was added dropwise at 3 to 5°C over 80 minutes. The reaction mixture was stirred for one hour at the same temperature as just referred to. The reaction was quenched with a 10% $Na_2S_2O_3$ solution and the organic layer was washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was recrystallized from acetonitrile to obtain 7.9 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as colorless crystals.

Example 4

(1) 2-(2-Dimethylaminbenzylthio)-5-methoxybenzimidazole:

2-Mercapto-5-methoxybenzimidazole (2.70 g) was dissolved in 60 ml of ethanol, followed by addition of 3.09 g of 2-dimethylaminobenzyl chloride hydrochloride. The resulting mixture was stirred at room temperature for 30 minutes. Crystals precipitated were collected by filtration. A saturated $NaHCO_3$ solution was added to the crystals, followed by extraction with chloroform. The chloroform solution was washed with saturated brine and then dried with anhydrous sodium sulfate. The chloroform was distilled off under reduced pressure to obtain 3.85 g of 2-(2-dimethylaminobenzylthio)-5-methoxybenzimidazole as a colorless oily matter.

(2) 2-(2-Dimethylaminobenzylthio)-5-methoxybenzimidazole (2.43 g) was dissolved in a mixed solvent which consisted of 25 ml of chloroform and 2 ml of methanol. After chilling the solution to 0°C, 3.86 g of m-chloroperbenzoic acid (purity: 70%) was added little by little. Ten minutes later, a saturated $NaHCO_3$ solution was added to the reaction mixture, followed by extraction with chloroform. The chloroform solution was washed with saturated brine and then dried with anhydrous sodium sulfate, followed by removal of the chloroform by distillation under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol:50/1) and then recrystallized from a mixed solvent of ether and hexane to obtain 1.50 g of 2-(2-dimehtylaminobenzylsulfinyl)-5-methoxybenzimidazole as light yellowish crystals. m.p. 105°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3270, 1625, 1485, 1390, 1205, 1175, 1030

^{1}H–NMR ($CDCl_3$)δ:
2.63 (s, 6H, $-N(CH_3)_2$), 3.81 (s, 3H, $-OCH_3$),
4.48 and 4.85 (each d, 2H, J=15Hz,

$-SCH_2-$), 6.60–7.80 (m, 7H, aromatic protons),
12.16 (br., 1H, >N*H*)

Example 5

(1) 2-(2-Diethylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (50.0 g) was suspended in 500 ml of ethanol, followed by addition of 77.9 g of 2-diethylaminobenzyl chloride hydrochloride. The resulting mixture was stirred at room temperature for 30 minutes. Crystals precipitated were collected by filtration and added with a saturated $NaHCO_3$ solution, followed by extraction with ethyl acetate. The ethyl acetate layer was washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was dissolved in ethanol. The resulting solution was treated with activated carbon. The activated carbon was removed by filtration and the ethanol by distillation under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate and hexane to obtain 88.7 g of 2-(2-diethylaminobenzylthio)benzimidazole as light brownish crystalline powder. m.p. 134–135°C.

(2) 2-(2-Diethylaminobenzylsulfinyl)bezimidazole:

2-(2-Diethylaminobenzylthio)benzimidazole (84.0 g) was dissolved in a mixed solvent which consisted of 600 ml of methylene chloride and 150 ml of methanol. After chilling the solution to 0°C, 79.8 g of m-chloroperbenzoic acid (purity: 60%) was added little by little. Ten minutes later, a saturated $NaHCO_3$ solution was added to the reaction mixture, followed by extraction with methylene chloride. The resulting methylene chloride solution was dried with anhydrous sodium sulfate. The methylene chloride was distilled off under reduced pressure and the residue was subjected to silica gel column chromatography (silica gel, 280 g; eluent, acetone:hex-

ane=1:2 v/v). The eluate was dissolved in a 1:8 v/v mixed solvent of ethanol and hexane and crystals precipitated were removed by filtration. The filtrate was concentrated under reduced pressure. The residue was recrystallized twice from isopropyl ether to obtain 32.3 g of 2-(2-diethylaminobenzylsulfinyl)benzimidazole as colorless crystals. m.p. 110.5–112°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3200, 2980, 1490, 1400, 1270, 1015, 765, 750

^{1}H–NMR ($CDCl_3$)δ:
1.01 (t, 6H, J=7Hz, $-CH_2CH_3\times2$)
3.00 (q, 4H, J=7Hz, $-CH_2CH_3\times2$)
4.46 and 4.97 (each d, 2H, J=13Hz, $-S(=O)CH_2-$), 6.80–7.90 (m, 8H, aromatic protons),
12.41 (br., 1H, >N*H*)

Example 6
(1) 2-(2-Dimethylaminobenzylthio)-4-methylbenzimidazole:
2-Dimethylaminobenzyl chloride hydrochloride (1.26 g) was added to a suspension of 1.0 g of 2-mercapto-4-methylbenzimidazole in 10 ml of ethanol. The resulting mixture was stirred at room temperature for 2 hours. Crystals precipitated were collected by filtration. After being washed successively with ethanol and ether, the crystals were dissolved in chloroform. The chloroform solution was neutralized with a saturated $NaHCO_3$ solution, washed with saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and ether was added to the residue. Crystals precipitated were collected by filtration to obtain 13.8 g of 2-(2-dimethylaminobenzylthio)-4-methylbenzimidazole as white crystalline powder.

^{1}H–NMR ($CDCl_3$):δ
2.52 (s, 3H,), 2.84 (s, 6H), 4.36 (s, 2H),
6.8–7.6 (m, 7H)

(2) 2-(2-Dimethylaminobenzylsulfinyl)-4-methylbenzimidazole (Inventive compound 9):
2-(2-Dimethylaminobenzylthio)-4-methylbenzimidazole (1.1 g) was dissolved in 15 ml of chloroform, followed by gradual addition of 0.8 g (purity: 80%) of m-CPBA with ice cooling. After being stirred at the same temperature for 10 minutes, the resulting mixture was washed successively with a saturated $NaHCO_3$ solution and saturated brine and then dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was recrystallized from acetonitrile to obtain 0.81 g of 2-(2-dimethylaminobenzylsulfinyl)-4-methylbenzimidazole as yellowish crystals. m.p. 112–114°C (decomposed).

IR ν_{max}^{KBr} cm^{-1}: 3200, 1480, 1440, 1420, 1290, 1040, 750

^{1}H–NMR ($CDCl_3$)δ:
2.2–2.8 (br. 3H), 2.60 (s, 6H), 4.52 and 4.84
(each d, J=13Hz, 2H), 6.7–7.6 (m, 7H)

Example 7
(1) 2-(2-Dimethylamino-6-methylbenzylthio)benzimidazole:
2-Dimethylamino-6-methylbenzyl chloride hydrochloride (4.41 g) was dissolved in 40 ml of acetone, followed by addition of 3.64 g of 2-mercaptobenzimidazole, 10 g of K_2CO_3 and 4 ml of water. The resulting mixture was stirred at room temperature for one hour. Chloroform and water were added to the reaction mixture and the chloroform layer was separated and washed with saturated brine. After drying the chloroform layer with anhydrous sodium sulfate, the solvents were distilled off under reduced pressure. The residue was crystallized from a mixed solvent of ethanol and hexane and the crystals were collected by filtration to obtain 4.68 g of 2-(2-dimethylamino-6-methylbenzylthio)benzimidazole as light brownish powder.

^{1}H–NMR ($CDCl_3$)δ:
2.42 (s, 3H,), 2.84 (s, 6H), 4.42 (s, 2H),
6.8–7.6 (m, 7H)

(2) 2-(2-Dimethylamino-6-methylbenzylsulfinyl)benzimidazole (Inventive compound 10):
2-(2-Dimethylamino-6-methylbenzylthio)benzimidazole (2.97 g) was dissolved in a mixed solvent which consisted of 30 ml of chloroform and 3 ml of methanol. With ice cooling 2.18 g of m-

CPBA (purity: 80%) was added little by little. The resulting mixture was stirred at the same temperature for 10 minutes, followed by washing first with a saturated $NaHCO_3$ solution and then with saturated brine, and thereafter dried with anhydrous sodium sulfate, followed by removal of the solvent by distillation under reduced pressure. The residue was recrystallized from a mixed solvent of chloroform and ethanol to obtain 0.75 g of 2-(2-dimethylamino-6-methylbenzylsulfinyl)benzimidazole as white crystalline powder. m.p. 141–142°C (decomposed).

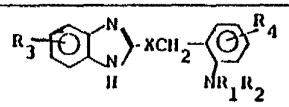
IR ν_{max}^{KBr} cm^{-1}: 3230, 1435, 1400, 1270, 1040, 740

^1H–NMR ($CDCl_3$)δ:
2.31 (s, 3H), 2.61 (s, 6H), 4.68 and
4.92 (each d, J=13Hz, 2H),
6.8–7.8 (m, 7H)

Examples 8–19

In the same manner as in Example 6 or 7, twelve compounds were further prepared, details of which are given in Table 5.

Table 5



Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
8 (Inventive compound 5)	CH_3	CH_3	5-$COOCH_3$	H	NMR ($CDCl_3$) δ ppm: 2.88 (s, 6H) 3.88 (s, 3H) 4.36 (s, 2H) 6.9-8.1 (m, 7H)	m.p. 147-148°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3175, 1725, 1490, 1425, 1290, 1080, 1040 NMR ($CDCl_3$) δ ppm: 2.62 (s, 6H) 3.94 (s, 3H) 4.48 and 4.88 (each d, J=13Hz, 2H) 6.8-8.0 (m, 7H)
9 (Inventive compound 6)	CH_3	CH_3	5-CH_3	H	NMR ($CDCl_3$) δ ppm: 2.38 (s, 3H) 2.80 (s, 6H) 4.34 (s, 2H) 6.7-7.5 (m, 7H)	m.p. 94-95°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3200, 1480, 1440, 1065, 1040, 935, 750 NMR ($CDCl_3$) δ ppm: 2.46 (s, 3H) 2.60 (s, 6H) 4.45 and 4.84 (each d, J=13Hz, 2H) 6.7-7.6 (m, 7H)
10 (Inventive compound 7)	CH_3	CH_3	5-Cl	H	NMR ($CDCl_3$) δ ppm: 2.88 (s, 6H) 4.36 (s, 2H) 6.9-7.5 (m, 7H)	m.p. 130.5-131.5°C (decomp'd) (ethanol-hexane) IR ν_{max}^{KBr} cm^{-1}: 3200, 1490, 1400, 1045, 1040, 760 NMR ($CDCl_3$) δ ppm: 2.66 (s, 6H) 4.49 and 4.83 (each d, J=13Hz, 2H) 6.7-7.8 (m, 7H)

Table 5 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
11 (Inventive compound 8)	CH_3	CH_3	5-CF_3	H	NMR ($CDCl_3$) δ ppm: 2.92 (s, 6H) 4.38 (s, 2H) 7.0-7.7 (m, 7H)	m.p. 148°C (decomp'd) (acetonitrile) NMR ($CDCl_3$) δ ppm: 2.66 (s, 6H) 4.50 and 4.88 (each d, J=13Hz, 2H) 6.8-8.1 (m, 7H)
12	CH_3	CH_3	5-NH_2	H	NMR ($CDCl_3$) δ ppm: 2.86 (s, 6H) 4.34 (s, 2H) 6.4-7.5 (m, 7H)	m.p. 146-148°C (decomp'd) (ethanol-ether) IR ν_{max}^{KBr} cm^{-1}: 3200, 1620, 1490, 1400, 1205, 1050, 760 NMR (CD_3OD) δ ppm: 2.57 (s, 6H) 4.54 and 4.79 (each d, J=13Hz, 2H) 6.6-7.4 (m, 7H)
13 (Inventive compound 11)	CH_3	CH_3	H	4-Cl	NMR ($CDCl_3$) δ ppm: 2.80 (s, 6H) 4.40 (s, 2H) 6.8-7.6 (m, 7H)	m.p. 139-140°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 1585, 1425, 1400, 1260, 1060, 950, 740 NMR ($CDCl_3$) δ ppm: 2.58 (s, 6H) 4.42 and 4.78 (each d, J=13Hz, 2H) 6.7-7.8 (m, 7H)
14 (Inventive compound 12)	CH_3	CH_3	H	5-OCH_3	NMR ($CDCl_3$) δ ppm: 2.84 (s, 6H) 3.72 (s, 3H) 4.32 (s, 2H) 6.6-7.6 (m, 7H)	m.p. 115-116.5°C (decomp'd) (ethyl acetate) IR ν_{max}^{KBr} cm^{-1}: 3200, 1495, 1400, 1280, 1245, 1150, 1020 NMR ($CDCl_3$) δ ppm: 2.60 (s, 6H) 3.50 (s, 3H) 4.47 and 4.87 (each d, J=13Hz, 2H) 6.6-7.8 (m, 7H)

Table 5 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
15 (Inventive compound 13)	CH_3	CH_3	H	5-Me	NMR ($CDCl_3$) δ ppm: 2.24 (s, 3H) 2.82 (s, 6H) 4.30 (s, 2H) 6.8-7.5 (m, 7H)	m.p. 141.5-142.5°C (decomp'd) (ethanol-hexane) IR ν_{max}^{KBr} cm^{-1}: 3220, 1600, 1410, 1270, 1045, 820, 740 NMR ($CDCl_3$) δ ppm: 2.09 (s, 3H) 2.62 (s, 6H) 4.45 and 4.84 (each d, J=13Hz, 2H) 6.9-7.8 (m, 7H)
16	CH_3	CH_3	H	3-Me	NMR ($CDCl_3$) δ ppm: 2.30 (s, 3H) 2.84 (s, 6H) 4.52 (s, 2H) 6.8-7.7 (m, 7H)	m.p. 155-156°C (decomp'd) (acetone-hexane) IR ν_{max}^{KBr} cm^{-1}: 3160, 1430, 1400, 1260, 1075, 1035, 860, 830 NMR ($CDCl_3$) δ ppm: 2.35 (s, 3H) 2.86 (s, 6H) 4.38 and 4.85 (each d, J=13Hz, 2H) 6.8-8.0 (m, 7H)
17	CH_3	CH_3	H	4-F	NMR ($CDCl_3$) δ ppm: 2.76 (s, 6H) 4.38 (s, 2H) 6.5-7.6 (m, 7H)	m.p. 118-119°C (decomp'd) (methylenechloride-acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3170, 1605, 1580, 1490, 1210, 1035, 980, 760 NMR ($CDCl_3$) δ ppm: 2.60 (s, 6H) 4.44 and 4.80 (each d, J=13Hz, 2H) 6.4-7.7 (m, 7H)

Table 5 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
18	CH_3	CH_3	5-OCH_3	6-CH_3	NMR ($CDCl_3$) δ ppm: 2.44 (s, 3H) 2.88 (s, 6H) 3.80 (s, 3H) 4.40 (s, 2H) 6.6-7.4 (m, 6H)	m.p. 143-144°C (decomp'd) (acetone-ether) IR ν_{max}^{KBr} cm^{-1}: 3220, 1440, 1190, 1140, 1035, 790 NMR ($CDCl_3$) δ ppm: 2.34 (s, 3H) 2.63 (s, 6H) 3.84 (s, 3H) 4.38 and 4.86 (each d, J=13Hz, 2H) 6.8-7.7 (m, 6H)
19	CH_3	CH_3	5-Cl	5-OCH_3	NMR ($CDCl_3$) δ ppm: 2.88 (s, 6H) 3.74 (s, 3H) 4.28 (s, 2H) 6.6-7.5 (m, 6H)	m.p. 161-162°C (decomp'd) (acetone) IR ν_{max}^{KBr} cm^{-1}: 3210, 1495, 1395, 1285, 1250, 1040, 1025, 810 NMR ($CDCl_3$) δ ppm: 2.61 (s, 6H) 3.58 (s, 3H) 4.40 and 4.82 (each d, J=13Hz, 2H) 6.6-7.8 (m, 6H)

Example 20

(2) 2-(2-Piperidinobenzylthio)benzimidazole:

To a solution of 1.42 g of 2-piperidinobenzyl chloride hydrochloride in 35 ml of ethanol were added 0.87 g of 2-mercaptobenzimidazole and 0.5 g of NaOH. The mixture was stirred at room temperature for 5 hours. The solvent was distilled off under reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The ethyl acetate solution was washed successively with a 10% NaOH solution and saturated brine. After drying the resulting solution with anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was washed with ether to obtain 1.0 g of 2-(2-piperidinobenzylthio)benzimidazole as yellow powder. m.p. 165°C.

NMR ($CDCl_3$)δ:
1.4–2.1 (m, 6H), 2.8–3.1 (m, 4H), 4.34 (s, 2H), 6.9–7.6 (m, 8H)

(2) 2-(2-Piperidinobenzylsulfinyl)benzimidazole (Inventive compound 14):

2-(2-Piperidinobenzylthio)benzimidazole (0.70 g) was dissolved in a mixed solvent which consisted of 50 ml of chloroform and 2 ml of methanol, followed by gradual addition of 1.3 g of m-CPBA (purity: 80%) with ice cooling. The resulting mixture was stirred at the same temperature for 10 minutes. Thereafter, the mixture was washed successively with a saturated $NaHCO_3$ solution and saturated brine and then dried with anhydrous sodium sulfate. The solvents were distilled off under reduced pressure and the residue was recrystallized from ether to obtain 0.45 g of 2-(2-piperidinobenzylsulfinyl)benzimidazole as white powder. m.p. 158°C (decomposed).

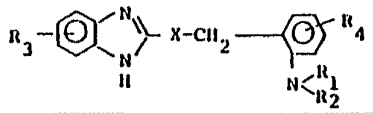
IR ν_{max}^{KBr} cm^{-1}: 3160, 1435, 1325, 1215, 1030, 920, 740

^{1}H–NMR (DMSO–d_6)δ:
1.3–1.8 (m, 6H), 2.6–2.8 (m, 4H), 4.41–4.74 (each d, J=12Hz, 2H), 6.8–7.8 (m, 8H)

Examples 21–26

In the same manner as in Example 20, six compounds were further prepared, details of which are given in Table 6.

Table 6



Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
21 (Inventive compound 15)		H	H	H	NMR ($CDCl_3$) δ ppm: 0.8-2.1 (m, 10H) 3.0-3.4 (br, 1H) 4.48 (s, 2H) 6.4-7.6 (m, 8H)	m.p. 89-92°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 2940, 1605, 1510, 1430, 1310, 1270, 1050, 750 NMR ($CDCl_3$) δ ppm: 0.7-2.1 (m, 10H) 2.9-3.3 (m, 1H) 4.35 and 4.64 (each d, J=14Hz, 2H) 6.3-7.9 (m, 8H)
22 (Inventive compound 16)		H	H	H	NMR ($CDCl_3$) δ ppm: 4.48 (s, 2H) 6.6-7.5 (m, 13H)	m.p. 89-92°C (decomp'd) (chloroform-ether) IR ν_{max}^{KBr} cm^{-1}: 3360, 1600, 1495, 1410, 1305, 1050, 750 NMR ($CDCl_3$) δ ppm: 4.47 and 4.78 (each d, J=14Hz, 2H) 6.5-8.0 (m, 13H)
23 (Inventive compound 17)		CH_3	H	H	NMR ($CDCl_3$) δ ppm: 3.18 (s, 3H) 4.40 (s, 2H) 6.4-7.6 (m, 13H)	m.p. 168-169°C (decomp'd) (chloroform-acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3050, 1590, 1485, 1400, 1260, 1055, 740 NMR ($CDCl_3$) δ ppm: 3.18 (s, 3H) 4.32 and 4.62 (each d, J=13Hz, 2H) 6.3-7.8 (m, 13H)

Table 6 (cont'd)

Example No.	R_1	R_2	R_3	R_4	Intermediate compound (X=S)	Inventive compound (X=SO)
24 (Inventive compound 18)	$-CH_2-\langle\bigcirc\rangle$	CH_3	H	H	NMR ($CDCl_3$) δ ppm: 2.66 (s, 3H) 4.04 (s, 2H) 4.56 (s, 2H) 6.9-7.5 (m, 13H)	m.p. 137°C (decomp'd) (acetonitrile) IR ν_{max}^{KBr} cm^{-1}: 3170, 1440, 1400, 1260, 1025, 940, 740 NMR ($CDCl_3$) δ ppm: 2.52 (s, 3H) 4.00 (s, 2H) 4.52 and 4.92 (each d, J=12Hz, 2H) 6.7-7.9 (m, 13H)
25	$-(CH_2)_5CH_3$	CH_3	H	H	NMR ($CDCl_3$) δ ppm: 0.98 (d, J=7Hz, 6H) 1.8-2.2 (m, 1H) 2.68 (d, J=8Hz, 2H) 2.80 (s, 3H) 4.48 (s, 2H) 6.9-7.8 (m, 8H)	m.p. 121°C (decomp'd) (chloroform-hexane) NMR ($CDCl_3$) δ ppm: 0.92 (d, J=7Hz, 6H) 1.5-2.0 (m, 1H) 2.62 (d, J=8Hz, 2H) 2.64 (s, 3H) 4.52 and 4.90 (each d, J=14Hz, 2H) 6.8-7.9 (m, 8H)
26 (Inventive compound 19)	$-CH_2CH(CH_3)_2$	CH_3	H	H	NMR ($CDCl_3$) δ ppm: 0.6-2.0 (m, 11H) 2.7-3.1 (m, 2H) 2.88 (s, 3H) 4.42 (s, 2H) 6.8-7.7 (m, 8H)	m.p. 90-92.5°C (decomp'd) (chloroform-hexane) NMR ($CDCl_3$) δ ppm: 0.7-1.7 (m, 11H) 2.64 (s, 3H) 2.7-3.0 (m, 2H) 4.48 and 4.89 (each d, J=12Hz, 2H) 6.7-8.0 (m, 8H)

The following examples illustrate the use of the benzimidazole components of the invention in antiulcer agents in various forms, the effective component in each case being a compound in accordance with the invention.

Example 27

Preparation Example (Tablets):

Each tablet (220 mg) contained the following components:

Effective component	50 mg
Lactose	103 mg
Starch	50 mg
Magnesium stearate	2 mg
Hydroxypropylcellulose	15 mg

Example 28

Preparation Example (Capsules):

Each hard gelatin capsule (350 mg) contained the following components:

Effective component	40 mg
Lactose	200 mg
Starch	70 mg
Polyvinylpyrrolidone	5 mg
Crystalline cellulose	35 mg

Example 29

Preparation Example (Granules):

Each granule (1 g) contained the following components:

Effective component	200 mg
Lactose	450 mg
Corn starch	300 mg
Hydroxypropylcellulose	50 mg

Example 30

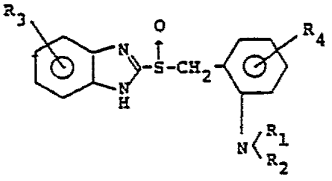
Preparation Example (Enteric Coated Tablets):

Each enteric coated tablet contained the components of Example 27.

The terms "lower alkyl", "lower alkoxy" and "lower alkoxycarbonyl" as used herein in the definition of groups R_3 and R_4 of Formula (I), are intended to mean alkyl and alkoxy groups having 1 to 5 carbon atoms, and alkoxycarbonyl groups in which the alkoxy moiety has 1 to 5 carbon atoms.

CLAIMS

1. A benzimidazole derivative represented by the formula (I),

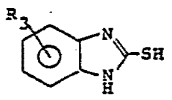


(I)

where R_1 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms, or a cycloalkyl, phenyl, or aralkyl group; R_2 is a hydrogen atom, or an alkyl group of 1 to 8 carbon atoms; or R_1 and R_2 form a ring together with the adjacent nitrogen atom; and R_3 and R_4 are in each case a hydrogen or halogen atom, or a trifluoromethyl, lower alkyl, lower alkoxy, lower alkoxycarbonyl, or amino group, and may be the same or different.

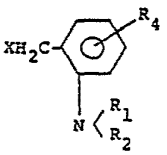
2. A benzimidazole derivative as claimed in Claim 1, substantially as hereinbefore described with reference to any of Examples 1 to 26.

3. A process for preparing a benzimidazole derivative as claimed in Claim 1, which comprises reacting a 2-mercaptobenzimidazole represented by the formula (II),



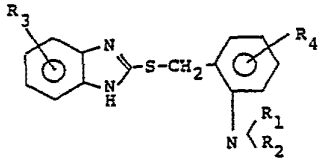
(II)

where R_3 is as defined in Claim 1, with a 2-aminobenzyl compound represented by the formula (III),



(III)

where R_1, R_2 and R_4 are as defined in Claim 1 and X is a reactive group, thereby forming a compound represented by the formula (IV),



(IV)

where R_1, R_2, R_3 and R_4 are as defined in Claim 1, and thereafter oxidizing the compound of the formula (IV).

4. A process for preparing a benzimidazole derivative as claimed in Claim 1, substantially as hereinbefore described with reference to any of Examples 1 to 26.

5. An antiulcer agent comprising as an effective component a benzimidazole derivative as claimed in Claim 1.

6. An antiulcer agent as claimed in Claim 5, substantially as described with reference to any of Examples 27 to 30.

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None

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(54) Medicaments containing sufotidine

(57) An anti-inflammatory pharmaceutical composition comprises a systemic non-steroidal anti-inflammatory drug and sufotidine or a physiologically acceptable salt thereof.

The two active ingredients, may be administered separately or may be combined in a single preparation. Suitable non-steroidal anti-inflammatory drugs are aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflurisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

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MEDICAMENTS

This invention relates to improvements in the treatment of inflammatory conditions. More particularly it relates to the use of a non-steroidal anti-inflammatory drug in conjunction with sufotidine in the treatment of such conditions, and to pharmaceutical compositions containing the two active ingredients.

Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin, ibuprofen and piroxicam, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric ulceration when administered orally. This side effect may be further enhanced in combination with other factors such as stress. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

Sufotidine is the approved name for 1-methyl-3-methylsulphonylmethyl-N-[3-[3-(1-piperidinylmethyl)-phenoxy]propyl]-1H-1,2,4-triazole-5-amine which is described and claimed in British Patent Specification No. 2075007B. The compound is a potent and long-acting histamine H_2-antagonist which may be used in the treatment of conditions where there is an advantage in lowering gastric acidity. Such conditions include duodenal and gastric ulceration, reflux oesophagitis and Zollinger-Ellison syndrome. Sufotidine may also be used prophylactically in surgical procedures, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator.

It has now been discovered that mucosal lesions of the gastrointestinal tract caused by non-steroidal anti-inflammatory drugs can be significantly reduced by co-administering sufotidine with the anti-inflammatory drug.

Such combination therapy may be used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteo-arthritis and ankylosing spondylitis and for analgesia in conditions such as dysmenorrhoea, especially where the use of

the anti-inflammatory drug is limited by gastro-intestinal side effects.

The present invention thus provides a method of treating inflammatory conditions which comprises administering to a human or animal subject a systemic non-steroidal anti-inflammatory drug and sufotidine or a physiologically acceptable salt thereof.

According to another aspect the invention provides for the use of a systemic non-steroidal anti-inflammatory drug for the manufacture of a medicament for administration in conjunction with sufotidine or a physiologically acceptable salt thereof, for the treatment of inflammatory conditions.

The systemic non-steroidal anti-inflammatory drug, and sufotidine or a physiologically acceptable salt thereof, may be administered as a single pharmaceutical composition comprising effective amounts of the two active ingredients. Alternatively the two active ingredients may be co- administered in the form of two separate pharmaceutical compositions for simultaneous or sequential use.

The systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin. They may be used according to the invention in their usual dosage amounts, e.g. 50 mg - 1g of aspirin, 10 - 100 mg of indomethacin, 5 - 50 mg of piroxicam and 100 - 500 mg of ibuprofen per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question. Particular non-steroidal anti-inflammatories for use according to the invention include indomethacin and, more preferably, piroxicam.

Sufotidine may be administered according to the invention in the form of either its free base or a physiologically acceptable salt. Such salts include salts of inorganic or organic acids such as the hydrochloride, hydrobromide, sulphate, methanesulphonate,

acetate, maleate, succinate, citrate, tartrate, benzoate and fumarate salts. Sufotidine in the form of its free base is particularly preferred. The amount of sufotidine employed in the invention will be an amount sufficient to reduce the gastrointestinal distress caused by the anti-inflammatory drug and will preferably be in the range of 50 to 600 mg per dosage unit, expressed as the weight of free base. The sufotidine is preferably administered once or twice daily.

The exact dose of the two active ingredients will depend on the route of administration and the condition being treated, and it will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. A particularly useful form of administration is by the oral route.

According to a further aspect the invention provides a pharmaceutical composition, for use in human or veterinary medicine, comprising a systemic non-steroidal anti-inflammatory drug, and sufotidine or a physiologically acceptable salt thereof.

Pharmaceutical compositions according to the invention may be presented in a conventional manner with the aid of at least one pharmaceutical carrier or excipient. The composition may take the form of, for example, tablets, capsules, powders, granules, solutions, syrups, suspensions or suppositories prepared by conventional means with acceptable excipients. The compositions may thus contain as excipients, for example, binding agents, compression aids, fillers, lubricants, disintegrants and wetting agents. If desired, other active ingredients may also be present in such compositions. Tablets may be coated in conventional manner, for example with a suitable film-forming material such as methyl cellulose, ethyl cellulose and/or hydroxypropylmethyl cellulose or with sugar. Liquid preparations may also contain, for example, edible oils such as peanut oil. Suppositories may contain, for example, fat-soluble or water miscible bases.

The pharmaceutical compositions of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the anti-inflammatory

drug and sufotidine or its salt may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine.

Alternatively, the pharmaceutical compositions of the invention may be presented in a suitable controlled release form so that the sufotidine or its salt is rapidly made available for absorption and the non-steroidal anti-inflammatory drug is released more slowly. Thus, for example, the pharmaceutical compositions may be presented for oral administration in a conventional manner associated with controlled release forms.

In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

Example 1 - Tablets

(a)

	mg/tablet
Sufotidine	300.00
Ibuprofen	400.00
Lactose	245.00
Hydroxpropyl methylcellulose	5.00
Sodium starch glycollate	40.00
Magnesium stearate	10.00
Compression weight	1000.00

The sufotidine and ibuprofen are sieved through a 250μm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using suitable punches.

(b)

	mg/tablet
Sufotidine	300.00
Indomethacin	50.00
Microcrystalline cellulose	46.00
Magnesium stearate	4.00
Compression weight	400.00

The sufotidine and indomethacin are sieved through a 250μm sieve and blended with the microcrystalline cellulose and magnesium stearate and compressed using 10.0mm punches.

(c)

	mg/tablet
Sufotidine	300.00
Piroxicam	20.00
Microcrystalline cellulose	76.00
Magnesium stearate	4.00
Compression weight	400.00

The sufotidine and piroxicam are sieved through a 250μm sieve and blended with the microcrystalline cellulose and magnesium stearate and compressed using 10.0mm punches.

Example 2 - Capsules

(a)

	mg/capsule
Sufotidine	300.00
Ibuprofen	400.00
Starch 1500**	96.00
Magnesium stearate	4.00
Fill weight	800.00

** A form of directly compressible starch supplied by Colorcon Ltd., Orpington, Kent.

The sufotidine and ibuprofen are sieved through a 250μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

(b)

	mg/capsule
Sufotidine	300.00
Indomethacin	50.00
Starch 1500	147.50
Magnesium stearate	2.5
Fill weight	500.00

The sufotidine and indomethacin are sieved through a 250μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 1 hard gelatin capsules using a suitable filling machine.

(c)

	mg/capsule
Sufotidine	300.00
Piroxicam	20.00
Starch 1500	177.50
Magnesium stearate	2.50
Fill weight	500.00

The sufotidine and piroxicam are sieved through a 250μm sieve and blended with the starch 1500 and magnesium stearate. The resultant mix is filled into size 1 hard gelatin capsules using a suitable filling machine.

Example 3 - Suppositories

(a)

	mg/suppository
Sufotidine	300.0
Piroxicam	10.0
Adeps Solidus	670.0
Colloidal silica	20.0
Fill weight	1000.0

The sufotidine and piroxicam are sieved through a 100μm sieve and blended with the molten Adeps Solidus containing the colloidal silica. The resultant mixture is filled into suppository cavities using a suitable filling machine.

(b)

	mg/suppository
Sufotidine	300.0
Indomethacin	100.0
Polyethylene glycol 400	80.0
Polyethylene glycol 4000	520.0
Fill weight	1000.0

The sufotidine and indomethacin are sieved through a 100μm sieve and blended with the molten polyethylene glycol mixture. The resultant mixture is filled into suppository cavities using a suitable filling machine.

CLAIMS

1. A pharmaceutical composition for use in human or veterinary medicine comprising a systemic non-steroidal anti-inflammatory drug and sufotidine or a physiologically acceptable salt thereof.

2. A pharmaceutical composition as claimed in claim 1 wherein the sufotidine is used in the form of the free base or as the hydrochloride, hydrobromide, sulphate, methanesulphonate, acetate, maleate, succinate, tartrate, benzoate or fumarate salt.

3. A pharmaceutical composition as claimed in claim 2 wherein the sufotidine is used in the form of the free base.

4. A pharmaceutical composition as claimed in any of claims 1 to 3 in unit dose form and containing from 50 to 600mg of sufotidine per unit dose expressed as the weight of free base.

5. A pharmaceutical composition as claimed in any of claims 1 to 4 wherein the non-steroidal anti-inflammatory drug is selected from aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

6. A pharmaceutical composition as claimed in claim 5 wherein the non-steroidal anti-inflammatory drug is piroxicam.

7. A pharmaceutical composition as claimed in claim 6 in unit dose form and containing 5 - 50mg of piroxicam per

unit dose.

8. A pharmaceutical composition as claimed in any of claims 1 to 7 in a form adapted for oral administration.

9. A pharmaceutical composition as claimed in any of claims 1 to 8 also containing at least one pharmaceutical carrier or excipient.

10. A method for the manufacture of a pharmaceutical composition as claimed in any of claims 1 to 9 which comprises processing the components by conventional techniques to form a pharmaceutical composition.

11. The use of sufotidine or a physiologically acceptable salt thereof for the manufacture of a medicament for administration in conjunction with a systemic non-steroidal anti-inflammatory drug in the treatment of an inflammatory condition.

12. The use as claimed in claim 11 wherein the sufotidine is used in the form of the free base or as the hydrochloride, hydrobromide, sulphate, methanesulphonate, acetate, maleate, succinate, tartrate, benzoate or fumarate salt.

13. The use as claimed in claim 12 wherein the sufotidine is used in the form of the free base.

14. The use as claimed in any of claims 11 to 13 wherein the medicament is in unit dose form containing from 50 to 600mg of sufotidine per unit dose expressed as the weight of free base.

15. The use as claimed in any of claims 11 to 14 wherein the non-steroidal anti-inflammatory drug is

selected from aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

16. The use as claimed in claim 15 wherein the non-steroidal anti-inflammatory drug is piroxicam.

17. The use as claimed in claim 16 wherein the piroxicam is used in unit dose form containing 5 - 50mg of piroxicam per unit dose.

18. The use as claimed in any of claims 11 to 17 wherein the medicament is in a form adapted for oral administration.

19. The use as claimed in any of claims 11 to 18 wherein the medicament is for administration in conjunction with the non-steroidal anti-inflammatory but separately therefrom.

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(54) Title: ANALGESIC AND ANTI-INFLAMMATORY COMPOSITIONS COMPRISING DIPHENHYDRAMINE AND METHODS OF USING SAME

(57) Abstract

Novel pharmaceutical compositions of matter comprising analgesic/non-steroidal anti-inflammatory drugs and diphenhydramine and methods of using said compositions to elicit an enhanced analgesic and/or anti-inflammatory response in mammalian organisms in need of such treatment.

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ANALGESIC AND ANTI-INFLAMMATORY COMPOSITIONS COMPRISING DIPHENHYDRAMINE AND METHODS OF USING SAME

BACKGROUND OF THE INVENTION

The present invention relates generally to novel pharmaceutical compositions of matter comprising diphenhydramine and one or more non-steroidal anti-inflammatory drugs (NSAID) having analgesic and anti-inflammatory properties, and to methods of using said compositions to elicit an enhanced analgesic or anti-inflammatory response in mammalian organisms in need of such treatment.

Non-narcotic analgesics, most of which are also known as non-steroidal anti-inflammatory drugs (NSAID), are widely administered orally in the treatment of mild to severe pain. Within this class, the compounds vary widely in their chemical structure and in their biological profiles as analgesics, anti-inflammatory agents and antipyretic agents. Aspirin, acetaminophen and phenacetin have long been among the most commonly used members of this group; more recently, however, a large number of alternative non-narcotic agents offering a variety of advantages over the earlier drugs have been developed. Tolerance or addiction to these drugs is not generally a problem with their continuous use in the treatment of pain or in the treatment of acute or chronic inflammatory states (notably, rheumatoid arthritis and osteoarthritis); nevertheless, these drugs generally have a higher potential for adverse side-effects at the upper limits of their effective dose ranges. Moreover, above each drug's upper limit or ceiling, administration of additional drug does not usually increase the analgesic or anti-inflammatory effect. Among the newer compounds

in the non-narcotic analgesic/nonsteroidal anti-inflammatory group are compounds such as diflunisal (Dolobid®), zomepirac sodium (Zomax®), ibuprofen (Motrin®), naproxen (Naprosyn®), fenoprofen (Nalfon®), piroxicam (Feldene®), flurbiprofen, mefenamic acid (Ponstel®) and sulindac. See also Physicians' Desk Reference, 35th edition, 1981, and The Merck Index, ninth edition, Merck & Co., Rahway, New Jersey (1976), for information on specific nonsteroidal anti-inflammatory agents. Also see, generally, Wiseman, " Pharmacological Studies with a New Class of Nonsteroidal Anti-Inflammatory Agents - The Oxicams - With Special Reference to Piroxicam (Feldene®), The American Journal of Medicine, February 16, 1982:2-8; Foley et al, The Management of Cancer Pain, Volume II - The Rational Use of Analgesics in the Management of Cancer Pain, Hoffman-LaRoche Inc., 1981; and Cutting's Handbook of Pharmacology, sixth edition, ed. T.Z. Czaky, M.D., Appelton-Century-Crofts, New York, 1979, Chapter 49: 538-550, including structural formulas for representative group members.

Diphenhydramine[2-(diphenylmethoxy)-N,N-dimethylethylamine] is also a well-known therapeutic agent in long standing use by clinicians as an antihistamine. It is recognized in both the U.S.P. and N.F. as an official antihistamine of the ethanolamine (or aminoalkyl ether) type and is available as the hydrochloride salt in Benadryl® and various alternative sources in 50 milligram delayed action tablets, 25 and 50 milligram capsules, elixirs (12.5 mg/5 ml) and sterile solution for injection (10 mg/ml). Depending upon the therapeutic indication, diphenhydramine is recommended in single or divided doses of between 12.5 to 50 milligrams with a maximum daily dosage not to

exceed 300 milligrams. The antihistaminic activity of diphenhydramine is directly attributable to its competition with histamine for cell receptor sites on effector cells although diphenhydramine also demonstrates, in addition, a number of therapeutic applications attributable to central actions unrelated to histamine antagonism. Antihistaminic indications for diphenhydramine include perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and as adjunctive therapy for anaphylactic reactions. Central nervous system side effects (non-histaminic actions) which have been capitalized upon include prophylactic and active treatment of motion sickness and, more broadly, as an antinauseant and in the treatment of mild forms of Parkinsonism. Diphenhydramine demonstrates both stimulant and depressant effects on the central nervous system although stimulation is only occasionally seen in patients given conventional doses with accompanying restlessness, nervousness and inability to sleep. The more predominant sedative action of diphenhydramine has been beneficially capitalized upon with the usage of diphenhydramine as a somnolent when employed at the maximum 50 milligrams dose in both prescription and over-the-counter forms. In this regard, it is noted that the Food and Drug Administration announced in the November 1983 FDA Drug Bulletin (Vol. 13, No. 3) that diphenhydramine (50 mg.) may now be marketed over-the-counter as a nighttime sleep aid.

An early study (1958) investigated the properties of diphenhydramine as a pre-anesthetic medication. (Lear, et al., "Comparative Studies of Tranquilizers Used in Anesthesia." JAMA, 1958, 166(12): 1438-1443). The authors concluded that

diphenhydramine, particularly when used in combination with meperidine, provides beneficial preoperative sedation with less overall depression than previously experienced with the use of routine doses or narcotics and barbiturates.

Diphenhydramine has also been investigated with varying results with respect to its potential as a weak analgesic. Diphenhydramine hydrochloride when introduced intravenously has been reported as being useful in obstetric analgesia alone and in combination with alcohol. See Cappe, B.E. et al, "Recent Advances in Obstetric Analgesia", JAMA, 1954, 154(5); 377-379. Campos et al in a comparative study found that diphenhydramine given either orally or intramuscularly could not be distinguished from placebo in patients with postoperative fractures or somatic pain. ["The Analgesic and Hypothermic Effects of Nefopam, Morphine, Aspirin, Diphenhydramine and Placebo", Journal of Clin. Pharmacology, January, 1980, pp. 42-49.]

Albal and Chandorkar studied an injectable combination analgesic consisting of analgin 375 mg, a centrally acting analgesic, diazepam 2.5 mg, and diphenhydramine 20 mg, and found relief from pain. They did not, however, study the unique contribution of diphenhydramine. [Albal, M.V., and Chandorkar, A.G. "Clinical Evaluation of Sedyn-a-Forte, an Analgesic Injection Containing Analgin, Diphenhydramine and Diazepam." Indian Journal of Ophthalmology, 1982, 30:271-273]. [Note: analgin referred to in the foregoing study is dypyrone; see The Merck Index, p. 3361, 1976.]

While diphenhydramine has been investigated with respect to its weak analgesic properties, it is also evident from the foregoing that its sedative and

local anesthetic properties may, in part, account for its suspected potential for relieving pain. In the Lear et al, supra, study diphenhydramine at 25 to 50 milligram doses was insufficient as a preanesthetic medication and combination with meperidine (a narcotic analgesic) was proposed to optimize the potential beneficial effects of diphenhydramine as an analgesic.

Hydroxyzine, which is a minor tranquilizer with antihistaminic activity, has been evaluated as an analgesic. Beaver and Feise found that, "This study unequivocally demonstrates analgesic activity for a 100 mg dose of intramuscular hydroxyzine in the general range of that produced by 8 mg of morphine. In addition, the analgesic activity of hydroxyzine appears additive with that of morphine when the two drugs are given together." The findings of the study do not indicate synergistic activity. (Beaver, W.T. & Feise, G. "Comparison of the Analgesic Effects of Morphine, Hydroxyzine, and Their Combination in Patients with Postoperative Pain." Advances in Pain Research and Therapy, 1976, 1:553-557)

Only recently have animal studies been conducted in which the analgesic activity of diphenhydramine has been investigated. Bluhm, et al., in a study conducted on mice, found that diphenhydramine potentiates morphine, a centrally acting drug, when administered parenterally. Oral administration of drugs was not studied. (Bluhm, et al., "Potentiation of Opioid Analgesia By H_1 and H_2 Antagonists." Life Sciences, 1982, 31:1229-1232)

Diphenhydramine has not been heretofore proposed for use in combination with any of the newer nonsteroidal analgesic/anti-inflammatory agents (i.e., excluding aspirin, acetaminophen and phenacetin). In

U.S. Patent No. 4,420,483 issued December 13, 1983, the present applicants disclose the hastening of the onset of analgesic and anti-inflammatory responses observed with several different nonsteroidal anti-inflammatory agents as well as the enhancement of the analgesic and anti-inflammatory response with such agents by the concomitant administration of caffeine as a potentiating adjuvant.

Applicants have now surprisingly found that diphenhydramine synergistically enhances the analgesic and anti-inflammatory properties of such non-steroidal anti-inflammatory drugs (NSAID).

SUMMARY OF THE INVENTION

It is, therefore, a primary object of the present invention to provide a novel pharmaceutical composition of matter for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism in need of such treatment comprising an analgesically and anti-inflammatorily effective amount of a non-steroidal anti-inflammatory drug (NSAID) in combination with diphenhydramine or a pharmaceutically acceptable salt thereof.

It is a further object of the present invention to provide methods for obtaining analgesic and anti-inflammatory responses in mammals, including humans, by the administration of preselected dosages of a non-steroidal anti-inflammatory agent, with diphenhydramine.

A still further object of the present invention is to provide a pharmaceutical composition of matter for obtaining a synergistic analgesic and anti-inflammatory response in mammals in which the

composition comprises an analgesically and anti-inflammatorily effective amount of a selected NSAID and a synergistic amount of diphenhydramine optionally in the presence of a pharmaceutically acceptable inert carrier.

Another object of the invention is to provide suitable dosage unit forms of one or more NSAID's and diphenhydramine adapted for, e.g., oral, rectal, parenteral, topical, etc., administration and useful in the treatment, management and mitigation of pain and/or inflammation.

These and other similar objects, advantages and features are accomplished according to the products, compositions and methods of the invention comprised of a non-steroidal anti-inflammatory drug or analgesic and diphenhydramine and analgesic and anti-inflammatory methods employing same.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has now been unexpectedly found in accordance with the present invention that the analgesic and anti-inflammatory effects observed upon the administration of a non-narcotic analgesically active non-steroidal anti-inflammatory drug (i.e., analgesic/NSAID), can be synergistically enhanced by the co-administration of diphenhydramine or a non-toxic pharmaceutically acceptable salt thereof.

As used herein, the terms "synergism" and "synergistic" are used to describe the potentiated analgesic and anti-inflammatory responses elicited by the co-administration of an analgesic NSAID and diphenhydramine (or pharmaceutically acceptable salts thereof). More specifically, these terms as used

herein are defined in contradistinction to merely additive effects. The effects of two compounds are additive if the response to a dose of both in combination does not change when a portion of one component is removed from the mixtures and replaced by an equipotent portion of the other. If such substitution increases the response, the mixing together of the compounds is said to potentiate their effects and synergism exists.

The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:

(1) the propionic acid derivatives;

(2) the acetic acid derivatives;

(3) the fenamic acid derivatives;

(4) the biphenylcarboxylic acid derivatives; and

(5) the oxicams.

The term "selected NSAID" as used herein is intended to mean any non-narcotic analgesic/non-steroidal anti-inflammatory compound falling within one of the five structural categories above but excluding aspirin, acetaminophen and phenacetin.

While some of these compounds are primarily used at the present time as anti-inflammatory agents and others are primarily used as analgesics, in fact all of the contemplated compounds have both analgesic and anti-inflammatory activity and can be used at appropriate dosage levels for either purpose in the compositions and methods of the present invention. The compounds in groups (1) through (4) typically contain a carboxylic acid function; however, those acids are sometimes administered in the form of their pharmaceutically acceptable acid addition or alkali metal salts, e.g., sodium salts.

The propionic acid derivatives for use herein include, but are not limited to, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the propionic acid group include ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen and fenbufen.

Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH(CH_3)COO^-Na^+$ or $-CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

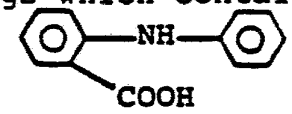
The acetic acid derivatives for use herein include, but are not limited to, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac and oxpinac. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the acetic acid group include tolmetin sodium, zomepirac sodium, sulindac and indomethacin.

Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs having a free $-CH_2COOH$ group (which

optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-CH_2COO^-Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives for use herein include, but are not limited to, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Presently preferred members of the fenamic acid group include mefenamic acid and meclofenamate sodium (meclofenamic acid, sodium salt).

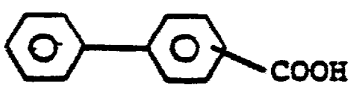
Thus, "fenamic acid derivative" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs which contain the basic structure



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^-Na^+$.

The biphenylcarboxylic acid derivatives for use herein include, but are not limited to, diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Preferred members of this group are diflunisal and flufenisal.

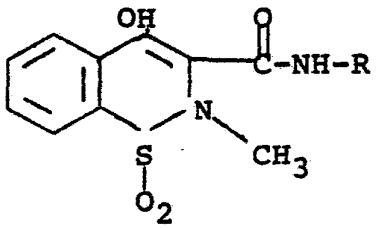
Thus, "biphenylcarboxylic acid derivative" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs which contain the basic structure



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g. $-COO^{-}Na^{+}$.

The oxicams for use herein include, but are not limited to, piroxicam, sudoxicam, isoxicam and CP-14, 304. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. A preferred member of this group is piroxicam.

Thus, "oxicams" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs which have the general formula



wherein R is an aryl or heteroaryl ring system.

The precise amount of non-narcotic analgesic/non-steroidal anti-inflammatory drug for use in the present compositions will vary depending, for example, on the specific drug chosen, the dosage form thereof, i.e., standard versus sustained release, the condition for which the drug is administered and the size and kind of the mammal.

For humans, typical effective analgesic/anti-inflammatory amounts of presently preferred NSAIDs for use in unit dose compositions of the invention are about 125 to 500 mg diflunisal, about 25 to 100 mg zomepirac sodium, about 50 to 400 mg ibuprofen, most preferably 100-400 mg, about 125 to 500 mg naproxen, about 25 to 50 mg flurbiprofen, and about 50 to 200 mg fenoprofen, about 10 to 20 mg piroxicam, about 125 to

250 mg mefenamic acid, about 100 to 400 mg fenbufen or about 25 to 50 mg ketoprofen; however, greater or lesser amounts can be employed if desired.

For example, in one preferred embodiment of this invention, the desired therapeutic response for ibuprofen therapy in mild to moderate pain is generally observed at 200 to 600 milligrams of ibuprofen every 4 to 6 hours as necessary up to about 2400 milligrams total daily dose. Consistent with the synergistic results achieved with the ibuprofen/diphenhydramine compositions and methods of the present invention, the desired analgesic and/or anti-inflammatory response can be achieved upon the administration of ibuprofen and diphenhydramine wherein the ibuprofen component can be administered at reduced levels of between about 50 to 400 milligrams of ibuprofen and, most preferably, 100 to 400 milligrams. Alternatively, the usual dosage regimen for ibuprofen may be followed when the composition of the present invention additionally comprising diphenhydramine is employed whereby the levels of analgesia and anti-inflammatory results are enhanced.

The amount of diphenhydramine present in the compositions according to the present invention ranges between about 12.5 to 50 milligrams and, preferably, between about 25 to 50 milligrams.

In any event, the amounts of NSAID and diphenhydramine to be administered in a total daily dose should not exceed the generally recognized as safe limits established for the particular NSAID and diphenhydramine when administered alone for their respective usual therapeutic indications.

In the compositions and methods of the invention, an NSAID and diphenhydramine may be co-administered in the same composition or concomitantly administered separately.

In accordance with the practices of the present invention, the NSAID/diphenhydramine compositions may be administered in admixture with suitable pharmaceutical diluents, carriers or other excipients (collectively referred to as "carrier" materials) suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active drug components may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc. Sweetening and flavoring agents and preservatives can also be included where appropriate. Similarly, injectable dosage units may be utilized to accomplish intravenous, intramuscular or subcutaneous administration and, for such parenteral administration, suitable sterile aqueous or non-aqueous solutions or suspensions, optionally containing appropriate solutes to effectuate isotonicity, will be employed.

Moreover, in accordance with another preferred embodiment of the present invention, where therapeutic indications warrant, such as in the case where the level of pain and inflammation associated with the disorder may interfere with normal sleep latency and maintenance dosage regimens may be contemplated, the NSAID/diphenhydramine compositions of the invention may be formulated for administration at bedtime as an analgesically and anti-inflammatorily effective nighttime sleep aid. Accordingly, the NSAID and diphenhydramine components of the composition may be formulated in dosage unit form to provide a dose of diphenhydramine (compared to the amount necessary to promote the desired synergistic response) to take advantage of the sleep-inducing side effect of diphenhydramine.

In another preferred embodiment, the advantageous analgesic and anti-inflammatory compositions of the invention may be formulated in sustained release form to provide the rate controlled release of either or both of the components to optimize analgesic and anti-inflammatory response while minimizing undesirable side effects in, for example, patients unusually sensitive to either or both of the active drugs. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices. Thus, with respect to such layered tablets, one layer may contain an initial dosing amount of, for example, ibuprofen, of 400 milligams and 25 milligrams of diphenhydramine, whereas two or more further layers

may contain, for instance, 100 milligrams of ibuprofen and 15 to 25 milligrams of diphenhydramine to be released serially every 4 to 6 hours consistent with the normal dosage schedule. Another advantage afforded the analgesic and anti-inflammatory compositions of the present invention by the inclusion of the diphenhydramine component is that gastro-intestinal disturbances, which are the most frequent adverse reactions reported for non-steroidal anti-inflammatory drugs, including complaints involving abdominal distress, epigastric pain, indigestion, nausea and vomiting may often be minimized or, at least, reduced. The foregoing advantage is both a function of the synergism exhibited by the NSAID/diphenhydramine composition which allows for the use of the NSAID component in quantities substantially less than dosages presently considered necessary as an analgesic or anti-inflammatory agent in humans, which lower doses result in lowering the incidence or severity of undesirable side effects, as well as the presence of diphenhydramine contributing valuable antinauseant and antiemetic properties to the composition.

In patients particularly susceptible to the tendency of either the NSAID or diphenhydramine to promote drowsiness or, in the extreme, sedation and, otherwise, in ambulatory patients where drowsiness and/or sedation may represent untoward side effects, the compositions of the present invention may further include caffeine to counteract drowsiness symptoms and to further take advantage of the potentiated analgesic and anti-inflammatory response effectuated by the addition of caffeine as disclosed in applicants U.S. Patent No. 4,420,483.

Example 1 - Pharmacologic Test for Synergism - Ibuprofen/Diphenhydramine.

The unexpected synergistic analgesic effect of the addition of diphenhydramine to ibuprofen is evidenced by tests conducted on mice. Blue Spruce Farm male mice weighing 18-28 grams at the time of testing are used throughout. All mice are dosed orally by gavage with ibuprofen and/or diphenhydramine. The formulation of each test article is a solution or suspension in 0.25% methylcellulose manufactured by Fisher Scientific Company. A dosing volume of 10 ml/mg is used. All doses are coded and the test is performed under a code not known to the observer. Doses are based upon the weights of the animal taken prior to dosing.

METHOD

A phenylquinone writhing assay in mice was conducted over a four day period to test for synergism of the analgesic activity of ibuprofen and diphenhydramine.

The assay consists of phenyl-p-benzoquinone (PPQ) introduced in mice thirty minutes post dose of the test treatment(s). The PPQ is prepared as a .02% aqueous solution in 5 ml ethyl alcohol q.s. to 100 ml with distilled water and is administered intraperitoneally at .25 ml/mouse. The mice are injected with the PPQ solution and are placed in individual plastic squares 4"x4"x5" deep and observed for a ten minute period post treatment dose for exhibition of the writhing syndrome. Complete blocking of the writhing syndrome for the ten minute observation period in any

one mouse is considered a positive response for that mouse. Conversely, if the mouse definitely writhes at least once, it is considered to be not protected from the PPQ.

Three hundred twenty-eight mice were randomly assigned to 40 groups. Two groups of ten mice per series were assigned to a control group (10 prior to the administration of the test treatments and 10 post administration) to verify the ability of the solutions to produce the writhing response.

The purpose of the assay on the first day is to estimate the ED_{50} (effective dose in 50% of treated mice) of ibuprofen alone and of diphenhydramine alone, and to estimate the relative potency, ρ, of ibuprofen to diphenhydramine, determined as the ratio of the ED_{50} of ibuprofen to the ED_{50} of diphenhydramine. Eight mice per group are dosed orally (via intubation) with 2, 5, 10 and 20 mg/kg of ibuprofen and 5, 10, 20 and 50 mg/kg of diphenhydramine. Table 1 shows the number of mice protected from writhing activity for each dose of ibuprofen and diphenhydramine. The method of Finney ["Statistical Method of Biological Assay", McMillan Pub., 3rd Edition, 1978] is used to estimate the ED_{50}'s of ibuprofen alone and diphenhydramine alone.

On the second day eight combination doses were studied. The doses were chosen based upon the ED_{50}'s established in the preceding day's experiment, which, under the assumption of additivity, would provide protection for 50% of the mice. These doses were tested in order to observe those ratio(s) of the combination drugs that would yield a synergistic effect. Combinations for which five or more mice exhibit blockage of writhing are candidates for further study. The doses of the constituent drugs in mg/kg for

the eight groups were for ibuprofen (I) and diphenhydramine (D) respectively, [abbreviated as (I,D)]: (22,4), (19,8), (16,12), (14,6), (11,20), (9,24), (6,28), (4,32). Table 2 shows for each of these combination doses, the number of mice protected from writhing activity.

On the third and fourth days the four specific fixed ratios that achieved 5 or more protected mice were studied in more detail, i.e., the first combination treatment used a ratio of ibuprofen to diphenhydramine of 19:8 and the doses of the constituent drugs in mg/kg that were studied were (8,3), (12,5), (16,7) and (28,12). The second combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 6:28 and the doses of the constituent drugs in mg/kg that were studied were (3,14), (4.5,21) and (9,42). The third combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 9:24 and the doses of the constituent drugs in mg/kg that were studied were (3,8), (6,16), (12,32) and (15,40). The fourth combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 4:32 and the doses of the constituent drugs in mg/kg that were studied were (3,24), (3.5,28) (4.5,36) and (5,40).

Under the assumption of additivity each dose of each combination is equivalent to a dose of ibuprofen, based on the relative potency (ρ) of diphenhydramine to ibuprofen obtained from the experiment on the first day. Thus, for example, in the dose ratio 19:8 the combination of 28 mg/kg of ibuprofen and 12 mg/kg of diphenhydramine is, under the assumption of additivity, equivalent to ($28+12\rho$) mg/kg of ibuprofen. Table 3 shows for each dose of each of the combination doses tested the number of mice observed to

be protected and the ibuprofen equivalent dose. For each of the four combination ratios, ED_{50}'s were estimated based on the observed number of mice protected at each ibuprofen equivalent dose using the method of Finney. Table 4 displays the estimated ED_{50}'s for each ratio.

RESULTS

The surprising synergistic effects of combining ibuprofen with diphenhydramine can be seen from the results of Tables 3 and 4 and Figure 1. Figure 1 summarizes all of the findings by depicting the ED_{50}'s obtained for each treatment alone, the ED_{50} line if the treatments were additive, the number of mice/protected from writhing for each treatment studied and the estimated ED_{50}'s for each combination ratio.

The ED_{50} of ibuprofen alone is estimated to be 24 mg/kg and for diphenhydramine to be 38 mg/kg. The relative potency of diphenhydramine to ibuprofen is 24/38. Among the 8 ratios tested on the second day, synergism appears to be present for four ratios, and these ratios were further investigated on days 3 and 4. The ED_{50}'s were found to be for the dosage ratio of 19:8, 23 mg/kg of ibuprofen, for the dosage ratio 6:28, 19 mg/kg of ibuprofen, for the dosage ratio 9:24, 18 mg/kg of ibuprofen, and for the dosage ratio 4:32, 23 mg/kg of ibuprofen. Two of these ED_{50}'s are substantially less than 24 mg/kg of ibuprofen which is the ED_{50} that would be expected if the effects were additive. This represents a 25% reduction of the amount of ibuprofen that is required to obtain the effect in 50% of the animals. The graph in Figure 1 indicates that many other dose ratios as well would produce an unexpected synergistic effect.

NUMBER OF MICE PROTECTED AT TESTED DOSE LEVELS OF IBUPROFEN AND DIPHENHYDRAMINE

Table 1

Dose of Ibuprofen mg/kg	Dose of Diphenhydramine mg/kg	Number of Mice Protected	Number of Mice Not Protected
2	-	0	8
5	-	0	8
10	-	1	7
20	-	3	5
-	5	1	7
-	10	2	6
-	20	3	5
-	40	4	4

Table 2

NUMBER OF MICE PROTECTED AT TESTED DOSES* OF THE COMBINATION OF IBUPROFEN AND DIPHENHYDRAMINE

Dose of Ibuprofen mg/kg	Dose of Diphenhydramine mg/kg	Number of Mice Protected	Number of Mice Not Protected
22	4	4	4
19	8	5	3
16	12	3	5
14	16	4	4
11	20	4	4
9	24	5	3
6	28	5	3
4	32	5	3

* Doses were chosen based upon ED_{50}'s of ibuprofen and diphenhydramine which under the assumption of additivity would provide protection for 50% of the mice.

Table 3

NUMBER OF MICE PROTECTED AT TESTED DOSE LEVELS OF FOUR DIFFERENT RATIOS OF DOSES OF IBUPROFEN TO DIPHENHYDRAMINE

Combination Dose Ratio	Dose of Ibuprofen mg/kg	Dose of Diphenhydramine mg/kg	Ibuprofen Equivalent Dose Under Assumption of Additivity mg/kg	Number of Mice Protected	Number of Mice Not Protected
19:8	8	3	9.9	1	7
	12	5	15.2	3	5
	16	7	20.4	2	6
	28	12	35.6	6	2
9:24	3	8	8.0	2	3
	6	16	16.1	2	6
	12	32	32.2	6	2
	15	40	40.2	8	0
6:28	3	14	11.8	2	6
	4.5	21	17.7	3	5
	9	42	35.5	7	1
4:32	3	24	18.1	2	6
	3.5	28	21.1	3	5
	4.5	36	27.2	6	2
	5	40	30.2	6	2

Table 4

ED_{50}'s OF COMBINATION TREATMENTS IN IBUPROFEN EQUIVALENT DOSES

Tested Combination Dose Ratios of Ibuprofen to Diphenhydramine		Ibuprofen Equivalent ED_{50} mg/kg
I	D	I
100	0	24
19	8	23
9	24	18*
6	28	19*
4	32	23
0	100	24

* ED_{50}'s substantially less than 24 mg/kg, the dose that would be expected were the effects additive.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. For example, effective dosages other than the preferred ranges set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal treated, severity of pain or inflammation, dosage related adverse effects, if any, observed and analogous considerations. Likewise, the specific pharmacological responses observed may vary depending upon the particular relative amounts of active components employed or whether same are used in combination with suitable pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

CLAIMS

1. A pharmaceutical composition of matter for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism, said composition comprising an analgesically and anti-inflammatorily effective amount of a nonsteroidal anti-inflammatory drug selected from the group consisting of propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenyl-carboxylic acid derivatives and oxicams and an amount of diphenhydramine sufficient to synergistically enhance said analgesic and anti-inflammatory response.

2. A composition according to Claim 1, wherein the nonsteroidal anti-inflammatory drug is a propionic acid derivative.

3. A composition according to Claim 1, wherein the nonsteroidal anti-inflammatory drug is an acetic acid derivative.

4. A composition according to Claim 1, wherein the nonsteroidal anti-inflammatory drug is a fenamic acid derivative.

5. A composition according to Claim 1, wherein the nonsteroidal anti-inflammatory drug is a biphenyl-carboxylic acid derivative.

6. A composition according to Claim 1, wherein the nonsteroidal anti-inflammatory drug is an oxicam.

7. A composition according to Claim 2, wherein the propionic acid derivative is ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaproxin, pranoprofen, miroprofen, tioxaprofen, suprofen, aluminoprofen, tiaprofenic acid, fluprofen or bucloxic acid.

8. A composition according to Claim 2, wherein the propionic acid derivative is ibuprofen.

9. A composition according to Claim 3, wherein the acetic acid derivative is indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac or oxepinac.

10. A composition according to Claim 3, wherein the acetic acid derivative is zomepirac sodium.

11. A composition according to Claim 4, wherein the fenamic acid derivative is mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid ortolfenamic acid.

12. A composition according to Claim 4, wherein the fenamic acid derivative is mefenamic acid.

13. A composition according to Claim 5, wherein the biphenylcarboxylic acid is diflunisal or flufenisal.

14. A composition according to Claim 5, wherein the biphenylcarboxylic acid is diflunisal.

15. A composition according to Claim 6, wherein the oxicam is piroxicam.

16. A pharmaceutical composition according to Claim 1, further comprising a nontoxic pharmaceutically acceptable inert carrier.

17. A pharmaceutical composition according to Claims 1 or 8, comprising from about 50 to 400 mg ibuprofen.

18. A pharmaceutical composition according to Claim 1, comprising from about 12.5 to 50 mg. diphenhydramine.

19. A pharmaceutical composition according to Claim 1, wherein said diphenhydramine is present as the pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition according to Claim 5, wherein said pharmaceutically acceptable salt is the hydrochloride.

21. A pharmaceutical composition according to Claims 1 or 8, comprising from about 100 to 400 mg ibuprofen and from about 25 to 50 mg diphenhydramine.

22. A pharmaceutical composition according to Claims 1 or 2, said composition being adapted for oral administration.

23. A pharmaceutical composition according to Claim 22, said composition being formulated as a tablet, capsule or elixir.

24. A pharmaceutical composition according to Claim 1, said composition being adapted for oral administration in sustained release form.

25. A pharmaceutical composition according to Claims 1 or 2, said composition being adapted for parenteral administration.

26. A pharmaceutical composition according to Claim 25, said composition being formulated for intramuscular administration.

27. A pharmaceutical composition of matter for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism, said composition comprising an analgesically and anti-inflammatorily effective amount of a nonsteroidal anti-inflammatory drug selected from the group consisting of about 100mg to 400 mg of propionic acid derivatives, about 25 mg to 200 mg ofacetic acid derivatives, about 125 mg to 250 mg of fenamic acid derivatives, about 125 mg to 500 mg of biphenyl-carboxylic acid derivatives and about 10 mg to 20 mg of oxicam and an amount of diphenhydramine sufficient to synergistically enhance said analgesic and anti-inflammatory response.

28. A method for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism in need of such treatment, comprising

administering to such organism an analgesically and anti-inflammatorily effective amount of a non-steroidal anti-inflammatory drug selected from the group consisting of propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenyl-carboxylic acid derivatives and oxicams and an amount of diphenhydramine sufficient to synergistically enhance said analgesic and anti-inflammatory response.

29. A method according to Claim 28, wherein the non-steroidal anti-inflammatory drug is a propionic acid derivative.

30. A method according to Claim 28, wherein the non-steroidal anti-inflammatory drug is an acetic acid derivative.

31. A method according to Claim 28, wherein the non-steroidal anti-inflammatory drug is a fenamic acid derivative.

32. A method according to Claim 28, wherein the non-steroidal anti-inflammatory drug is a biphenyl carboxylic acid derivative.

33. A method according to Claim 28, wherein the non-steroidal anti-inflammatory drug is an oxicam.

34. A method according to Claim 28, wherein the propionic acid derivative is ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaproxin, pranoprofen, miroprofen, tioxaprofen, suprofen, aluminoprofen, tiaprofenic acid, fluprofen or bucloxic acid.

35. A method according to Claim 28, wherein the propionic acid derivative is ibuprofen.

36. A method according to Claim 28, wherein the acetic acid derivative is indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac or oxepinac.

37. A method according to Claim 28, wherein the acetic acid derivative is zomepirac sodium.

38. A method according to Claim 28, wherein the fenamic acid derivative is mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid ortolfenamic acid.

39. A method according to Claim 28, wherein the fenamic acid derivative is mefenamic acid.

40. A method according to Claim 28, wherein the biphenylcarboxylic acid is diflunisal or flufenisal.

41. A method according to Claim 28, wherein the biphenylcarboxylic acid is diflunisal.

42. A method according to Claim 28, wherein the oxicam is piroxicam.

43. A method according to Claim 29, comprising from about 50 to 400 mg ibuprofen.

44. A method according to Claim 43, comprising from about 100 to 400 mg ibuprofen.

45. A method according to Claim 28, comprising from about 12.5 to 50 mg diphenhydramine.

46. A method according to Claim 45, comprising from about 25 to 50 mg diphenhydramine.

47. A method according to Claim 28, wherein said composition is administered orally.

48. A method according to Claim 47, wherein said composition is administered daily in divided doses comprising from about 100 to 400 mg ibuprofen and 25 to 50 mg diphenhydramine.

49. A method for promoting an enhanced analgesic and anti-inflammatory response in a mammalian organism in need ofsuch treatment, comprising administering to such organism an analgesically and anti-inflammatorily effective amount of the composition according to Claim 27.

50. A method according to Claim 13, wherein said composition is administered orally at bedtime as an analgesically and anti-inflammatorily effective nighttime sleep aid.

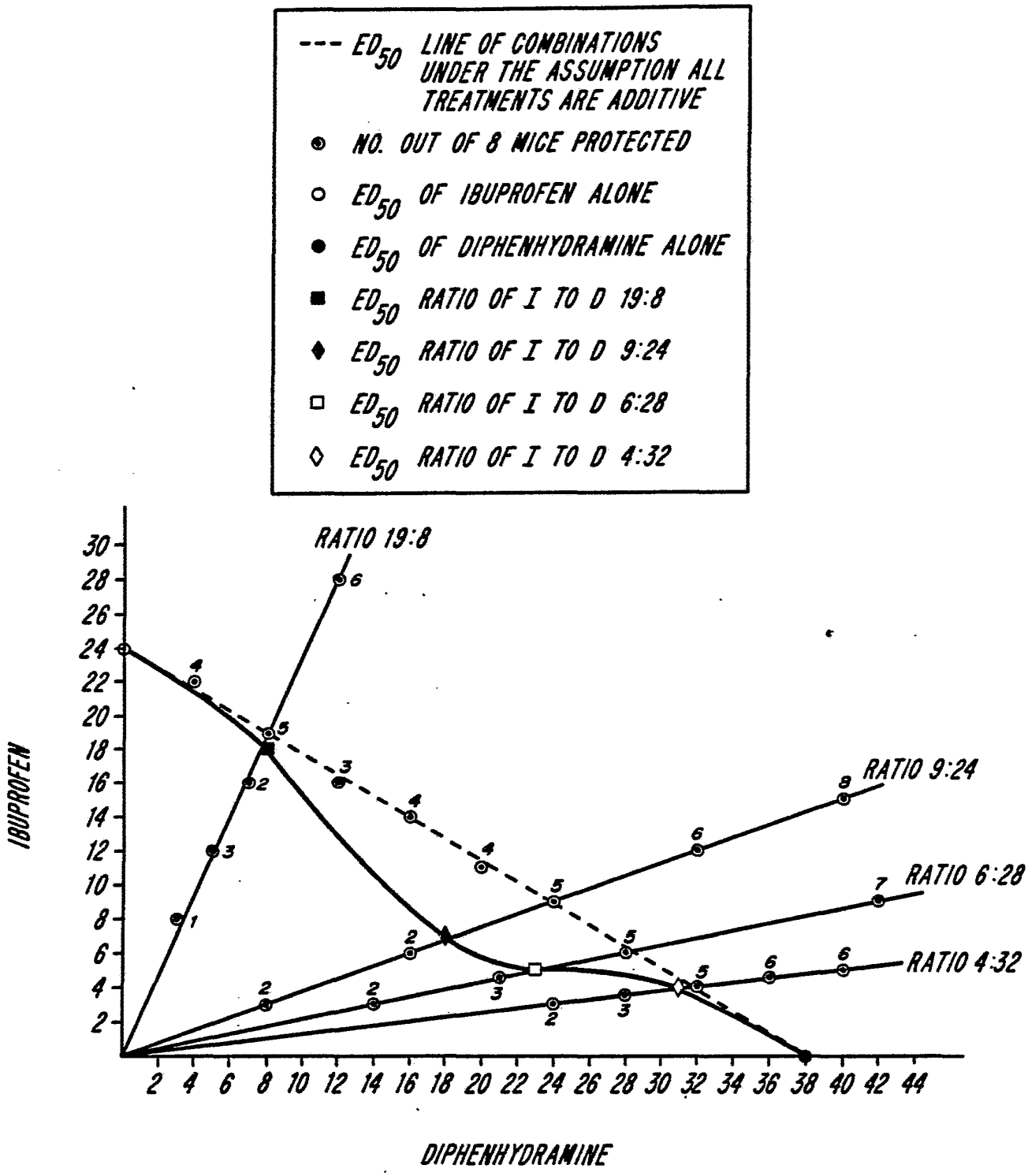

--- ED_{50} LINE OF COMBINATIONS UNDER THE ASSUMPTION ALL TREATMENTS ARE ADDITIVE
NO. OUT OF 8 MICE PROTECTED
ED_{50} OF IBUPROFEN ALONE
ED_{50} OF DIPHENHYDRAMINE ALONE
ED_{50} RATIO OF I TO D 19:8
ED_{50} RATIO OF I TO D 9:24
ED_{50} RATIO OF I TO D 6:28
ED_{50} RATIO OF I TO D 4:32
RATIO 19:8
RATIO 9:24
RATIO 6:28
RATIO 4:32
IBUPROFEN
DIPHENHYDRAMINE
30 28 26 24 22 20 18 16 14 12 10 8 6 4 2
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/00195

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 45/06; A 61 K 31/19 // (A 61 K 31/19; 31/135)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Unlisted Drugs, vol. 20, no. 11, November 1968 (Chatham, New Jersey, US) page 167e "Infacete"	1-27
A	Dictionnaire Vidal, 1961, O.V.P. (Paris, FR) page 51: "Allerga-Aspirine"	1-27
A	Rote Liste, 1961, Edition Cantor (Aulendorf/Württ., DE) page 841 "Schwöpyrin"	1-27
P,X	Chemical Abstracts, vol. 101, no. 23, 3 December 1984 (Columbus, Ohio, US) D.L. Traber: "Ibuprofen and diphenhydramine reduce the lung lesion of endotexemia in sheep", see page 39, left-hand column, abstract no. 204101x, & J. Trauma 1984, 24(9), 835-40	1-27

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26th April 1985	31 MAI 1985
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 4420483 (ABRAHAM SUNSHINE) 13 December 1983 (cited in the application)	1-27

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [x] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. [x] Claim numbers °)..... because they relate to subject matter not required to be searched by this Authority, namely:

°) 28-50. See Rule 39.1:iv : Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 8500195 (SA 8863)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/05/85

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4420483	13/12/83	BE-A-	897355	14/11/83
		FR-A-	2530468	27/01/84
		WO-A-	8400487	16/02/84
		AU-A-	1828783	23/02/84
		SE-A-	8401537	20/03/84
		NL-A-	8320239	01/06/84
		GB-A-	2132891	18/07/84
		DE-W-	3390114	10/01/85

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(54) Title: NEW THERAPEUTICALLY ACTIVE COMPOUND AND A PROCESS FOR ITS PREPARATION

(57) Abstract

The novel compound 5-fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and physiologically acceptable salts thereof as well as intermediates, pharmaceutical compositions containing the compound as active ingredient, and the use of the compound in medicine.

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New Therapeutically Active Compound and a Process for its Preparation

DESCRIPTION

Field of the invention

The object of the present invention is to provide a novel compound, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.

The present invention also relates to the use of the compound of the invention, especially therapeutically acceptable salts thereof, for inhibiting gastric acid secretion in mammals including man. In a more general sense, the compound of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome. Furthermore, the compound may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. It may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound may also be useful in the treatment of diseases related to bone metabolism disorders as well as the treatment of glaucoma.

The invention also relates to pharmaceutical compositions containing the compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to processes for preparation of such new compound, to novel intermediates in the preparation of the compound of the invention, and to the use of the active compound for the preparation of pharmaceutical compositions for the medical use indicated above.

It is a specific primary object of the invention to provide a compound with a high level of bioavailability. The compound of the invention will also exhibit high stability properties at neutral pH and a high potency in regard to inhibition of gastric acid secretion. Bioavailability is defined as the fraction, or percent, of the administered dose of compound that is absorbed unchanged into the systemic blood. Potency is in this application defined as the ED_{50} value.

Prior art and background of the invention

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents. Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, EP 124 495, US 4 555 518, US 4 727 150, US 4 628 098, EP 208 452 and Derwent abstract 87-294449/42. Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory diseases are disclosed in US 4 539 465.

The invention

Compounds described in the prior art, as described above, are effective acid secretion inhibitors, and are thus

useful as antiulcer compounds. In order to further enhance the usefulness of this type of drugs, a higher bioavailability has been desired, but still the compounds should have a high potency in inhibiting gastric acid secretion and also a high chemical stability at neutral pH.

It has been recognized that 2-[(2-pyridinylmethyl)-sulfinyl]-1H-benzimidazoles tested show a great variability in bioavailability as well as in potency and stability, and it is difficult to identify compounds possessing all the three advantageous properties. There is no guidance in the prior art on how to obtain compounds with this combination of properties.

It has been found that the compound of the invention shows exceedingly high bioavailability, and still the compound is very effective as inhibitor of gastric acid secretion and exhibits a high chemical stability in solution at a neutral pH. Thus the compound of the invention can be used in the indications given above in mammals including man.

The compound of the invention is 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl) methyl]sulfinyl])-1H-benzimidazole (compound I) and physiologically acceptable salts thereof. The compound of the invention has an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. Also five synthetic intermediates and process for the preparation are within the scope.

Preparation

The compound of the invention, may be prepared according to the following method:

Oxidizing 5-fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-thio-1H-benzimidazole (compound II) to give the compound of the invention. This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers, ketones.

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbiotically by using a suitable microorganism.

Depending on the process conditions and the starting materials, the compound of the invention is obtained either in neutral or salt form. Both the neutral compound and the salts of this are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates.

Alkaline salts of the compound of the invention are examplified by its salts with Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, and $N^+(R)_4$, where R is (1-4 C)alkyl. Particularly preferred are the Na^+, Ca^{2+} and Mg^{2+} salts. Especially preferred are the Na^+ and Mg^{2+} salts. Such salts may be

prepared by reacting the compound with a base capable of releasing the desired cation.

Examples of bases capable of releasing such cations, and examples of reaction conditions are given below.

a) Salts wherein the cation is Li^+, Na^+ or K^+ are prepared by treating the compound of the invention with LiOH, NaOH or KOH in an aqueous or nonaqueous medium or with LiOR, $LiNH_2$, $LiNR_2$, NaOR, $NaNH_2$, $NaNR_2$, KOR, KNH_2 or KNR_2, wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous medium.

b) Salts wherein the cation is Mg^{2+} or Ca^{2+}, are prepared by treating the compound of the invention with $Mg(OR)_2$, $Ca(OR)_2$ or CaH_2, wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran.

Racemates obtained can be separated into the pure enantiomers. This may be done according to known methods, e.g. from racemic diastereomeric salts by means of chromatography or fractional crystallization.

The starting materials described in the intermediate examples may be obtained according to processes known per se.

For clinical use the compound of the invention is formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administration. The pharmaceutical formulation contains the compound of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These

pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing the compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound of the

invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of the compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1 Preparation of 5-fluoro-2-[[(4-cyclopropyl-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

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5- Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-thio]-1H-benzimidazole (1.25 g, 0.0036 mol) was dissolved in CH_2Cl_2 (40 ml). $NaHCO_3$ (0.6 g, 0.0072 mol) dissolved in H_2O (20 ml) was added and the mixture was cooled to +2°C. m-Chloroperbenzoic acid, 84% (0.73 g, 0.0036 mol) dissolved in CH_2Cl_2 (5 ml) was added under stirring. Stirring was continued at room temperature for 15 min. The two phases were separated and NaOH (0.29 g, 0.0072 mol) dissolved in H_2O (25 ml) was added to the organic phase. The mixture was stirred, the phases were separated and the H_2O phase was treated with Norite and filtered. Methylformiate (0.45 ml, 0.0073 mol) dissolved in H_2O

(5 ml) was added dropwise under stirring. After extraction with CH_2Cl_2 and drying with Na_2SO_4 the solvent was evaporated. In this way the title compound was obtained (0.93 g, 69%). NMR data for the final product is given below.

Example 2. Preparation of 5-fluoro-2-[[(4-cyclopropyl-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, sodium salt

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5-Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole (5 g; 14.5 mmol) dissolved in dichloromethane (100 ml) and sodium hydroxide (0.56 g; 14 mmol) dissolved in water (100 ml) were transferred to a separatory funnel. The mixture was shaken to equilibrium whereupon the solvent phases were separated. The water solution was washed with dichloromethane (2 x 25 ml) and then freeze dried. The residue was recrystallized from dichloromethane/diethyl ether. Yield: 3.7 g (71 %) of the title compound. NMR data is given below.

Table 1

Ex.	Solvent	NMR data δ ppm (500 MHz)
1.	$CDCl_3$	0.22 (m, 2H); 0.60 (m, 2H); 1.10 (m, 1H); 3.45 (m, 1H); 3.60 (m, 1H); 4.52 (d, 1H); 4.70 (d, 1H); 6.65 (d, 1H); 6.70 (dd, 1H); 7.08 (m, 1H); 7.30-7.90 (b, 2H); 8.28 (d, 1H)
2.	D_2O $\delta(D_2O,4.82)$	0.09 (m, 2H); 0.49 (m, 2H); 0.88 (m, 1H); 2.92 (m, 1H); 3.34 (m, 1H); 4.62 (d, 1H); 4.71 (d, 1H); 6.05 (d, 1H); 6.75 (m, 1H); 7.05 (m, 1H); 7.33 (m, 1H); 7.58 (m, 1H); 8.23 (d, 1H)

Preparation of synthetic intermediates

Example I 1. Preparation of 4-cyclopropylmethoxy-2-methylpyridine-1-oxide.

To sodium hydride (55% pure) (4.4 g, 0.1 mol) (washed with petroleum ether), cyclopropyl-methanol (50 ml) was added. Then a solution of 2-methyl-4-nitropyridine-N-oxide (6.5 g, 0.042 mol) in cyclopropylmethanol (30 ml) was added during about 1 h. The dark brown mixture was heated to 90°C and stirred at 90° C for about 1 h. Thereafter the cyclopropylmethanol was distilled off under reduced pressure and methylene chloride (100 ml) was added to the residue. The mixture was stirred for about 30 minutes, then filtered and concentrated which gave 9.5 g of crude material.

The crude material was purified by flash chromatography on silica with methylene chloride-methanol (90-10) as eluent, giving 4.0 g (53%) of pure title compound. NMR data is given below.

Example I 2. Preparation of 2-acetoxymethyl-4-cyclopropylmethoxypyridine.

4-cyclopropylmethoxy-2-methylpyridine-1-oxide (3.8 g 0.021 mol) was dissolved in acetic anhydride (10 ml) and was added dropwise to acetic anhydride (20 ml) (warmed to 90°C). After the addition the temperature was raised to 110°C and the mixture was stirred at 110°C for 1 h and then the solvent was distilled off and the crude product was used without purification. NMR data is given below.

Example I 3. Preparation of 4-cyclopropylmethoxy-2-hydroxymethylpyridine

To the crude 2-acetoxymethyl-4-cyclopropylmethoxy pyridine, NaOH (100 ml 2 M) was added and the mixture was refluxed for 2 hours. The mixture was extracted with methylene chloride, and the phases were separated. The organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated off, yielding 2.7 g of crude title compound. NMR data is given below. The crude product was used without any further purification.

Example I 4. Preparation of 4-cyclopropylmethoxy-2-chloromethylpyridine hydrochloride

4-cyclopropylmethoxy-2-hydroxymethyl pyridine (93% pure) (0.9 g 0.0046 mol) was dissolved in methylene chloride (10 ml) and cooled to 0°C. $SOCl_2$ (0.5 ml, 0.0069 mol) in methylene chloride (5 ml) was added dropwise at 0°C and the reaction mixture was stirred 15 min at room temperature. Isopropanol (0.5 ml) was added and the mixture was evaporated giving the desired product (0.68 g, 78%). NMR-data is given below.

Example I 5. Preparation of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl)thio]-1H-benzimidazole used as starting material

To 5-fluoro-2-mercapto-1H-benzimidazole (0.88 g, 0.0051 mol) in methanol (25 ml) NaOH (0.2 g, 0.0051 mol) dissolved in H_2O (1 ml) and 4-cyclopropylmethoxy-2-chloromethyl-pyridine hydrochloride (0.91 g, 0.0046 mol)

dissolved in methanol (10 ml) were added in the given order. The mixture was heated to boiling and NaOH (0.2 g, 0.005 mol) dissolved in H_2O (1 ml) was added and the mixture was refluxed for 1 hour. After evaporation of methanol, CH_2Cl_2 (75 ml) and H_2O (50 ml) were added and pH adjusted to 10. The mixture was vigorously stirred, the phases were separated, the organic phase was dried over Na_2SO_4 and evaporated giving the desired product (1.25 g, 72%). NMR data for the product is given below.

Table 2.

Ex	Solvent	NMR data δ ppm
I 1.	$CDCl_3$ (500 MHz)	0.36 (m, 2H); 0.68 (m, 2H); 1.26 (m, 1H); 2.52 (s, 3H); 3.83 (d, 2H); 6.70 (dd, 1H); 6.77 (d, 1H); 8.16 (d, 1H)
I 2.	$CDCl_3$ (500 MHz)	0.37 (m, 2H); 0.69 (m, 2H); 2.16 (s, 3H); 3.87 (d, 2H); 6.75 (dd, 1H); 6.87 (d, 1H); 8.42 (d, 1H)
I 3.	$CDCl_3$ (500 MHz)	0.36 (m, 2H); 0.67 (m, 2H); 1.27 (m, 1H); 3.86 (d, 2H); 4.69 (s, 2H); 6.72 (dd, 1H), 6.78 (d, 1H); 8.33 (d, 1H)
I 4.	DMSO-d_6 (300 MHz)	0.40 (m, 2H); 0.60 (m, 2H), 1.30 (m, 1H); 4.20 (d, 2H); 5.00 (s, 2H); 7.45 (dd, 1H); 7.65 (d, 1H); 8.70 (d, 1H)
I 5.	$CDCl_3$ (500 MHz)	0.36-0.39 (m, 2H); 0.67-0.71 (m, 2H); 1.27 (m, 1H); 3.89 (d, 2H), 4.29 (s, 2H); 6.81 (dd, 1H); 6.89 (d, 1H); 6.94 (m, 1H); 7.24 (dd, 1H); 7.46 (dd, 1H), 8.43 (d, 1H)

The best mode of carrying out the invention known at present is to use the sodium salt of the compound of the invention, thus the compound described in Example 2.

Pharmaceutical preparations containing the compound of the invention as active ingredient are illustrated in the following formulations.

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 1	1.0	g
Sugar, powder	30.0	g
Saccharine	0.6	g
Glycerol	5.0	g
Flavouring agent	0.05	g
Ethanol 96%	5.0	g
Distilled water q.s. to a final volume of	100	ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 1 as Mg salt	500	g
	Lactose	700	g
	Methyl cellulose	6	g
	Polyvinylpyrrolidone cross-linked	50	g
	Magnesium stearate	15	g
	Sodium carbonate	6	g
	Distilled water	q.s.	

II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to example 1, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^{R}, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to Example 1	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 1	4 g
Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Biological Effects

Bioavailability

Choice of Species for Testing.

The results from tests on two different animal species, rat and dog, vary in regard to measured level of bioavailability for the same compound. We believe that the rat is the more relevant species for bioavailability testing. This is based on our belief that liver metabolism has the most predominant impact upon bioavailability, and that the liver metabolic pattern in man for this type of compounds is quite similar to that of

the male rat (more so than of the female rat and the dog). Moreover, test results of bioavailability in the male rat will tend to give a broader "spread" compared with the test results in the dog, and thus the male rat model will give more clear differences in bioavailability between different compounds. Stated in another way, the bioavailability as tested in the male rat can be expected to give a better estimate of the relative differences in man between different test compounds compared with the test results obtained when using the same compounds in the dog.

Assessment of Bioavailability.

Bioavailability is assessed by calculating the quotient between the area under plasma concentration (AUC) curve following intraduodenal (id) administration and intravenous (iv) administration from the rat or the dog. Low, therapeutically relevant doses, were used. This method is scientifically recognized as valid for assessing bioavailability (see for instance: M. Rowland and T.N. Tozer, Clinical Pharmacokinetics, 2nd ed., Lea & Febiger, London 1989, p 42). The data from both the rat and the dog are provided in Table 3.

Rough Screening Model.

Since the bioavailability model described above is time and labour intensive, and requires a large number of plasma analyses, also a rough screening model, based on relative potencies to inhibit acid secretion, has been used (see for instance: A. Goth, Medical Pharmacology, 7th ed., C.V. Mosby Company, Saint Louis 1974, p 19). Thus, the ratio (called "Bioavailability" in Table 3) between the ED_{50} at intravenous administration and the ED_{50} at

intraduodenal administration was calculated. Also these data are provided in Table 3.

Potency

The potency for inhibition of acid secretion has been measured in the male rat and the dog, both intravenously and intraduodenally. When it comes to relevance of the animal test data for potency of a given compound in man for the present type of compounds, it is believed that potency in man will correspond to a level somewhere between what is measured in the male rat and what is measured in the dog. Potency data from the two animal species are given in Table 3.

Biological Tests

Inhibition of Gastric Acid Secretion in the Conscious Male Rat.

Male rats of the Sprague-Dawley strain were used. They were equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of gastric secretions and administration of test substances, respectively. A fourteen days recovery period after surgery was allowed before testing commenced.

Before secretory tests, the animals were deprived of food but not water for 20 h. The stomach was repeatedly washed through the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion was stimulated with a infusion during 3.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions were collected in 30-min fractions. Test substances or vehicle were given iv or id at 90 min after starting the stimulation, in a volume of 1

ml/kg. Gastric juice samples were titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output calculated as the product of titrant volume and concentration. Further calculations were based on group mean responses from 4-5 rats. The acid output during the periods after administration of test substances or vehicle were expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition was calculated from the fractional responses elicited by test compound and vehicle. ED_{50}-values were obtained from graphical interpolation on log dose-response curves, or estimated from single-dose experiments assuming a similar slope for all dose-response curves. An estimation of the bioavailability was obtained by calculating the ratio ED_{50}iv/ED_{50}id. The results reported are based on gastric acid secretion during the second hour after drug/vehicle administration.

Bioavailability in the Male Rat.

Male adult rats of the Sprague-Dawley strain were used. One day, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein. (Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substances. The same dose (4 µmol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given

dose. The samples were frozen as soon as possible until analysis of the test compound.

The area under the blood concentration vs time curve, AUC, was determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following intraduodenal administration was calculated as

$$F(\%) = \frac{AUC_{id}}{AUC_{iv}} \times 100$$

Inhibition of Gastric Acid Secretion and Bioavailability in the Conscious Dog.

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated ventricular fistula for the collection of gastric secretions.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given id or iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0.

Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED_{50}-values were obtained by graphical interpolation on log dose - response curves, or estimated from single-dose experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

Blood samples for the analysis of test compound concentration in plasma were taken at intervals up to 3 h after dosing. Plasma was separated and frozen within 30 min after collection. AUC (area under the plasma concentration - time curve), extrapolated to infinite time, was calculated by the linear trapezoidal rule. The systemic bioavailability (F%) after id administration was calculated as 100 x (AUC_{id}/AUC_{iv}).

Chemical Stability

The chemical stability of various compounds of the invention has been followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 3 show the half life (t 1/2) at pH 7, that is the time period after which half the amount of the original compound remains unchanged.

Results of biological and stability tests

Table 3 gives a summary of the test data available for the compound of the invention and a structurally closely related compound in the prior art, called Ref. in Table 3, namely 5-fluoro-2-[[(4-isopropoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole described in US 4 727 150. As can be seen from Table 3 the compound according to the invention has a high bioavailability (F =

82% in the rat), high potency (ED_{50}iv = 1.2 µmol/kg, ED_{50}id = 2.2 µmol/kg in the rat) and a high chemical stability (t 1/2 = 23 h). Moreover, considering the most distinguishing property for the compound of the invention, the bioavailability, the compound of the invention has a much higher value (82% vs 31%) compared to that of the Ref. compound, and is better in the other properties as well (ED_{50}iv = 1.8 µmol/kg, ED_{50}id = 4.0 µmol/kg and t 1/2 = 14 h for the Ref compound).

Table 3, Biological Test Data and Stability Data

Test compound Example no.	Inhibition of acid secretion				"Bioavailability" measured by the Rough Screening Model Rat ED_{50} iv/ /ED_{50} id (%)	Bioavailability measured by the AUC-method F%		Chemical stability at pH 7
	Dog ED_{50} (µmol/kg)		Rat, ED_{50} (µmol/kg					half-life (t 1/2) h
	Route of adm. iv	id	iv	id		Dog	Rat	
1	1)	1.0	1.2	2.2	55	80	82	23
Ref.	n.t.	2)	1.8	4.0	45	n.t.	31	14

n.t. = not tested

1) Dog 1 1 µmol/kg gave 35% inhibition
Dog 2 1 " gave no effect
Dog 3 2 " gave 98% inhibition.

Thus no ED_{50} value could be estimated.

2) Dog 4 3 µmol/kg gave 95% inhibition
Dog 5 3 " gave 98% inhibition

Thus no ED_{50} value could be estimated.

CLAIMS

1. 5-Fluoro-2[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole (compound I) and physiologically acceptable salts thereof, as well as its optical enantiomers.

2. The sodium salt of the compound according to claim 1.

3. The magnesium salt of the compound according to claim 1.

4. A pharmaceutical composition containing as active ingredient the compound according to claim 1.

5. A compound as defined in claim 1 for use in therapy.

6. A compound as defined in claim 1 for use in inhibiting gastric acid secretion in mammals including man.

7. A compound as defined in claim 1 for use in the treatment of gastrointestinal inflammatory diseases in mammals including man.

8. Use of a compound according to claim 1 for the manufacture of a medicament for inhibiting gastric acid secretion in mammals including man.

9. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases in mammals including man.

10. A process for the preparation of a compound according to claim 1, by oxidizing 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole whereupon, compound

I thus obtained if desired, is converted to a salt or into a pure optical isomer.

11. 4-cyclopropylmethoxy-2-methylpyridine-1-oxide.

12. 2-acetoxymethyl-4-cyclopropylmethoxypyridine.

13. 4-cyclopropylmethoxy-2-hydroxymethylpyridine.

14. 4-cyclopropylmethoxy-2-chloromethylpyridine hydrochloride.

15. 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]-thio]-1H-benzimidazole.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 89/00740

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 401/12, 213/68, 213/89, A 61 K 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A1, 0175464 (TAKEDA CHEMICAL INDUSTRIES LTD) 26 March 1986, see the whole document --	1-15

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
2nd March 1990	1990 -03- 14
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Göran Karlsson

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 89/00740

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0175464	26/03/86	JP-A- 61050979	13/03/86
		US-A- 4727150	23/02/88

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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING IBUPROFEN AND A PROSTAGLANDIN

(57) Abstract

A pharmaceutical composition includes a core of an NSAID selected from ibuprofen and ibuprofen salts, which core is surrounded by an intermediate coating impermeable to the passage of ibuprofen and a mantle coating of a prostaglandin surrounding the coated ibuprofen core.

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PHARMACEUTICAL COMPOSITION CONTAINING IBUPROFEN AND A PROSTAGLANDIN

Background of the Invention

The invention herein is directed to a new pharmaceutical composition which consists of a generally trilayer tablet having an inner core, an intermediate barrier coating and an outer mantle coating surrounding the inner core. The inner core includes the NSAID ibuprofen or a salt of ibuprofen. The mantle coating includes a prostaglandin, described hereinafter in more detail.

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis (OA) and rheumatoid arthritis (RA). While the NSAIDs present a beneficial therapeutic value they also exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use. The chronic use of NSAIDs, the use of high dosages of NSAIDs and the use of NSAIDs by the elderly can lead to NSAID induced ulcers. NSAID induced

ulcers in the stomach can be dangerous. Such ulcers generally exhibit little or few symptoms and may cause dangerous bleeding when undetected. In some instances, bleeding ulcers can prove fatal. The United States Food and Drug Administration requires a class warning for all NSAIDs, which states: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy.

Certain prostaglandins have been shown to prevent NSAID induced ulcers. Acceptable prostaglandin compounds for the invention herein and their preparation are described in U.S. Patents 3,965,143, 4,060,691, 4,271,314, and 4,683,328. The prostaglandin compound commercially available under the USAN (United States Adopted Name) name misoprostol is a pharmaceutically acceptable prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States. Misoprostol is commercially available by prescription in such countries.

While prostaglandins are beneficial compounds and have found therapeutic usage, prostaglandins are generally considered highly unstable. Therefore, it is desirable to find prostaglandins with the desired anti-ulcerogenic

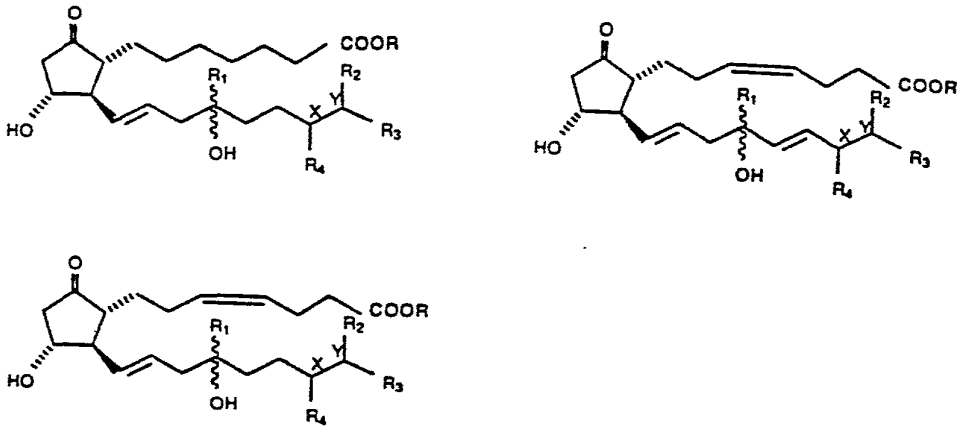
properties and which can be stabilized or provided in stabilized formulations especially with respect to contemplated oral methods of delivery.

It would be desirable to provide a pharmaceutical composition which would exhibit the beneficial properties of an NSAID and which composition would exhibit the beneficial properties of a prostaglandin for countering (by inhibiting, reducing or preventing) the ulcerogenic side effects attendant to NSAID administration.

Summary of the Invention

The invention herein is directed to a pharmaceutical composition comprising a core consisting of an NSAID selected from ibuprofen and ibuprofen salts. An intermediate barrier coating surrounds the core. Such an intermediate coating prevents contact between the NSAID and the prostaglandin to thereby inhibit any deleterious or otherwise non-beneficial interaction of the NSAID and prostaglandin such as degradation of the prostaglandin by the NSAID. A mantle coating of a prostaglandin surrounds the core and intermediate coating. The prostaglandin preferably is an orally available prostaglandin.

Acceptable prostaglandins for use herein include prostaglandins having the following structure



wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2, R_3, and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R_3 or R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X–Y bond can be saturated or unsaturated.

An especially preferred pharmaceutical composition herein has a structure wherein the core comprises the NSAID ibuprofen in a therapeutic amount such as from 300 to 800 milligrams (mg), an intermediate coating comprising

a material impervious/impermeable to the ibuprofen, and a mantle coating surrounding the core consisting of misoprostol in a therapeutic amount of 100 to 200 micrograms (mcg). An especially preferred intermediate coating can be formed from a crystalline-forming material such as a sugar, and more specifically sucrose.

The invention herein will be more fully understood with regard to the following brief description of the accompanying drawings and the following detailed description.

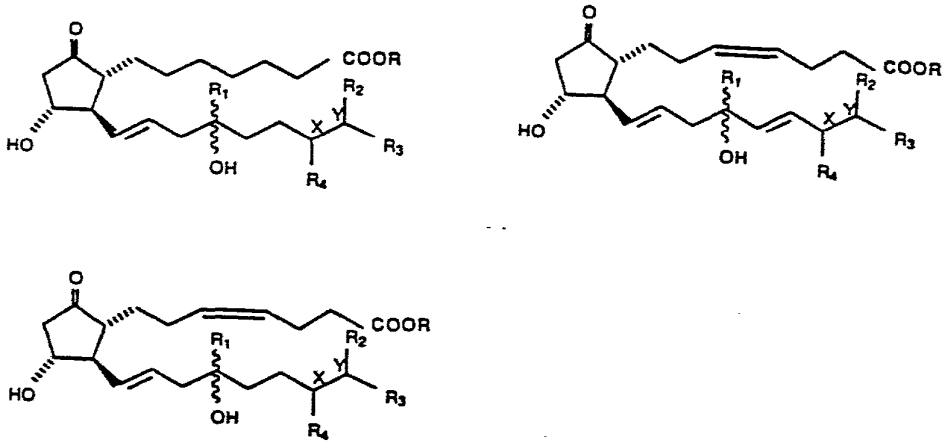
Brief Description of the Drawings

Figure 1 is a schematic representation of a tablet comprising the pharmaceutical composition herein.

Detailed Description of the Invention

The invention herein is directed to a pharmaceutical composition which is a generally trilayer tablet consisting of a core of the nonsteroidal anti-inflammatory drug (NSAID), ibuprofen and ibuprofen salts. Ibuprofen is the USAN name for (±)-2-(p-isobutylphenyl)-propionic acid. Surrounding the core is an intermediate

coating of an impervious/impermeable material to the ibuprofen. An especially preferred intermediate coating can be formed from a crystalline forming material such as a sugar, and more specifically sucrose. Surrounding the core and intermediate coating is a mantle coating which consists of a prostaglandin of the structure



wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2, R_3, and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R_3 or R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X-Y bond can be saturated or unsaturated.

The pharmaceutical composition herein can be described with regard to the accompanying drawings wherein Figure 1 schematically represents the preferred embodiment of the composition herein.

Figure 1 represents a cross sectional view of a pharmaceutical composition herein. The pharmaceutical composition consists of a generally trilayer tablet 10 which can have any geometric shape but, as is shown in Figure 1, is preferably a bi-convex tablet. It should be noted that a bi-convex tablet can have a cylindrical shape between the convex surfaces, although for ease of description herein an oval cross section is shown. The tablet 10 includes an inner core 12 which includes the NSAID consisting of ibuprofen or its salt. The inner core 12 can be formulated by compressing the ibuprofen or ibuprofen salts in any suitable tableting equipment. Standard compression tableting techniques can be employed for forming the core.

The ibuprofen can be present in any therapeutically acceptable amount. For normal dosing of ibuprofen, ibuprofen is administered in a dosing range from 400 mg to 3200 mg per day. The Physicians' Desk Reference, 44th Edition, states that the recommended dosage for osteoarthritis and rheumatoid arthritis is 1200 to 3200 mg

per day in divided doses. For mild to moderate pain the recommended dosage is 400 mg every 4 to 6 hours as necessary for relief of pain. For dysmenorrhea the recommended dosage is 400 mg every 4 hours as necessary for the relief of pain. The inner core for the pharmaceutical composition herein therefore can be in an amount to accomplish such a dosing regimen and can contain from 150 to 800 mg of ibuprofen and preferably in a dosage of 400 mg. Various excipients can also be combined with the ibuprofen as is well known in the pharmaceutical art and including the inactive ingredients listed in the PDR 44th edition for ibuprofen as sold under the brand name and trademark MOTRIN by The Upjohn Company.

If the inner core is an ibuprofen salt, the ibuprofen salt can be present in a therapeutically acceptable amount as is referred to in the above discussion with respect to the acid.

Surrounding the core 12 is a barrier or an intermediate coating 14. The intermediate coating 14 can be any suitable coating which prevents passage of the ibuprofen. Ibuprofen is a compound that exhibits sublimation. Therefore an intermediate coating material is selected from those materials which prevent the passage of such a gaseous phase. It has been found herein that

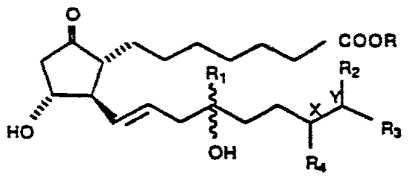
crystalline forming materials are impervious to ibuprofen in a gas phase. Any material which forms a crystalline structure can be used for the intermediate coating. An especially preferred class of compounds which can be used include crystalline forming sugars and more preferably sucrose. Sucrose is especially preferred as it exhibits crystalline properties at 55°C and it remains in the crystalline state and does not absorb any appreciable amounts of water up to a very high relative humidity value (84%). The intermediate coating 14 segregates the NSAID from the prostaglandin. The intermediate coating 14 prevents the degradation of the prostaglandin by the presence of the NSAID. Studies have shown that an admixture of misoprostol and ibuprofen is undesirably unstable for a commercially acceptable product. Solid state stability studies have shown that misoprostol is extremely unstable in the presence of ibuprofen and degrades at a rapid rate. A 10:1 mixture of ibuprofen:misoprostol stored at 55°C yields only 44% misoprostol after 4 days and only 18% after storage at 65°C for 3 days. It is, therefore, highly desirable to formulate a composition (dosage form) which would effectively separate the two active ingredients while providing a delivery system for each ingredient.

Additional studies have shown that an intermediate coating of certain polymers is unacceptable due to ibuprofen bleed through of the polymer which ibuprofen then interacts with and degrades the misoprostol. The intermediate coating can be coated onto the inner core using standard coating techniques. For example, aqueous or solvent coating techniques can be used to apply the coating to the inner core.

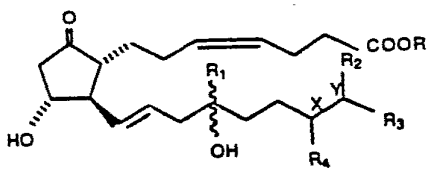
The mantle coating 16 surrounds the inner core of the NSAID and the intermediate coating, encapsulating the intermediate coated NSAID core. The mantle coating includes of a prostaglandin and more preferably an orally available prostaglandin. The mantle coating can be applied by compression coating or solvent coating techniques such as are well known in the tableting art.

The terms "prostaglandin" and/or its accepted acronym "PG" or, as more appropriately for the E-series prostaglandins, "PGE," are used herein to refer to naturally occurring or man-made E-series prostaglandins and their analogs and derivatives.

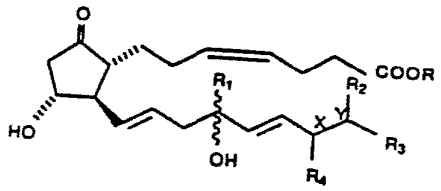
It has been found herein that acceptable prostaglandins include the E_1 prostaglandins shown by the following Formula I



E_2 prostaglandins shown by the following Formula II



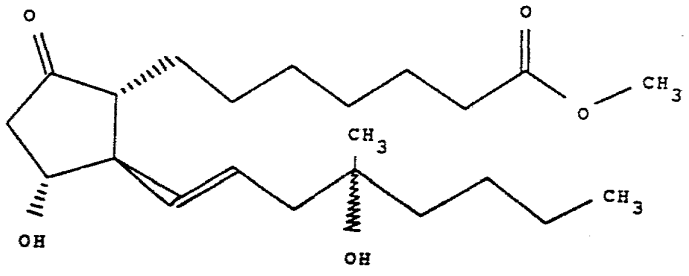
and E_3 prostaglandins shown by the following Formula III



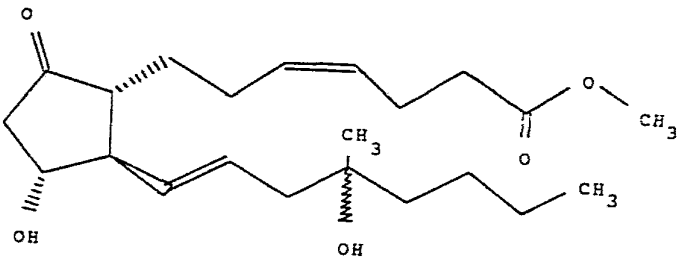
wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2, R_3, and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R_3 or R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X-Y bond can be saturated or unsaturated.

By lower alkyl is meant straight or branched chain alkyl such as methyl, ethyl, propyl, isopropyl, butyl, secondary butyl or tertiary butyl, pentyl, or hexyl with the indicated limitation of the number of carbon atoms. With regard to the illustrated structures, the dashed line indicates the grouping being behind the plane of the paper and the solid, blackened triangular shape indicates that the group is in front of the plane of the paper.

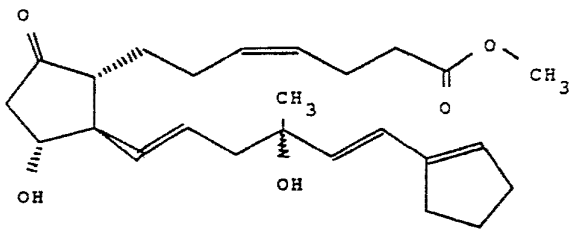
It has been found herein that acceptable prostaglandins include the prostaglandin misoprostol represented by the following Formula:



the prostaglandin enisoprost, (±)methyl 11α,16-dihydroxy-16-methyl-9-oxoprosta-4Z,13E-dien-1-oate represented by the following Formula:



and the prostaglandin methyl 7-[2B-[6-(1-cyclopenten-1-yl)-4-hydroxy-4-methyl-1E,5E-hexadienyl]-3α-hydroxy-5-oxo-1R,1α-cyclopentyl]-4Z-heptenoate represented by the following formula:



With regard to the illustrated structures, the dashed line indicates the grouping being behind the plane of the paper and the solid, blackened triangular shape indicates that the group is in front of the plane of the paper.

The prostaglandins useful in the composition herein can be prepared by known reaction schemes such as by the methods taught in U.S. Patents 3,965,143, 4,271,314 and 4,683,328. The individual isomers can be obtained by chromatographic separation.

When the prostaglandin is misoprostol, (±)methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate, the misoprostol can be present in an amount from 50 to about 500 mcg and preferably from 100 to about 200 mcg.

The invention will be further understood with regard to the following examples.

Example 1

A pharmaceutical composition was prepared consisting of an ibuprofen central core, a sucrose intermediate coating and a misoprostol mantle. The tablet had the following composition.

Component	Unit Formula (mg)
ibuprofen	400.00
pregelatinized cornstarch	155.00
croscarmallose sodium	43.00
stearic acid	12.30
acacia	5.00
sugar (sucrose)	29.00
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.10
hydroxypropyl methylcelluose	9.90
colloidal silicon dioxide	4.60
calcium sulfate	77.00
starch U.S.P.	41.00
HPMC 6 cps (Pharmacoat 606)	58.50

Example 2

A pharmaceutical composition was prepared consisting of an ibuprofen central core, a sucrose intermediate coating and a misoprostol mantle. The composition had the following composition.

Component	Unit Formula (mg)
ibuprofen	600.00
pregelatinized cornstarch	155.00
croscarmallose sodium	43.00
stearic acid	12.30
acacia	5.00
sugar (sucrose)	29.00
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.20
hydroxy propyl methyl celluose*	20.0
colloidal silicon dioxide	4.60
calcium sulfate	77.00
starch U.S.P.	41.00
HPMC 6 cps (Pharmacoat 606)	58.50

Example 3

A pharmaceutical composition is prepared consisting of an ibuprofen central core, a sucrose intermediate coating and a misoprostol mantle. The composition has the following composition.

Component	Unit Formula (mg)
ibuprofen	800.00
pregelatinized cornstarch	155.00
croscarmallose sodium	43.00
stearic acid	12.30
acacia	5.00
sugar (sucrose)	29.00
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.20
hydroxy propyl methyl celluose*	20.0
colloidal silicon dioxide	4.60
calcium sulfate	77.00
starch U.S.P.	41.00
HPMC 6 cps (Pharmacoat 606)	58.50

Example 4

The following polymers were evaluated as barriers to ibuprofen sublimation. The determination of their abilities to perform as a barriers was made by bromocresol green (BCG) indicator or by misoprostol degradation. The BCG was applied in the outer coating rather than misoprostol. The BCG coating initially was a bright shade of blue when applied but as it came into contact with the acidic ibuprofen a color change occurred and shades of green to yellow were observed.

Hydroxypropyl methylcellulose 6 cps (aqueous)

Ethyl cellulose (aqueous)

Eudragit E30D (aqueous)

Eudragit E100 (ethanol)

Polyvinyl alcohol (ethanol)

Shellac (aqueous, ethanol)

Polyvinyl acetate phthalate (aqueous)

Cellulose acetate phthalate (methylene chloride-acetone)

The observed stability data showed rapid and extensive misoprostol degradation for all of the polymer barriers tested.

Example 5

The following chemical barriers were evaluated to determine their efficacy as barriers to ibuprofen as the acid molecule.

Aluminum hydroxide/HPMC

Aluminum hydroxide/Eudragit E30D

Tricalcium Phosphate/HPMC

Calcium oxide/HPMC

Magnesium hydroxide/HPMC

Magnesium oxide/HPMC

The observed stability data showed rapid and extensive misoprostol degradation for all of the chemical barriers tested.

The composition that is the invention herein provides an ease of delivery of the NSAID ibuprofen for its therapeutic value such as the alleviation of inflammation in a system which limits the undesirable side effects of such NSAID therapy. That is, the composition herein consisting of a generally trilayer tablet provides a prostaglandin in combination with the NSAID ibuprofen whereby the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.

A particularly beneficial aspect of the invention herein is that the combination of the two components in a trilayer tablet assures compliance with the therapeutic regimen of the two active components. That is, a co-administration of the active components (ibuprofen and prostaglandin) separately can be difficult to achieve and can be difficult for a patient to faithfully follow. By placing the two active components in the same tablet or composition, adherence to the therapeutic regimen is controlled as the administration of the tablet containing the NSAID assures compliance of the administration of the prostaglandin.

The composition herein is especially utile as the composition herein exhibits a stability for the prostaglandin and the ibuprofen in such a fixed combination as herein described.

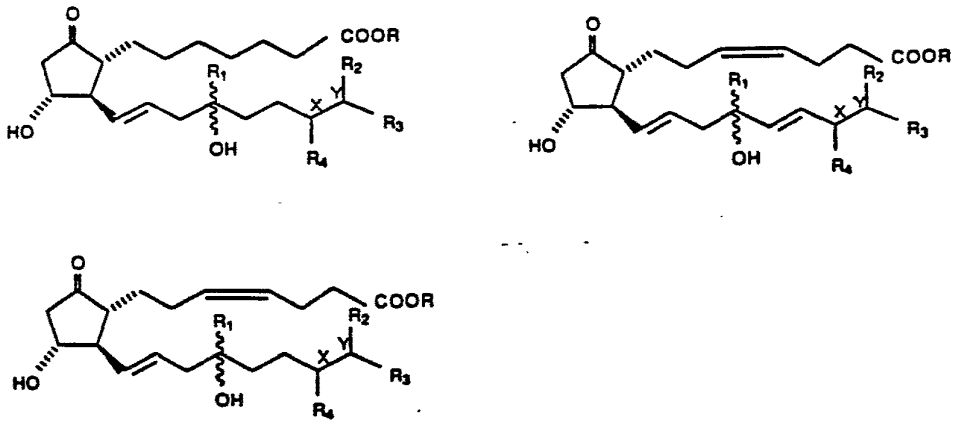
Claims

1. A pharmaceutical composition comprising:

   a. a core consisting of an NSAID selected from ibuprofen and ibuprofen salts; and

   b. an intermediate coating surrounding the core

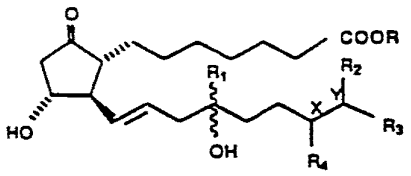
   c. a mantle coating surrounding the core consisting of a prostaglandin of the structural formula



wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2, R_3, and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y

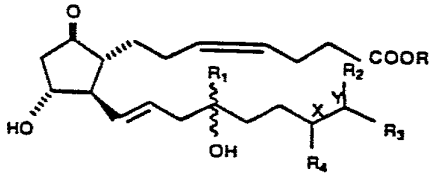
form a cycloalkenyl having 4 to 6 carbon atoms or R_3 or R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X-Y bond can be saturated or unsaturated.

2. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises a prostaglandin of the structural formula



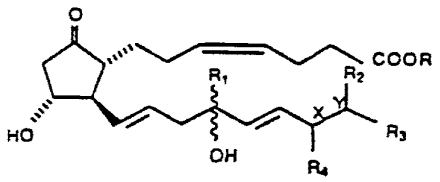
3. A pharmaceutical composition as recited in Claim 2 wherein the prostaglandin comprises misoprostol.

4. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises the structural formula



5. A pharmaceutical composition as recited in Claim 4 wherein the prostaglandin comprises enisoprost.

6. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises a structural formula



7. A pharmaceutical composition as recited in Claim 1 wherein the NSAID comprises ibuprofen.

8. A pharmaceutical composition as recited in Claim 1 wherein the NSAID comprises an ibuprofen salt.

9. A pharmaceutical composition as recited in Claim 1 wherein the intermediate coating comprises a sucrose coating.

10. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin mantle coating comprises a stabilized prostaglandin formulation.

11. A pharmaceutical composition as recited in Claim 1 wherein the NSAID comprises ibuprofen from about 150 to 800 mg, the intermediate coating comprises sucrose and the mantle coating comprises a stabilized

prostaglandin formulation containing about 100 to 200 mcg of misoprostol.

12. A method of treating inflammation comprising administering to a patient in need of such treatment, a therapeutically effective amount of a composition according to Claim 1.

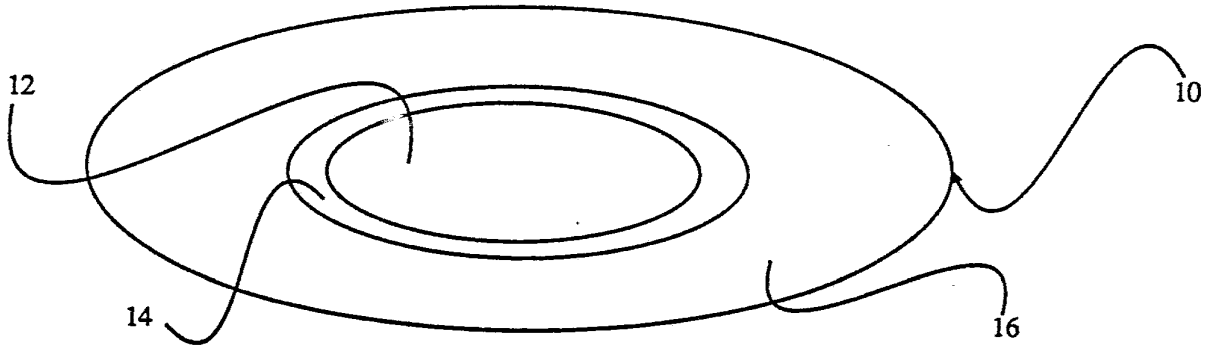


FIG 1

INTERNATIONAL SEARCH REPORT

International Appl. ion No PCT/US 91/02984

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/24 A 61 K 31/19 A 61 K 31/557

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0298666 (AMERICAN HOME PRODUCTS CORP.) 11 January 1989, see page 2, lines 1-2; pages 16-18, examples 11,12; claims 1,10 ---	1,7-9, 11
A	DE,A,2363963 (ALZA CORP.) 11 July 1974, see page 2, paragraph 1; pages 35,36, examples 19,20,21 ---	1-6,10
A	EP,A,0202112 (MAY & BAKER LTD) 20 November 1986, see page 1, line 13 - page 2, line 14; page 7, example 2 ---	1-6
A	US,A,4301146 (D.R. SANVORDEKER) 17 November 1981, see column 1, lines 26-54; column 2, example 1 --- -/-	1-6

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03-09-1991	26. 09. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PEIS M. Peis

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	GB,A,2135881 (FARMITALIA CARLO ERBA S.p.A.) 12 September 1984, see page 5, lines 46-57; page 11, formulation 1; claims	1

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. [X] Claim numbers 12 because they relate to subject matter not required to be searched by this Authority, namely:

   Pls. see Rule 39.1(iv) - PCT:
   Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6 4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9102984 SA 48471

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/09/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0298666	11-01-89	US-A- 4904477	27-02-90
DE-A- 2363963	11-07-74	US-A- 3811444	21-05-74
		AT-B- 341100	25-01-78
		AU-A- 6380473	19-06-75
		BE-A- 809161	16-04-74
		CA-A- 1046408	16-01-79
		CH-A- 603165	15-08-78
		FR-A,B 2247259	09-05-75
		GB-A- 1417527	10-12-75
		JP-A- 49094818	09-09-74
		NL-A- 7317731	01-07-74
		SE-B- 433908	25-06-84
		US-A- 4180064	25-12-79
		CA-A- 1009955	10-05-77
EP-A- 0202112	20-11-86	JP-A- 61263920	21-11-86
US-A- 4301146	17-11-81	None	
GB-A- 2135881	12-09-84	BE-A- 899033	29-08-84
		DE-A- 3404209	06-09-84
		JP-A- 59164719	17-09-84

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(74) Agents: WILLIAMS, Roger, A. et al.; G.D. Searle & Co., P.O. Box 5110, Chicago, IL 60680-5110 (US).

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(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract

A pharmaceutical composition including a core (18) of an NSAID selected from diclofenac and piroxicam which core is surrounded by a mantle coating (22) of a prostaglandin, wherein an intermediate coating (20) can be present between the NSAID core and prostaglandin mantle coating.

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PHARMACEUTICAL COMPOSITION

Background of the Invention

The invention herein is directed to a pharmaceutical composition which consists of a core/mantle tablet having an inner core and an outer mantle coating surrounding the inner core. The inner core consists of an NSAID selected from diclofenac and piroxicam. The mantle coating consists of a prostaglandin such as will be described hereinafter in more detail.

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis (OA) and rheumatoid arthritis (RA). While the NSAIDs present a beneficial therapeutic value they also exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated

with chronic use. The chronic use of NSAIDs, the use of high dosages of NSAIDs and the use of NSAIDs by the elderly can lead to NSAID induced ulcers. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit few or no symptoms and may cause dangerous bleeding when undetected. In some instances, bleeding ulcers can prove fatal. The United States Food and Drug Administration requires a class warning for all NSAIDs, which states: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy.

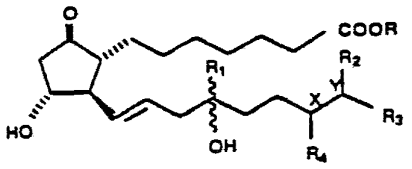
Certain prostaglandins have been shown to prevent NSAID induced ulcers. Acceptable prostaglandin compounds for the invention herein and their preparation are described in U.S. Patents 3,965,143, 4,060,691, 4,271,314 and 4,683,328. The prostaglandin compound commercially available under the USAN (United States Adopted Name) name misoprostol is a pharmaceutically acceptable prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States. Misoprostol is commercially available by prescription in such countries.

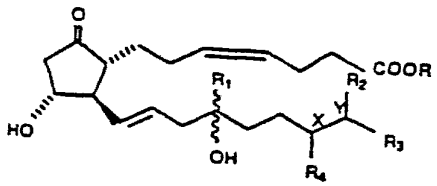
While prostaglandins are beneficial compounds and have found therapeutic usage, prostaglandins are generally considered highly unstable. Therefore, it is desirable to find prostaglandins with the desired anti-ulcerogenic properties and which can be stabilized or provided in stabilized formulations especially with respect to contemplated oral methods of delivery.

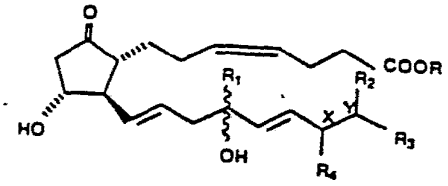
It would be desirable to provide a pharmaceutical composition which would exhibit the beneficial properties of an NSAID and which composition would exhibit the beneficial properties of a prostaglandin for countering (by inhibiting, reducing or preventing) the ulcerogenic side effects attendant to NSAID administration.

Summary of the Invention

The invention herein is directed to a pharmaceutical composition comprising a core consisting of an NSAID selected from diclofenac and piroxicam and a mantle coating consisting of a prostaglandin surrounding the core. The prostaglandin preferably is an orally available prostaglandin. Acceptable prostaglandins for use herein include prostaglandins having the following structure







wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms; R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2, R_3, and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R_3 and R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbons and wherein the X-Y bond can be saturated or unsaturated.

Another embodiment of the invention herein is a pharmaceutical composition wherein a coating is provided which is an intermediate coating that surrounds the core but lies underneath the mantle coating. Such an intermediate coating can be an additional coating for

preventing contact between the NSAID and the prostaglandin to thereby inhibit any deleterious or otherwise non-beneficial interaction of the NSAID and prostaglandin such as degradation of the prostaglandin. Such an intermediate coating can be an enteric coating which aids in reducing the likelihood of the NSAID dissolving in the stomach and thereby directly exposing the stomach to the NSAID.

A preferred pharmaceutical composition herein has a structure wherein the core comprises the NSAID, diclofenac in a therapeutic amount such as from 25 to 75 milligrams (mg) and a mantle coating surrounding the core comprising the prostaglandin misoprostol in a therapeutic amount of about 100 to 200 micrograms (mcg).

Another embodiment of the invention herein is a pharmaceutical composition including an NSAID core, an undercoating on the core surface of hydroxypropyl methylcellulose (HPMC), an enteric coating, an overcoat on the enteric coating of HPMC, and a mantle coating of the prostaglandin.

The invention herein will be more fully understood with regard to the following brief description of the accompanying drawings and the following detailed description.

Brief Description of the Drawings

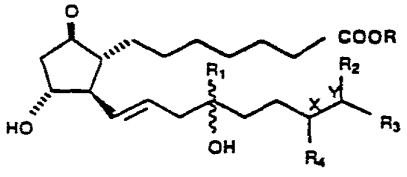
Figure 1 is a schematic representation of a tableted pharmaceutical composition herein illustrating the core/mantle structure;

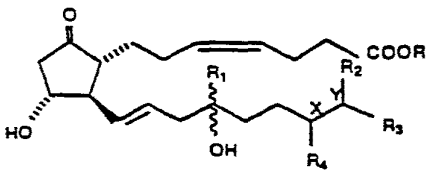
Figure 2 is a schematic representation of another embodiment of a tableted pharmaceutical composition herein; and

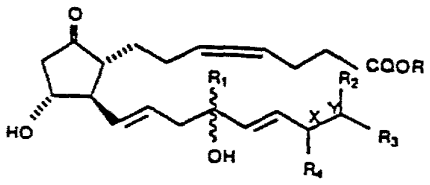
Figure 3 is a schematic representation of still another embodiment of a tableted pharmaceutical composition herein.

Detailed Description of the Invention

The invention herein is directed to a pharmaceutical composition which is a core/mantle tablet consisting of a core of a nonsteroidal anti-inflammatory drug (NSAID) selected from diclofenac and piroxicam. Surrounding the core is a mantle coating which consists of a prostaglandin of the structure







wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms; R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2, R_3, and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R_3 and R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbons and wherein the X-Y bond can be saturated or unsaturated.

The pharmaceutical composition herein can be described with regard to the accompanying drawings wherein Figures 1, 2 and 3 represent separate embodiments of the tableted composition herein.

The pharmaceutical composition will first be described with regard to the embodiment shown in Figure 1. Figure 1 represents a schematic illustration of a pharmaceutical composition herein. The pharmaceutical composition consists of a core/mantle tablet 10 which can have any geometric shape. For example, a bi-convex tablet (general pill shape) can be used which has a generally oval cross section taken along a vertical cross section and a circular cross section taken along a horizontal cross section. A bi-convex tablet can include a straight side wall (cylindrical) portion although such a tablet is not

shown in the drawings herein. For ease of discussion herein a vertical cross sectional view providing an oval cross section will be used to describe the invention herein although it is understood that other shapes can be used without departing from the intended scope of the invention. A generally oval cross-section is shown in Figure 1. The tablet 10 includes an inner core 12 which is comprised of an NSAID that is compatible with the prostaglandin as will be described in further detail hereinafter. The inner core 12 can consist of the NSAID, diclofenac or piroxicam or the pharmaceutically acceptable salts of such NSAIDs. The inner core 12 can be formulated by compressing the diclofenac or piroxicam in any suitable tableting equipment using compression tableting techniques well known in the art.

For a tablet wherein the inner core comprises diclofenac it has been found that the diclofenac can be present as diclofenac sodium. The diclofenac can be present in any therapeutically acceptable amount. For normal pharmaceutically acceptable dosing of diclofenac, diclofenac is administered in a therapeutic dosing range using tablets containing from 25 mg to 75 mg per tablet. The Physicians' Desk Reference (PDR), 44th Edition, states that the recommended dosage for treating osteoarthritis is

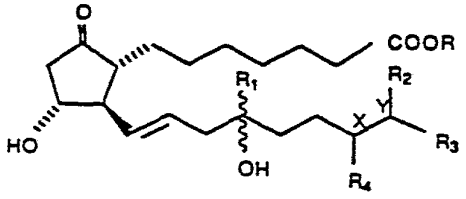
100 to 150 mg per day in divided doses. For treating rheumatoid arthritis the recommended dosage is 150 to 200 mg per day in divided doses. For ankylosing spondylitis the recommended dosage is 100 to 125 mg per day in divided doses. The inner core for the pharmaceutical composition herein can contain an amount from 25 to 75 mg of diclofenac and preferably a dosage of 50 mg. Various excipients such as binders, bulking agents, lubricants, fillers and the like, can be combined with the diclofenac in the core as is well known in the pharmaceutical art. Excipients used are selected from those which do not exhibit a destabilizing effect on either the diclofenac or prostaglandin.

If the inner core is piroxicam, the piroxicam can be present in a therapeutically acceptable amount. Currently, commercially available piroxicam tablets contain either 10 mg or 20 mg of piroxicam. The PDR, 44th Edition, recommends that piroxicam be administered in a single daily dose of 20 mg for rheumatoid arthritis and osteoarthritis. For the pharmaceutical composition herein the inner core can contain from 10 to 20 mg of piroxicam. Various excipients can be used in constructing a piroxicam core which excipients do not exhibit a destabilizing effect on either the piroxicam or the prostaglandin.

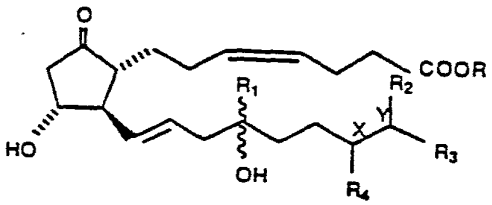
A mantle coating 14 surrounds the inner NSAID core and encapsulates the NSAID. The mantle coating includes a prostaglandin and more preferably an orally available prostaglandin.

The terms "prostaglandin" and/or its accepted acronym "PG" or, as more appropriately for the E-series prostaglandins, "PGE," are used herein to refer to naturally occurring or man-made E-series prostaglandins and their analogs and derivatives.

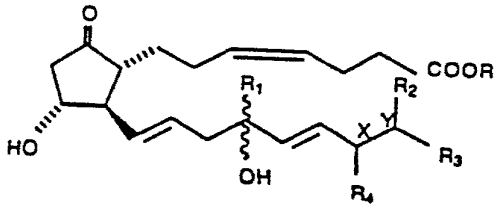
It has been found herein that acceptable prostaglandins include E_1 prostaglandins represented by the following Formula I:



E_2 prostaglandins represented by the following Formula II:



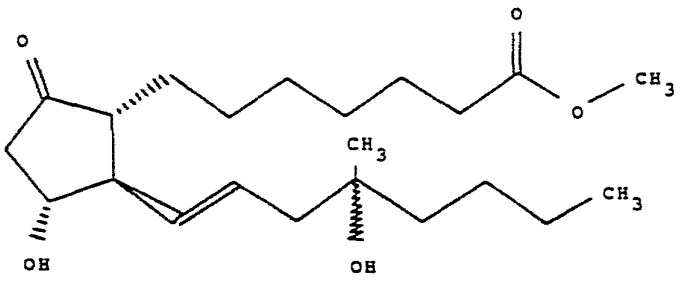
and E_3 prostaglandins represented by the following Formula III:



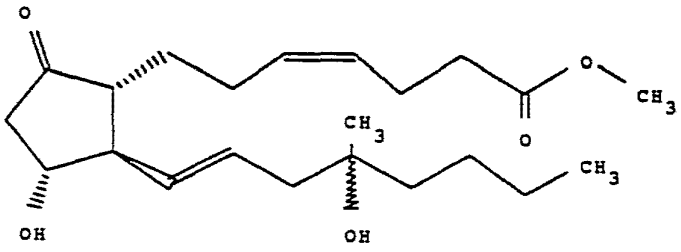
wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2, R_3, and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R_3 or R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon and wherein the X-Y bond can be saturated or unsaturated.

By lower alkyl is meant straight or branched chain alkyl such as methyl, ethyl, propyl, isopropyl, butyl, secondary butyl or tertiary butyl, pentyl, or hexyl with the indicated limitation of the number of carbon atoms. The bond between carbon X and carbon Y can be saturated or unsaturated.

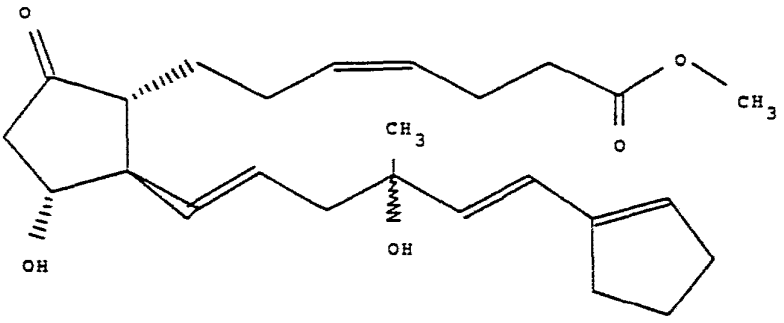
It has been found herein that acceptable prostaglandins include misoprostol represented by the following Formula :



the prostaglandin enisoprost, (±)methyl 11α,16-dihydroxy-16-methyl-9-oxoprosto-4Z,13E-diene-1-oate, represented by the following Formula:



and the prostaglandin methyl 7-[2B-[6-(1-cyclopenten-1-yl)-4-hydroxy-4-methyl-1E,5E-hexadienyl]-3α-hydroxy-5-oxo-1R,1α-cyclopentyl]-4Z-heptenoate represented by the following Formula:



With regard to the illustrated structures, the dashed line indicates the grouping being behind the plane of the paper and the solid, blackened triangular shape indicates that the group is in front of the plane of the paper.

The prostaglandins useful in the composition of the invention herein can be prepared by known reaction schemes such as by the methods taught in U.S. Patents 3,965,143; 4,271,314; and 4,683,328. The individual isomers can be obtained by chromatographic separation.

When the prostaglandin is misoprostol, (±)methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate, the misoprostol is present in an amount from about 50 to about 500 mcg and preferably from about 100 to about 200 mcg.

A second embodiment of the composition is shown in Figure 2. In Figure 2 a tablet 16 is schematically illustrated in cross section. The tablet 16 includes an inner core 18 of an NSAID diclofenac, piroxicam or their salts such as disclosed with regard to the core 12 of Figure 1. Surrounding the core 18 is an enteric coating 20. The enteric coating 20 can be formulated from any suitable enteric coating material, many of which are known to those skilled in the art and many of which are employed for coating commercially available NSAID's. The coating 20 aids in segregating the NSAID from the prostaglandin

and in directing the dissolution of the NSAID core in the lower G.I. tract as opposed to the stomach. The coating 20 can aid in the prevention of degradation of the prostaglandin by the presence of the NSAID. The enteric coating can be coated onto the inner core using standard coating techniques. For example, aqueous or solvent coating techniques can be used to apply the enteric coating to the inner core. Surrounding the coated inner core is a mantle 22 consisting of a prostaglandin as described with regard to mantle 14 in the composition embodiment represented in Figure 1.

A third embodiment of the composition is shown in Figure 3. In Figure 3 a tablet 24 is illustrated in cross section. The tablet 24 consists of an inner core 26 comprising an NSAID or its salt as disclosed with regard to the core 12 of Figure 1. Surrounding the core 26 is an undercoat 28 which can provide a surface for the enteric coat which undercoat can have a greater affinity for the enteric coat than the core alone. The coating 28 can be any suitable coating material and preferably is HPMC in an amount about two percent (2%) by weight of the core.

An aqueous enteric coating 30 can be used to segregate the NSAID from the prostaglandin and to aid in controlling release of the NSAID. The undercoat 28 prevents water which can be present in the aqueous enteric coat 30 from penetrating into the NSAID core to cause any undesirable effects on the NSAID which might be caused by water. The enteric coating 30 can aid in the prevention of degradation of the prostaglandin by the presence of the NSAID as well as direct delivery of the NSAID in the lower G.I. tract rather than the stomach. Any aqueous enteric coating can be used and the enteric coating can be coated onto the inner core using standard coating techniques as described with regard to the embodiment shown in Figure 2.

An overcoat 32 is coated over the enteric coat 30. The overcoat 32 can provide an intermediate coating providing affinity between the enteric coat and mantle. The overcoat can be any suitable material, preferably the overcoat is HPMC in an amount about three percent (3%) by weight of the core. The overcoat 32 prevents water which can be present in the aqueous enteric coating from passing into the prostaglandin mantle. Further, the overcoat can aid in maintaining the integrity of the enteric coating during the compression coating step as the mantle is formed on the tablet.

A mantle 34 consisting of a prostaglandin as described with regard to mantle 14 in the composition embodiment shown in Figure 1 is coated, such as by compression coating, over the overcoat 32.

It has been found herein that an especially preferred composition is the use of misoprostol as the prostaglandin in the mantle and the use of diclofenac in the inner core.

The invention will be further described with regard to the following examples.

Example 1

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
purified water	
Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose (HPMC)	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 2

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an enteric coating and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
purified water	
Core coating	
cellulose acetate phthalate	5.4
diethyl phthalate	1.5
Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 3

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an aqueous enteric coating, an overcoat and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Enteric coating (aqueous)	
methacrylic acid copolymer type C	3.68
sodium hydroxide	0.049
talcum	1.84
triethyl citrate	0.37

Overcoating	
HPMC	2.72
polyethylene glycol (PEG 400)	0.054
Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 4

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an undercoat, an enteric coating, and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Undercoat	
HPMC	1.84
PEG 400	0.037
Enteric coating (aqueous)	
methacrylic acid copolymer type C	3.68
sodium hydroxide	0.049
talcum	1.84
triethyl citrate	0.37

Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 5

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an undercoat, an enteric coating, an overcoat and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Undercoat	
HPMC	1.84
PEG 400	0.037
Enteric coating (aqueous)	
methacrylic acid copolymer type C	3.68
sodium hydroxide	0.049
talcum	1.84
triethyl citrate	0.37

Overcoating	
HPMC	2.72
PEG 400	0.054
Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 6

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an enteric coating, an overcoat and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Enteric coating (aqueous)	
methacrylic acid	
copolymer type C	3.68
talcum	1.84
triethyl citrate	0.37

Overcoating	
HPMC	2.72
PEG 400	0.054
Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 7

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an enteric coating, an overcoat and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Enteric coating (aqueous)	
Aquateric	6.53
polysorbate 80	0.13
diethyl phthalate (DEP)	1.96

Overcoating	
HPMC	2.72
PEG 400	0.054
Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 8

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an undercoat, an enteric coating, and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Undercoat	
HPMC	1.84
PEG 400	0.037
Enteric coating (aqueous)	
Aquateric	6.56
polysorbate 80	0.13
diethyl phthalate (DEP)	1.97

Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

Example 9

A pharmaceutical tablet composition was prepared consisting of a diclofenac sodium central core, an undercoat, an enteric coating, an overcoat and a misoprostol mantle. The tablet had the following composition.

Core	Unit Formula (mg)
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
cornstarch	8.4
povidone K-30	4.8
magnesium stearate	0.9
Undercoat	
HPMC	1.84
PEG 400	0.037
Enteric coating (aqueous)	
Aquateric	6.56
polysorbate 80	0.13
diethyl phthalate (DEP)	1.97

Overcoating	
HPMC	2.70
PEG 400	0.054
Mantle	
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.2
hydroxypropyl methylcellulose	20.0
crospovidone	10.0
colloidal silicon dioxide	0.5
hydrogenated castor oil	1.0
microcrystalline cellulose	233.3

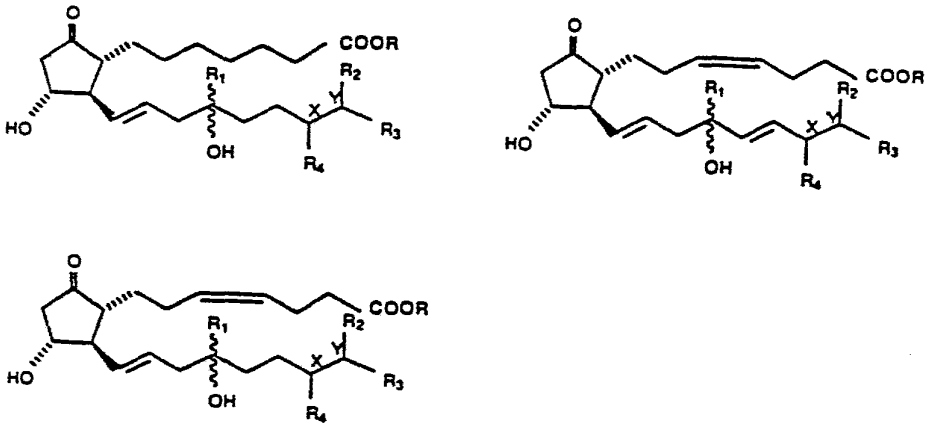
The composition that is the invention herein provides an ease of delivery of an NSAID for its therapeutic value such as the alleviation of inflammation in a system which limits the undesirable side affects of ulcerogenesis associated with such NSAID therapy. That is, the composition herein consisting of essentially a core/mantle tablet provides a prostaglandin along with the NSAID whereby the prostaglandin can be administered for its beneficial therapeutic value in preventing and or inhibiting the incidence of NSAID induced ulcers.

A particularly beneficial aspect of the invention herein is that the combination of the two components in a core/mantle tablet assures compliance with the therapeutic regimen of the two active components. That is, a co-administration of the active components (NSAID and prostaglandin) separately can be difficult to achieve and can be difficult for a patient to faithfully follow. By placing the two active components in the same tablet or composition, adherence to the therapeutic regimen is controlled as the administration of the tablet containing the NSAID assures compliance of the administration of the prostaglandin also present in the tablet.

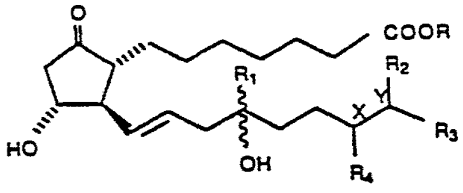
The composition herein is especially utile as the composition herein exhibits a stability for the prostaglandin and the NSAID.

Claims

1. A pharmaceutical composition comprising:
   a. a core consisting of an NSAID selected from diclofenac and piroxicam; and
   b. a mantle coating surrounding the core consisting of a prostaglandin of the structural formula

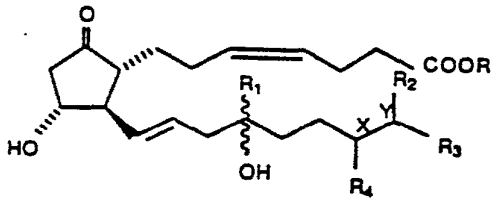


2. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises a prostaglandin of the structural formula



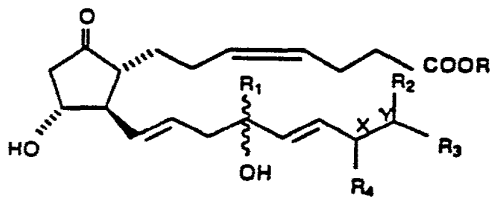
3. A pharmaceutical composition as recited in Claim 2 wherein the prostaglandin comprises misoprostol.

4. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises the structural formula



5. A pharmaceutical composition as recited in Claim 4 wherein the prostaglandin comprises enisoprost.

6. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises a structural formula



7. A pharmaceutical composition as recited in Claim 1 wherein the NSAID comprises diclofenac.

8. A pharmaceutical composition as recited in Claim 1 wherein the NSAID comprises piroxicam.

9. A pharmaceutical composition as recited in Claim 1 further comprising an intermediate coating surrounding the core.

10. A pharmaceutical composition as recited in Claim 9 wherein the intermediate coating comprises an enteric coating.

11. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin mantle coating comprises a stabilized prostaglandin formulation.

12. A pharmaceutical composition as recited in Claim 1 wherein the NSAID comprises diclofenac from about 25 to 75 mg and the mantle coating comprises a stabilized prostaglandin formulation containing an amount of about 200 mcg of misoprostol.

13. A method of treating inflammation comprising administering to a patient in need of such treatment, a therapeutically effective amount of a composition according to Claim 1.

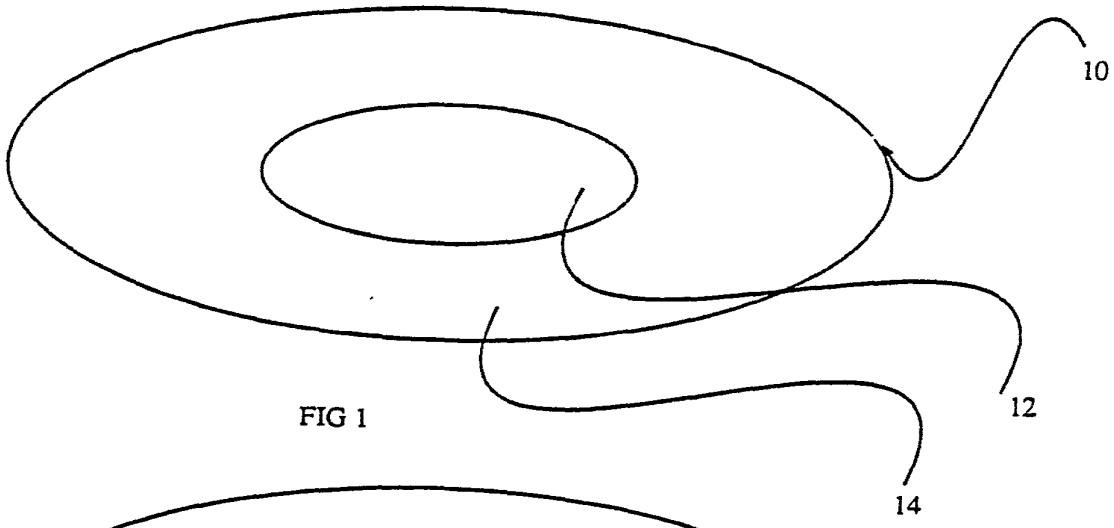


FIG 1

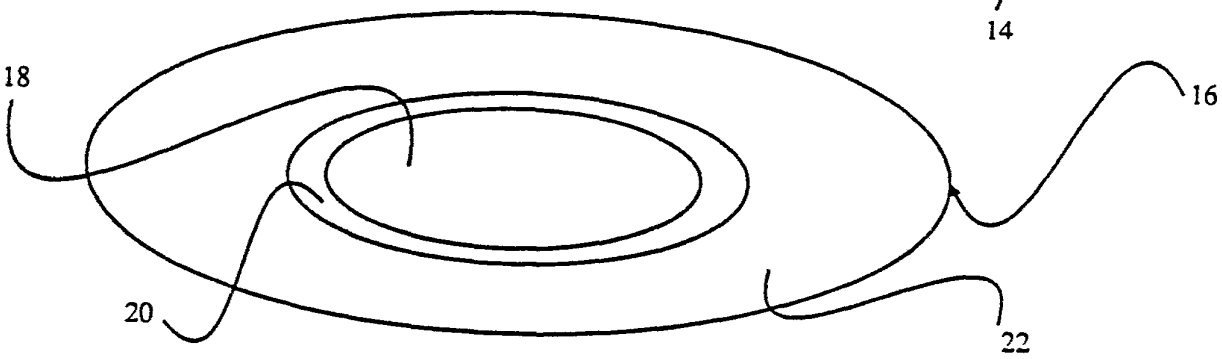


FIG 2

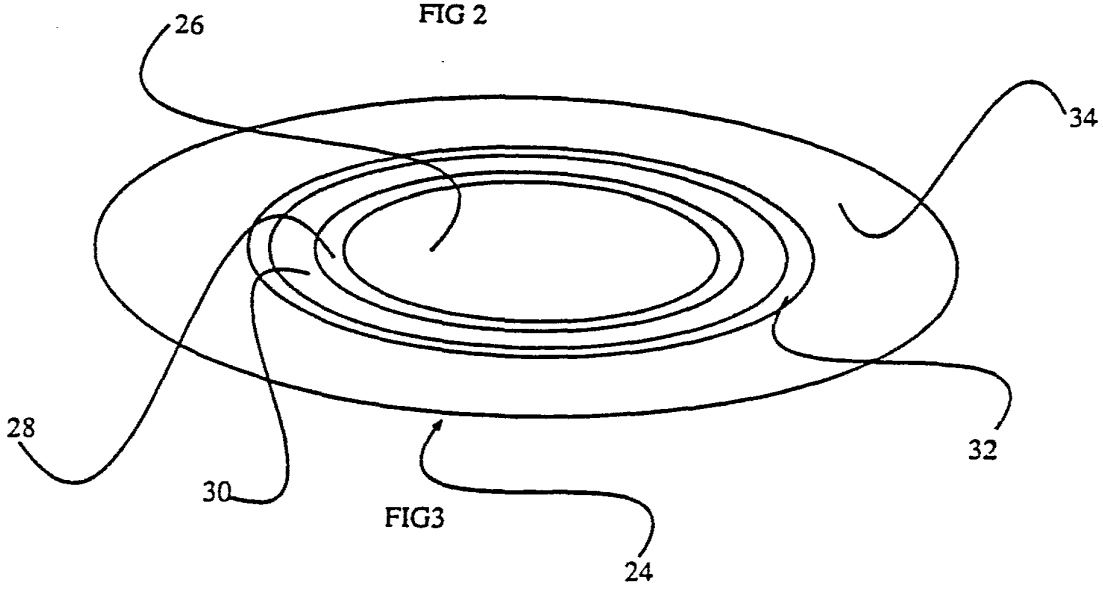


FIG3

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/02980

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/557 A 61 K 9/22 //(A 61 K 31/557 A 61 K 31:54 A 61 K 31:195)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	GB,A,2135881 (FARMITALIA CARLO ERBA SpA) 12 September 1984, see page 12, line 1 - page 16, line 48; claims 1-29	1-12

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26-08-1991	08. 10. 91
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Nuria TORIBIO

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. [X] Claim numbers 13 because they relate to subject matter not required to be searched by this Authority, namely:
see PCT-Rule 39.1(iv)

2. [ ] Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6 4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple Inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

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[ ] The additional search fees were accompanied by applicant's protest

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9102980 SA 47633

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2135881	12-09-84	BE-A- 899033	29-08-84
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(54) Title: PHARMACEUTICAL COMPOSITION FOR USE IN TREATING PAIN

(57) Abstract

A pharmaceutical composition and a method for treating mild to moderate pain in a subject in need of such treatment is performed by administering an analgesic agent selected from diclofenac, ibuprofen, piroxicam and their pharmaceutically acceptable salts in a dosage which by itself would provide less than the therapeutic effect, and administering misoprostol in a dosage which is sufficient to potentiate the analgesic effect of the analgesic agent to the therapeutic effect.

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PHARMACEUTICAL COMPOSITION FOR USE IN TREATING PAIN

BACKGROUND OF THE INVENTION

The invention herein is directed to a new pharmaceutical composition useful in the treatment of pain which comprises two active ingredients, namely a nonsteroidal anti-inflammatory agent and a prostaglandin, which prostaglandin exhibits analgesic activity. The nonsteroidal anti-inflammatory agent can be selected from diclofenac, ibuprofen and piroxicam. The prostaglandin is misoprostol, (±) methyl 11a, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate. The invention herein is also directed to a new method for treating mild to moderate pain by administering one of the above-mentioned nonsteroidal anti-inflammatory agents in an amount which by itself would provide less than a therapeutic analgesic effect and misoprostol in an amount sufficient to potentiate the analgesic effect of the nonsteroidal anti-inflammatory agent to the desired therapeutic analgesic effect.

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as experienced in inflammatory diseases like osteoarthritis (OA) and rheumatoid arthritis (RA). NSAIDs are also widely regarded as having high therapeutic value in the treatment of mild to moderate pain. While the NSAIDs present a beneficial therapeutic value they also have been known to exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use. In chronic use of NSAIDs, use of high dosages of NSAIDs and especially the use of NSAIDs by the elderly can lead to NSAID induced ulcers. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit little or few symptoms and can cause dangerous

bleeding when undetected. The United States Food and Drug Administration requires a class warning for all NSAIDs, which states: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy.

Certain prostaglandins have been shown to prevent NSAID induced ulcers. The prostaglandin compound commercially available under the USAN (United States Adopted Name) name misoprostol is a pharmaceutically acceptable prostaglandin which has been accepted for use in the prevention of NSAID induced ulcers in many countries, including the United States. Misoprostol is commercially available by prescription in such countries.

E-type prostaglandins are recognized as modulators of pain sensitivity. However, the extent and nature of the modulation is not well understood nor predictable. A review of the scientific literature reveals that the nature and direction of this modulatory effect can differ depending upon experimental design and investigator. Both PGE_1 and PGE_2 have been reported to potentiate the behavioral response (writhing) to intraperitoneal phenylbenzoquinone injection in mice (G.W.L. James & M. K. Church, Arzneimittelforschung 28, 804-7 (1978)) and to intracarotid injection of bradykinin in rats (T. Mikami and K. Miyasaka, J. Pharm. Pharmacol. 31, 856-7 (1979)) after systemic administration. PGE_2 has also been shown to potentiate bradykinin-induced writhing in mice (T. Walter, T. T. Chau, and B. M. Weichman, Agents and Actions 27, 375-7 (1979)) and to increase sensitivity to noxious thermal and mechanical stimuli after administration to the spinal cord in rats (Y. Taiwo and J. D. Levine, J. Neurosci 8, 1346-9 (1988)). Subdermal injection of PGE_1 has been found to increase the sensitivity of pain

sensory fibers (nociceptors) which respond to a variety of sensory stimuli (S. Pateromichelakis, J. R. Rood, Brain Research 232, 89-96 (1982)). However, Sanyal et al. reported that PGE_1 can induce an analgesic effect in the rat after peripheral (A. K. Sanyal, S. K. Bhattacharya, P. R. Keshary, D. N. Srivastava, P. K. Debnath, Clin. Exp. Pharmacol. Physiol. 4, 247-255 (1977)) and intracerebroventricular administration (A. K. Sanyal, D. N. Srivastava, S. K. Bhattacharya, P.K.S.P. Reddy, P. K. Debnath, A. K. Sanyal, Clin. Exp. Pharmacol. Physiol. 2, 353-357 (1975)). However, these results conflict with an earlier report that PGE_1 antagonizes the analgesic effect of morphine. (S. Ferri, A. Santagostino, P. C. Boraga, I. Galatulas, Psychopharmacologia 34, 231-5 (1974)).

A review of these references shows that the effects of PGE_1 on pain sensitivity have been reported to be either facilitory (hyperalgesic) or analgesic. It is therefore impossible to predict the nature of the effects of a PGE_1 analogue, such as misoprostol, on pain responsivity. In view of the unpredictability of any analgesic effect of a PGE_1 analogue, it is further unpredictable to assess the analgesic effect of a combination of a PGE_1 prostaglandin and a nonsteroidal anti-inflammatory agent (NSAID) and especially the effect of the PGE_1 analogue on the analgesic activity of the NSAID. The literature reports that NSAIDs and E-Type prostaglandins have opposite effects on pain sensitivity (G.W.L. James and M. K. Church, Arzneimittel-Forschung 28, 804-7 (1978); Y. O. Taiwo and J. D. Levine, J. Neurosci 8, 1346-9 (1988)).

It would be desirable to provide a pharmaceutical composition which would exhibit the beneficial properties of an NSAID and which composition would exhibit the beneficial properties of a prostaglandin for countering (by inhibiting, reducing or preventing) the undesirable side effect of ulcerogenesis induced by

NSAID administration and which composition would exhibit enhanced analgesic activity. Such a composition could thereby provide the same or greater analgesic therapeutic benefit using less NSAID and thereby further decrease the likelihood of the undesirable NSAID ulcerogenic side effect due to the decreased amount of NSAID and the cytoprotective activity of the prostaglandin. Such a combination would provide an improved NSAID with respect to both efficacy and safety.

SUMMARY OF THE INVENTION

The present invention is directed to a method for imparting analgesia, relief from mild to moderate pain, to a patient in need thereof by administering, concomitantly or simultaneously, a nonsteroidal anti-inflammatory agent and the prostaglandin, misoprostol in an effective dose to potentiate the analgesic effect of the NSAID. In particular, the present invention is directed to a method for treating mild to moderate pain in a subject in need of such therapy, which method provides a desired therapeutic analgesic effect sufficient to relieve the mild to moderate pain. The method is performed by administering an analgesic agent, selected from the nonsteroidal anti-inflammatory agents (NSAIDs) diclofenac, ibuprofen and piroxicam, or their pharmaceutically acceptable salts, in a dosage which by itself would provide less than the desired therapeutic analgesic effect and administering misoprostol in an effective dosage which is sufficient to potentiate the analgesic effect of the selected dosage of the analgesic agent to the desired therapeutic analgesic effect.

The invention herein is also directed to a pharmaceutical composition useful for achieving a desired therapeutic analgesic effect in the treatment of mild to moderate pain in a subject in need of such treatment. The composition includes an analgesic agent selected from diclofenac, ibuprofen, piroxicam and their pharmaceutically acceptable salts in an amount of the analgesic agent which by itself would provide less than the desired therapeutic analgesic effect. The composition also includes the prostaglandin, misoprostol, in an amount which is sufficient to potentiate the analgesic effect of the analgesic agent to the desired therapeutic analgesic effect.

BRIEF DESCRIPTION OF THE DRAWINGS

The method and composition that are the subject of the invention herein will be better understood with reference to the accompanying drawings wherein:

Figure 1 is an isobolographic analysis of coadministered misoprostol and diclofenac calculated ED_{50} values;

Figure 2 is an isobolographic analysis of coadministered misoprostol and ibuprofen calculated ED_{50} values;

Figure 3 is an isobolographic analysis of coadministered misoprostol and piroxicam calculated ED_{50} values;

Figure 4 is a graphic analysis of coadministered misoprostol and diclofenac showing a comparison of actual versus predicted responses;

Figure 5 is a graphic analysis of coadministered misoprostol and ibuprofen showing a comparison of actual versus predicted responses;

Figure 6 is a graphic analysis of coadministered misoprostol and piroxicam showing a comparison of actual versus predicted responses; and

Figure 7 is a graphic representation illustrating the possible dose ranges for misoprostol and an analgesic agent.

DETAILED DESCRIPTION OF THE INVENTION

The invention herein is directed to a composition and a method for treating mild to moderate pain in a subject (either human or animal, i.e., mammal) in need of such treatment by administering, concomitantly or simultaneously, misoprostol and a nonsteroidal anti-inflammatory agent selected from diclofenac, ibuprofen, piroxicam and their pharmaceutically acceptable salts. For ease of description herein these agents will be referred to as analgesic agents. One benefit derived from the method herein is that the

administration of the misoprostol potentiates the analgesic activity of the analgesic agent such that the analgesic agent can be used in a dosage less than the dosage which would be used if the analgesic agent were used by itself. The administration of the misoprostol enhances the analgesic activity of the analgesic agent by potentiation such that the amount of analgesic agent administered to obtain a desired therapeutic analgesic effect can be reduced but the desired therapeutic analgesic effect can be achieved. The opportunity to use less NSAID especially in combination with a cytoprotective prostaglandin, reduces the likelihood of occurrence of the undesirable side effect of the NSAID inducing an ulcer. In view of the known deleterious side effect of ulcerogenesis incumbant with the use of NSAIDs, the practice of the method and use of the composition herein can diminish the likelihood and/or occurrence of such a deleterious side effect. It is further possible that other benefits can be derived from the composition and method herein. For example, prostaglandins, including misoprostol, have shown anti-inflammatory activity. Therefore, the combination of the prostglandin with the NSAID can beneficiate or increase the anti-inflammatory activity of the combination or coadministration regimen. That is, the composition or coadministration regimen can exhibit a greater anti-inflammatory activity than the administration of the NSAID alone.

It has been found herein that the prostaglandin misoprostol exhibits a potentiating effect on the analgesic activity exhibited by the above-described analgesic agents. Misoprostol is shown by the following formula:

With regard to the illustrated structure, the dashed line indicates the group extends behind the plane of the paper and the solid, blackened triangular shape indicates that the group projects from the plane of the paper.

The prostaglandin, misoprostol, can be prepared by known reaction schemes such as by the methods taught in U. S. Patents 3,965,143, 4,452,994, 4,529,811 and 4,777,275. The individual isomers can be obtained by chromatographic separation such as taught in U.S. Patent 4,060,691.

An effective but non-toxic quantity of the prostaglandin is employed in the treatment. The dosage regimen for the method of this invention is selected in accordance with a variety of factors including the type, age, weight, sex, and medical condition of the patient, the route of administration, the extent of the mild to moderate pain of the patient and the particular nonsteroidal anti-inflammatory agent employed. Dosages of misoprostol useful in the method herein are in the range up to 1600 μg per day. A preferred range is up to 800 μg per day. Greater or lesser dosages can be used, depending upon the above-noted factors. It is preferred to use as low a dose of misoprostol as possible to obtain the desired potentiation of the therapeutic analgesic benefit of the analgesic agent. The lowest dose of misoprostol is dependent upon the analgesic agent with which it is to be administered and is balanced against the desire to use a low dosage of the selected analgesic agent. Based upon the studies described hereinafter, misoprostol can be used in an amount from about 5 μg to about 200 μg per tablet and in a dosage from about 25 μg to about 1600 μg per day.

The term "nonsteroidal anti-inflammatory agent" and "analgesic agent" as used herein, include diclofenac,

piroxicam, ibuprofen and their pharmaceutically acceptable salts.

The term "desired therapeutic analgesic effective dosage" as used herein means, with respect to the nonsteroidal anti-inflammatory agent, the dose sufficient for imparting the requisite suppression/alleviation of mild to moderate pain in a patient in need of such therapy. The specific dose is dependent upon the same factors noted above with respect to the dosage of prostaglandin. The determination of the specific dosage for a subject is well within the skill of the prescribing physician. The Physician's Desk Reference, 44th Edition (1990) lists the daily single dosages for various nonsteroidal anti-inflammatory agents.

The term "mild to moderate pain" is a term accepted and understood by those skilled in the medicinal arts and especially, trained medical doctors. Generally, such a term as a mild pain means a pain which does not cause the subject to modify a behavior and a moderate pain means a pain which would cause a subject to modify a behavior. Further, such a term as mild to moderate pain refers to a pain for which a physician would prescribe the general class of NSAID's as an analgesic agent for relieving the pain. While pain is a subjective condition, physicians are trained to evaluate a patient's overall condition, history and description of the level of discomfort so as to assess and thereby diagnose the extent of pain. Following such observation and evaluation the physician can prescribe the desired therapeutic analgesic dosage and dosing regimen.

The analgesic agent can be present in any dosage which would be below the therapeutically acceptable amount if such analgesic agent at such dosage were administered alone. The Physicians' Desk Reference, 44th Edition, states that the recommended dosage of

diclofenac for treating osteoarthritis is 100 to 150 mg per day in divided doses. For treating rheumatoid arthritis the recommended dosage is 150 to 200 mg per day in divided doses. For treating ankylosing spondylitis the recommended dosage is 100 to 125 mg per day in divided doses. Diclofenac is currently, commercially available by prescription in tablets containing 25, 50 and 75 mg and is administered in prescribed dosing ranges utilizing these 25 mg, 50 mg and 75 mg tablets.

The pharmaceutical composition herein can include an amount up to about 75 mg of diclofenac. Such an amount as up to 75 mg can provide an analgesic effect up to or greater than the current largest commercially available amount of 75 mg. In a preferred practice of the invention herein, the composition can contain up to but less than 25 mg of diclofenac and exhibit the same or better therapeutic analgesic effect as the 25 mg current commercially available tablet. The composition can contain up to but less than 50 mg, or greater than 25 mg but less than 50 mg, of diclofenac and exhibit the same or better therapeutic analgesic effect as the 50 mg current commercially available tablet. The composition can contain up to but less than 75 mg, or greater than 50 mg but less than 75 mg, of diclofenac and exhibit the same or better therapeutic analgesic effect as the 75 mg current commercially available tablet. Preferably the pharmaceutical composition includes a dosage of up to about 25mg. An amount up to 25 mg is desirable as it is less than the current commercially available lowest dosage but is an amount which can provide the same or better analgesic therapeutic effect than the commercially available 25 mg tablet. Such a dosage provides an advantage in that it can provide a therapeutic benefit using a relatively low dosage of the NSAID. Various excipients can be combined with the diclofenac as is well known in the

pharmaceutical art provided such excipients do not exhibit a destabilizing effect on the prostaglandin. For the practice of the method herein, the diclofenac can be administered in an amount up to about 200 mg per day and preferably in an amount up to about 100 mg per day in divided doses or in a single dose. For the practice of the method herein the current commercially available diclofenac tablets can be administered.

The NSAID can be piroxicam. Currently commercially available piroxicam capsules contain either 10 mg or 20 mg of piroxicam. The PDR, 44th Edition, recommends that piroxicam be administered in a single daily dose of 20 mg for rheumatoid arthritis and osteoarthritis. The pharmaceutical composition herein can contain up to 20 mg and preferably contains less than 10 mg of piroxicam. The use of an amount up to 20 mg can provide an analgesic therapeutic benefit equivalent or greater than a 20 mg dosage of piroxicam by itself. Similarly, the use of an amount up to 10 mg can provide a therapeutic analgesic benefit equivalent or greater than the use of 10 mg of piroxicam by itself, which 10 mg is the lowest dosage now currently available. In a preferred practice of the invention herein, the composition can contain up to but less than 10 mg of piroxicam and exhibit the same or better therapeutic analgesic effect as the 10 mg current commercially available tablet. The composition can contain up to but less than 20 mg, or greater than 10 mg but less than 20 mg, of piroxicam and exhibit the same or better therapeutic analgesic effect as the 20 mg current commercially available tablet. Various excipients can be present, provided such excipients do not exhibit a destabilizing effect on either the piroxicam or the prostaglandin. For the practice of the method herein, the piroxicam can be administered in an amount up to about 20 mg per day and preferably in an amount up to about 10 mg per day in either divided doses or in a

single dose. For the practice of the method herein the current commercially available piroxicam tablets can be administered.

The NSAID can be ibuprofen. Ibuprofen is available as an over-the-counter analgesic agent in tablets containing 200 mg. Ibuprofen is available by prescription in tablets containing 300, 400, 600 and 800 mg of ibuprofen. The PDR, 44th Edition, recommends that ibuprofen be administered in dosages of 1200 mg to 3200 mg daily for rheumatoid and osteoarthritis; in dosages of 400 mg every 4 to 6 hours as necessary for relief of mild to moderate pain; and in dosages of 400 mg every 4 hours for dysmenorrhea. The PDR states: "In controlled analgesic clinical trials, doses of MOTRIN (Upjohn's brand of ibuprofen) greater than 400 mg were no more effective than the 400 mg dose." The pharmaceutical composition herein can include up to about 800 mg of ibuprofen and preferably up to about 200 mg of ibuprofen. An amount up to 800 mg can provide the equivalent or greater analgesic therapeutic benefit than the use of 800 mg of ibuprofen by itself. The use of up to 200 mg can provide an analgesic therapeutic benefit equivalent or greater than the current commercially available lowest dosage tablet of 200 mg. In a preferred practice of the invention herein, the composition can contain up to but less than 200 mg of ibuprofen and exhibit the same or better therapeutic analgesic effect as the 200 mg current commercially available tablet. The composition can contain up to but less than 300 mg, or greater than 200 mg but less than 300 mg, of ibuprofen and exhibit the same or better therapeutic analgesic effect as the 300 mg current commercially available tablet. The composition can contain up to but less than 400 mg, or greater than 300 mg but less than 400 mg, of ibuprofen and exhibit the same or better therapeutic analgesic effect as the 400 mg current commercially available

tablet. The composition can contain up to but less than 600 mg, or greater than 400 mg but less than 600 mg, of ibuprofen and exhibit the same or better therapeutic analgesic effect as the 600 mg current commercially available tablet. The composition can contain up to but less than 800 mg, or greater than 600 mg but less than 800 mg, of ibuprofen and exhibit the same or better therapeutic analgesic effect as the 800 mg current commercially available tablet. Various excipients can be present, provided such excipients do not exhibit a destabilizing effect on either the ibuprofen or the prostaglandin. For the practice of the method herein, the ibuprofen can be administered in an amount up to about 3200 mg per day and preferably in an amount up to about 1200 mg per day in either divided doses or in a single dose. For the practice of the method herein the current commercially available ibuprofen tablets can be administered.

Regardless of the route of administration selected, the misoprostol, NSAID or composition herein, can be formulated into pharmaceutically acceptable dosage forms by conventional methods known to the pharmaceutical art. For purposes of the practice of the method herein the commercially available forms, formulations and compositions of the NSAIDs and misoprostol can be used. Similar formulations but with lower amounts of the NSAIDs can be used in the practice of the invention herein. A particularly preferred formulation for misoprostol is taught in U.S. Patent 4,301,146.

The misoprostol, NSAID or composition herein can be administered in such oral unit dosage forms as tablets, capsules, pills, powders, or granules. They can be administered intraperitoneally, subcutaneously, or intramuscularly, using forms known in the pharmaceutical art. In general, the preferred form of administration is oral. An advantage of the present

method and composition is that the misoprostol is an orally available prostaglandin and can be formulated into orally available dosage forms. An advantage of oral availability is that the methodology of administration is easy to follow and does not require an attending, skilled medical professional. Oral availability is also an accepted and expected method of treatment for mild to moderate pain relief.

The method herein is performed by administering the nonsteroidal anti-inflammatory agent and misoprostol to the patient in need of such therapy in the dosage forms and the dosages set forth herein. The two components can be administered simultaneously or concomitantly. The order of administration of the two active ingredients is not critical, although it can be beneficial to administer the misoprostol first to benefit from the cytoprotective properties in preventing NSAID induced ulcers. A particularly preferred manner of treatment is the co-administering of the two active ingredients in a single dosage form such as a tablet or capsule. The sequencing and timing of the performance of the steps of the method herein are well within the skill of a physician prescribing an analgesic regimen.

The selection of the dose of NSAID and misoprostol can be further understood by considering the graph shown in Figure 7. Figure 7 illustrates a plot of the dosage of NSAID versus the dosage of misoprostol. The dosage for the NSAID is represented along the y axis and the dosage for misoprostol is represented along the x axis. The point represented by A along the x axis is the minimum effective amount of misoprostol which potentiates the analgesic activity of an NSAID, which amount is about 25 micrograms (mcg or μg) per day or about 5 mcg per tablet. The point represented by B along the x axis is the maximum tolerable daily dosage for misoprostol, which has been found to be as high as

about 1600 mcg per day. The PDR, 44th Edition states that cumulative daily doses of 1600 mcg have been tolerated by humans with only symptoms of gastrointestinal discomfort being reported. Therefore, it is preferable to use an amount of misoprostol up to about 1600 mcg per day and preferably as low a dosage as possible when balanced against the dosage of NSAID administered. The PDR also states that the recommended adult oral dose for Cytotec (G.D.Searle and Co's brand of misoprostol) for the prevention of NSAID induced gastric ulcers is 200 mcg four times daily with food, thereby providing a recommended daily dosage of 800 mcg.

The points along the y axis will be described in general terms as the specifics of the locations of such points depend upon the NSAID selected. The point represented by C along the y axis is the minimum dosage of an NSAID which would provide a therapeutic benefit in alleviating mild to moderate pain. The point represented as D on the graph is the maximum daily dosage for an NSAID. The point represented by E is the combined dosage for the NSAID and misoprostol and represents the activity for the minimum dosage of NSAID and minimum dosage of misoprostol. The point identified as F is the intersection of the lines extended from the maximum dosages for both the misoprostol and NSAID. The line EF represents the line which would be formed interconnecting the minimum dosages for the misoprostol and NSAID in combination for the ED values, e.g., ED_{10}, ED_{20}, ED_{30}, etc. The area bounded by the lines A B F D C A represent acceptable pharmaceutical dosages for the combination of misoprostol with an NSAID. The area bounded by the lines E F D C E represents the preferred dosages for the combination of NSAID and misoprostol as such an area represents the greatest analgesic activity with the minimum acceptable dose of misoprostol. For each

of the NSAIDs herein, such an area is reflected in a range of NSAID to misoprostol of 3:1 for diclofenac, 5:1 for ibuprofen and 1:1 for piroxicam.

The efficacy of the method herein has been demonstrated through animal models. The animal model studies are well accepted for evaluating analgesic activity of chemical compounds as shown in Pong et al., Prediction of Human Analgesic Dosages of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) from Analgesic ED_{50} Values in Mice," Arch. int. Pharmacodyn. 273, 212-220 (1985); Otterness et al., Journal of Pharmaceutical Sciences, Vol. 77, No. 9, September 1988, pp 790-795; and Dubinsky et al., Agents and Actions, Vol. 20, 1/2 (1987) pp 50-60.

The efficacy of the composition herein for use in treating mild to moderate pain was shown in the phenyl-benzoquinone-induced writhing test in the mouse. This model is widely used as a primary in vivo efficacy screen for the detection of a wide variety of analgesic agents. Diclofenac (sodium-[o-[2,6-dichlorophenyl]-amino]phenyl]-acetate) is an NSAID that exhibits an ED_{50} value in this mouse writhing assay of 2.0 mg/kg. The following example illustrates the effect of misoprostol and the NSAIDs herein in pain relief in the mouse writhing assay.

Example 1

Method for Mouse Writhing Assay.

This experiment is recognized for the screening of compounds for use as analgesic agents. Diclofenac has been reported in the literature to be active in this assay following oral administration, with an ED_{50} value of 4.3 mg/kg i.g., Menasse et al, "Pharmacological Properties of Diclofenac Sodium and its Metabolites," Scand. J. Rheumatology 22(suppl.): 5-16; 1978. In this experiment the ability of misoprostol, certain NSAIDs and combinations of misoprostol with such NSAIDs to suppress the chemically induced writhing response in mice was determined.

Male albino mice (Charles River Laboratory; CD-1, 20-30 grams were randomly divided into groups of ten and weighed. Twenty-five minutes after intragastric (i.g.) administration of the test compound, 0.025% w/v phenylbenzoquinone (PBQ) was injected intraperitoneally (i.p.; 0.1 ml/10 grams of body weight). Five minutes after i.p. injection of PBQ, each animal was placed into a large glass beaker and the number of writhes that occurred in the subsequent ten minutes was counted. A writhe consisted of a dorsoflexion of the back, extension of the hindlimbs, and strong contraction of the abdominal musculature. Test compounds were considered to have significantly inhibited the writhing response if the number of writhes observed was less than or equal to one half of the median number of writhes recorded for the control group of mice on the same day (Taber, R.I., "Predictive Value of Analgesic Assays in Mice and Rats," Advances in Biochemical Psychopharmacology, vol. 8, p 191, (1974)). The number of writhes for each animal was converted to the square root function. The effective dose (ED_{50}) that inhibited writhing 50% compared to control values was determined by a regression analysis of the least squared means. Based on these results, an

estimation of the number of writhes could be determined for each drug at various dose levels and a statistical prediction could be made as to the additive effects of various combinations of misoprostol and NSAID. The differences between the predicted and actual number of writhes was calculated. These differences were analyzed for significance using a T-test. Isobolographic analysis was used to determine whether the actual effect of the combinations of the two drugs were additive, synergistic or antagonistic ("Criteria For Analyzing Interactions Between Biologically Active Agents," M.C. Berenbaum; Advances in Cancer Research, vol. 25, pp269-335, (1981)). Simplistically, this procedure of analysis is performed by first determining the ED_{50} values for the two agents separately and plotting these values on separate axes. A line is drawn between the two values which line represents the theoretical dose-additivity line. If the pharmacological effects of the two drugs when coadministered add together, then any dose combination represented by a point on the line will produce an ED_{50} efficacy. The next step in the analysis was the evaluation of a series of dose combinations and identification of combinations which would generate an ED_{50} response. These values are plotted on the graph. If the values fall on the line, then the drugs are additive. If the values are inside the line (toward the origin) then the effects are supraadditive, that is they synergize with one another to produce a much greater effect than predicted. If the values are outside of the line, then the two drugs are infraadditive, that is the effect of the combination is less than expected. As can be seen from the drawings of the isobolographs in Figures 1 through 3 which depict the results of the experiments herein, the combinations herein studied and comprising the invention herein fall inside the lines. The

isobolographs for the combination of misoprostol with diclofenac, piroxicam and ibuprofen all show the empirically determined values to be inside the line of additivity and, therefore, synergistic.

In regard to Figure 1 there is shown the isobolographic analysis of coadministered misoprostol and diclofenac. The ED_{50} for diclofenac alone was 1.8 mg/kg. The ED_{50} for misoprostol alone was 0.6 mg/kg. The isobolographic analysis shows that an ED_{50} for the coadministered misoprostol and diclofenac could be obtained using 0.05 mg/kg of diclofenac with a 0.02 mg/kg of misoprostol. This represents a 36 fold decrease in the ED_{50} value.

With regard to Figure 2 an isobolographic analysis is illustrated for the coadministered misoprostol with ibuprofen. The graph is based upon results from the mouse writhing assay. As can be seen from the graph the ED_{50} for misoprostol 0.6 mg/kg and for ibuprofen is 3 mg/kg. When the ibuprofen was coadministered with misoprostol wherein misoprostol was present in amount of 0.01 mg/kg. The ibuprofen was present in amount of about 0.08 mg/kg. The ibuprofen exhibited about a 38 fold decrease in dose. That is 1/38 the amount of ibuprofen can be used when coadministered with misoprostol to thereby obtain the same analgesic activity as would be predicted for a dose 38 times as great.

Figure 3 represents the isobolographic analysis of coadministered misoprostol and piroxicam. The misoprostol is plotted along the x axis and piroxicam is plotted along the y axis. As can be seen from Figure 3 and the results of the mouse writhing assay performed using coadministered misoprostol and piroxicam there was about a 67 fold decrease in the amount of piroxicam required when combined with 0.009 mg/kg of misoprostol.

The graphs shown in Figures 1-3 also show that there was about a 30 fold increase in the analgesic effect of misoprostol when combined with any of the NSAIDs. Regardless of the NSAID selected, such a thirty fold increase in effect was observed. The amount of misoprostol selected to be used in the composition or method herein can be 1/30 of the amount which would normally be prescribed if it were prescribed alone without the presence of an NSAID.

The results were further statistically analyzed and the results of this further analysis are shown in Figures 4 through 6. The dose response data for misoprostol alone and the dose response data for the respective NSAID alone were used to calculate a predicted level of response for each of the various dose combinations studied. A determination was made of the difference between the actual and the predicted response levels. The difference showed that the actual values were statistically clearly different from the predicted. Figures 4 through 6 show the plot of the difference in predicted response versus the observed response for the combined dosages of misoprostol and NSAID. The results of the mouse writhing assay that were performed for misoprostol, the various NSAIDs and the combinations of misoprostol with the selected NSAIDs are reported in Table 1.

TABLE 1

Compound	[mg/kg]	Results	ED_{50}
Misoprostol	0.3	02/10	0.60
	1.0	07/10	
	10.0	10/10	
Diclofenac	1.00	03/10	1.80
	3.00	06/10	
	10.00	10/10	
Misoprostol + Diclofenac	0.003 + 0.01	02/10	0.010 + 1.0
	0.003 + 1.00	03/1	0.020 + 0.01
	0.030 + 0.01	06/10	0.060 + 0.1
	0.030 + 0.10	04/10	0.30 + 0.004
	0.030 + 1.00	06/09	
	0.300 + 0.01	06/10	
	0.300 + 0.10	07/10	
	0.300 + 1.00	08/10	
	3.000 + 1.00	09/10	
Ibuprofen	10.0	09/10	3.0
	3.0	05/10	
	1.0	01/10	
Misoprostol + Ibuprofen	0.3 + 1.5	08/10	0.015 + 0.076
	0.03 + 0.15	06/10	
	0.001 + 0.005	02/10	
Piroxicam	10.0	10/10	0.6
	3.0	09/10	
	1.0	06/10	
	0.3	03/10	
Misoprostol + Piroxicam	0.3 + 0.3	10/10	0.008 + 0.008
	0.03 + 0.03	05/10	
	0.001 + 0.001	03/10	

These studies show that there was clear evidence of enhancement of analgesic activity between misoprostol and the nonsteroidal anti-inflammatory agents.

The use of the method herein can enhance the analgesic effect of a mild to moderate pain relief therapeutic regimen which includes the administration of a nonsteroidal anti-inflammatory agent. The method can thus provide the desired extent of pain relief by using a lower dose of the nonsteroidal anti-inflammatory

agent. The method can, therefore, reduce the incidence of gastrointestinal side effects of the nonsteroidal anti-inflammatory agent. The use of an amount of NSAID which is less than the normal amount which would be prescribed, i.e., the normal therapeutic amount, is a significant improvement over the current NSAID therapeutic regimen. Heretofore, prostaglandins have been disclosed as being useful in adjunctive therapy with normal therapeutic dosages of NSAIDs in order to diminish the ulcerogenic side effects of the NSAID administration. The improved method and composition herein is beneficial in that it provides the opportunity to use less NSAID (lower dosage) than heretofore was believed to be therapeutic. The combination of an NSAID with misoprostol creates an attractive therapy for mild to moderate pain relief. The invention herein of employing a prostaglandin which potentiates the analgesic effect of a particular NSAID (one which is capable of interacting with a potentiating prostaglandin to produce an analgesic-potentiated effect) in an effective amount to potentiate such effect is especially beneficial in that it reduces the amount of NSAID administered, it reduces the liklihood of ulcer formation, it aids in the healing of ulcers (if formed), and it alleviates the mild to moderate pain for which it was administered.

In the formulation of the composition herein, the formulation can be formed in an admixture as disclosed in copending patent application ser. no._____, titled "Stabilized Pharmaceutical Admixture Composition," of Franz et. al. (docket no. 2609) or in a tablet such as disclosed in copending patent application ser. no._____, titled "Pharmaceutical Composition Containing Ibuprofen and A Prostaglandin," of Chemburkar et. al.(docket no. 2610) and copending patent application ser. no._____, titled "Pharmaceutical Composition," of Gimet et. al. (docket

no. 2611), the entire disclosures of which are hereby incorporated herein by this reference.

What is claimed is:

1. A method for treating mild to moderate pain in a subject in need of such treatment, which method provides a desired therapeutic analgesic effect, the method comprising the step of administering to the subject:
an analgesic agent selected from diclofenac, ibuprofen, piroxicam and their pharmaceutically acceptable salts, in a dosage of the analgesic agent which dosage by itself would provide less than the desired therapeutic analgesic effect; and
misoprostol in a dosage which is sufficient to potentiate the analgesic effect of the analgesic agent to the desired therapeutic analgesic effect.

2. A method for treating mild to moderate pain as recited in claim 1 wherein the analgesic agent is selected from diclofenac in a dosage up to about 200 mg per day, ibuprofen in a dosage up to about 3200 mg per day, and piroxicam in a dosage up to about 20 mg per day; and
the prostaglandin misoprostol is present in an analgesic-agent-potentiating effective dose up to about 1600 mcg per day.

3. A method for treating mild to moderate pain as recited in claim 2 wherein the analgesic agent is selected from diclofenac in a dosage up to about 100 mg per day, ibuprofen in a dosage up to about 1200 mg per day, and piroxicam in a dosage up to about 20 mg per day; and
the prostaglandin misoprostol is present in an analgesic-agent-potentiating effective dose up to about 800 mcg per day.

4. A method for treating mild to moderate pain as recited in claim 1 wherein the prostaglandin misoprostol is administered in an analgesic-agent-potentiating effective dose from about 25 mcg to about 1600 mcg per day.

5. A method for treating mild to moderate pain as recited in claim 1 wherein the prostaglandin misoprostol is administered in an analgesic-agent-potentiating effective dose up to about 1600 mcg per day and wherein the weight ratio of diclofenac to misoprostol is at least 3:1, the weight ratio of ibuprofen to misoprostol is at least 5:1, and the weight ratio of piroxicam to misoprostol is at least 1:1.

6. A method for treating mild to moderate pain as recited in claim 1 wherein the analgesic agent comprises diclofenac administered in an amount up to about 200 mg per day; and wherein the prostaglandin misoprostol is administered in an analgesic-agent-potentiating effective dose up to about 1600 mcg per day and the weight ratio of diclofenac to misoprostol is at least 3:1.

7. A method for treating mild to moderate pain as recited in claim 1 wherein the analgesic agent comprises ibuprofen administered in an amount up to about 3200 mg per day; and wherein the prostaglandin misoprostol is administered in an analgesic-agent-potentiating effective dose up to about 1600 mcg per day and the weight ratio of ibuprofen to misoprostol is at least 5:1.

8. A method for treating mild to moderate pain as recited in claim 1 wherein the analgesic agent comprises piroxicam administered in an amount up

to about 20 mg per day; and wherein the prostaglandin misoprostol is administered in an analgesic-agent-potentiating effective dose up to about 1600 mcg per day and the weight ratio of piroxicam to misoprostol is at least 1:1.

9. A method for treating mild to moderate pain as recited in claim 1 wherein the analgesic agent and the misoprostol are administered simultaneously.

10. A method for treating mild to moderate pain as recited in claim 1 wherein the analgesic agent and the misoprostol are administered concomitantly.

11. A method for treating mild to moderate pain as recited in claim 1 wherein the administration is performed by oral administration.

12. A pharmaceutical composition useful for achieving a therapeutic analgesic effect in the treatment of mild to moderate pain in a subject in need of such treatment, the composition comprising:
an analgesic agent selected from diclofenac, ibuprofen and piroxicam in a dosage of the analgesic agent which dosage by itself would provide less than the therapeutic analgesic effect; and
misoprostol in a dosage which is sufficient to potentiate the analgesic effect of the analgesic agent to the therapeutic analgesic effect.

13. A pharmaceutical composition as recited in claim 12, wherein the analgesic agent is selected from diclofenac in a dosage up to about

75 mg, ibuprofen in a dosage up to about 800 mg, and piroxicam in a dosage up to about 20 mg; and wherein the prostaglandin misoprostol is present in an analgesic-agent-potentiating effective dose up to about 200 mcg.

14. A pharmaceutical composition as recited in claim 13, wherein the analgesic agent is selected from diclofenac in a dosage up to about 25 mg, ibuprofen in a dosage up to about 200 mg, and piroxicam in a dosage up to about 10 mg; and wherein the prostaglandin misoprostol is present in an analgesic-agent-potentiating effective dose up to about 200 mcg.

15. A pharmaceutical composition as recited in claim 14 comprising diclofenac in an amount from about 0.7 mg to about 25 mg.

16. A pharmaceutical composition as recited in claim 15 comprising misoprostol in an amount from about 5.0 mcg to about 200 mcg.

17. A pharmaceutical composition as recited in claim 14 comprising ibuprofen in an amount from about 5.33 mg to about 200 mg.

18. A pharmaceutical composition as recited in claim 17 comprising misoprostol in an amount from about 5.0 mcg to about 200 mcg.

19. A pharmaceutical composition as recited in claim 14 comprising piroxicam in an amount from about 0.15 mg to about 10 mg.

20. A pharmaceutical composition as recited in claim 19 comprising misoprostol in an amount from about 5.0 mcg to about 200 mcg.

21. A pharmaceutical composition as recited in claim 12, wherein the analgesic agent is selected from:
diclofenac in a dosage selected from less than 25 mg, greater than 25 mg but less than 50 mg, and greater than 50 mg but less than 75 mg;
ibuprofen in a dosage selected from less than 200 mg, greater than 200 mg but less than 300 mg, greater than 300 mg but less than 400 mg, greater than 400 mg but less than 600 mg, greater than 600 mg but less than 800; and
piroxicam in a dosage selected from less than 10 mg and greater than 10 mg but less than 20 mg.

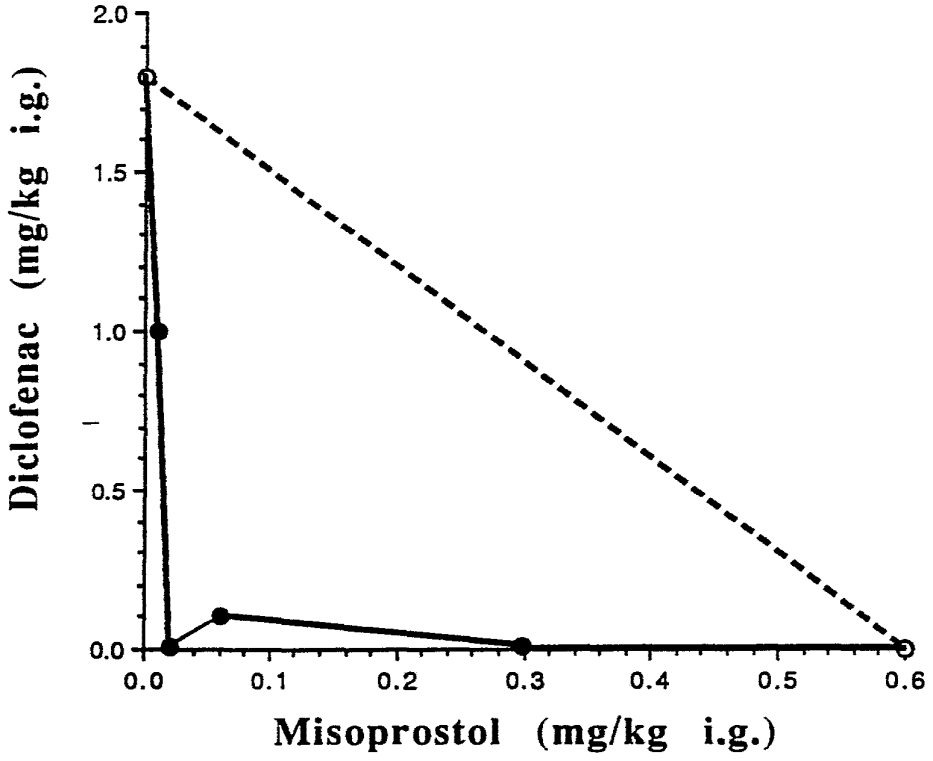


Figure 1

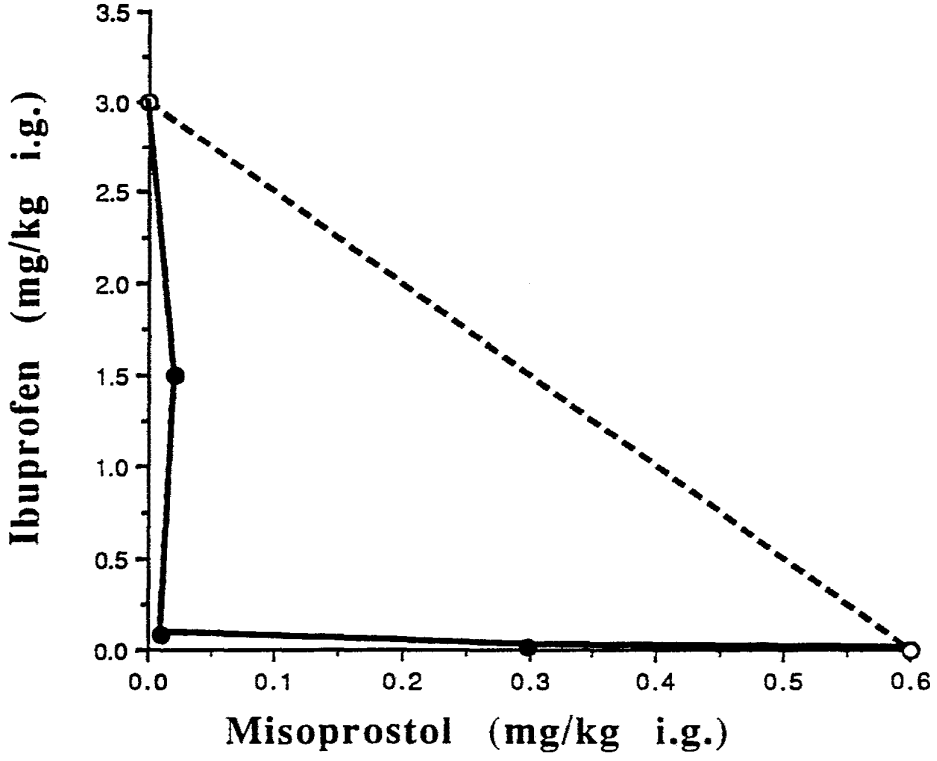


Figure 2

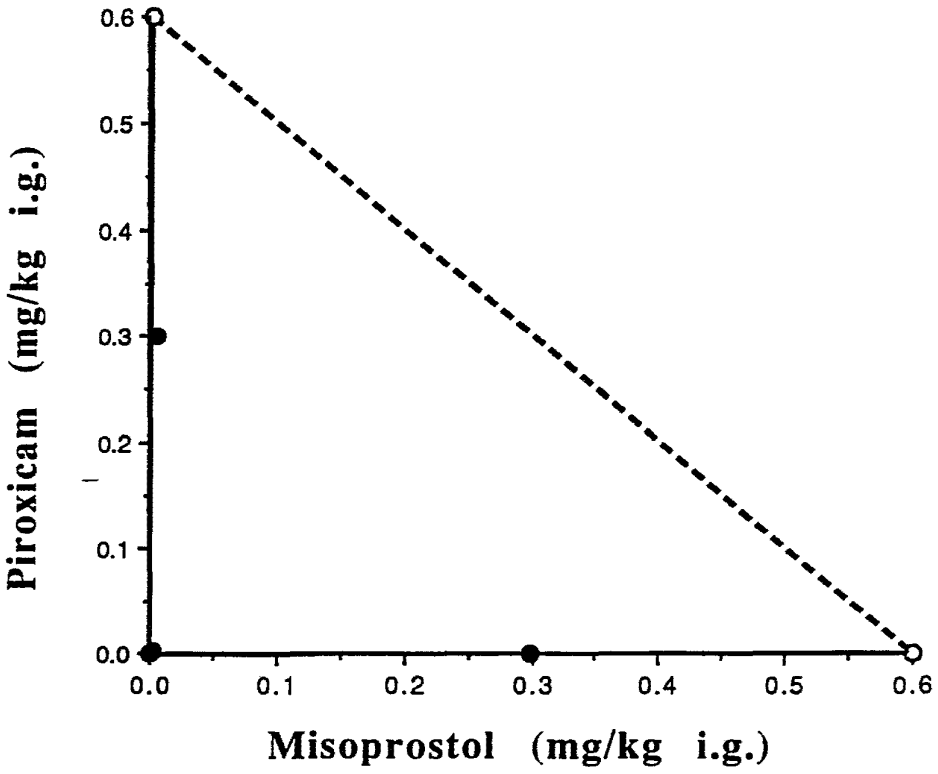


Figure 3

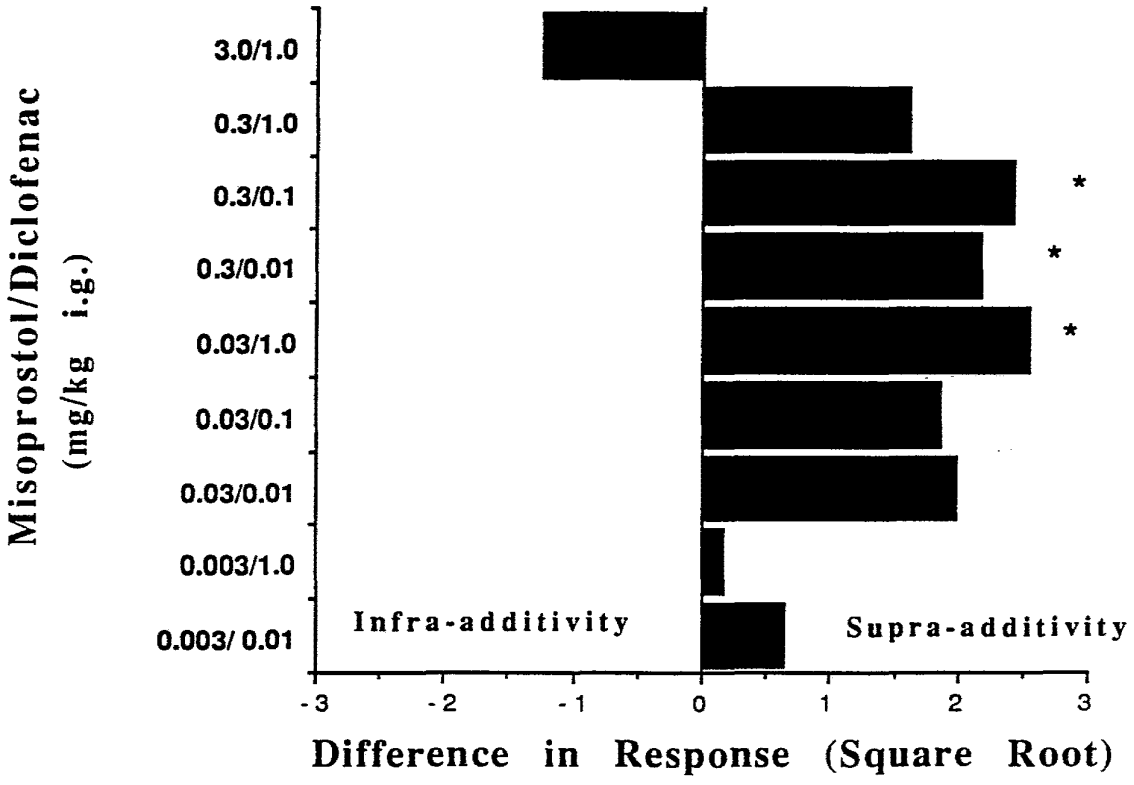


Figure 4

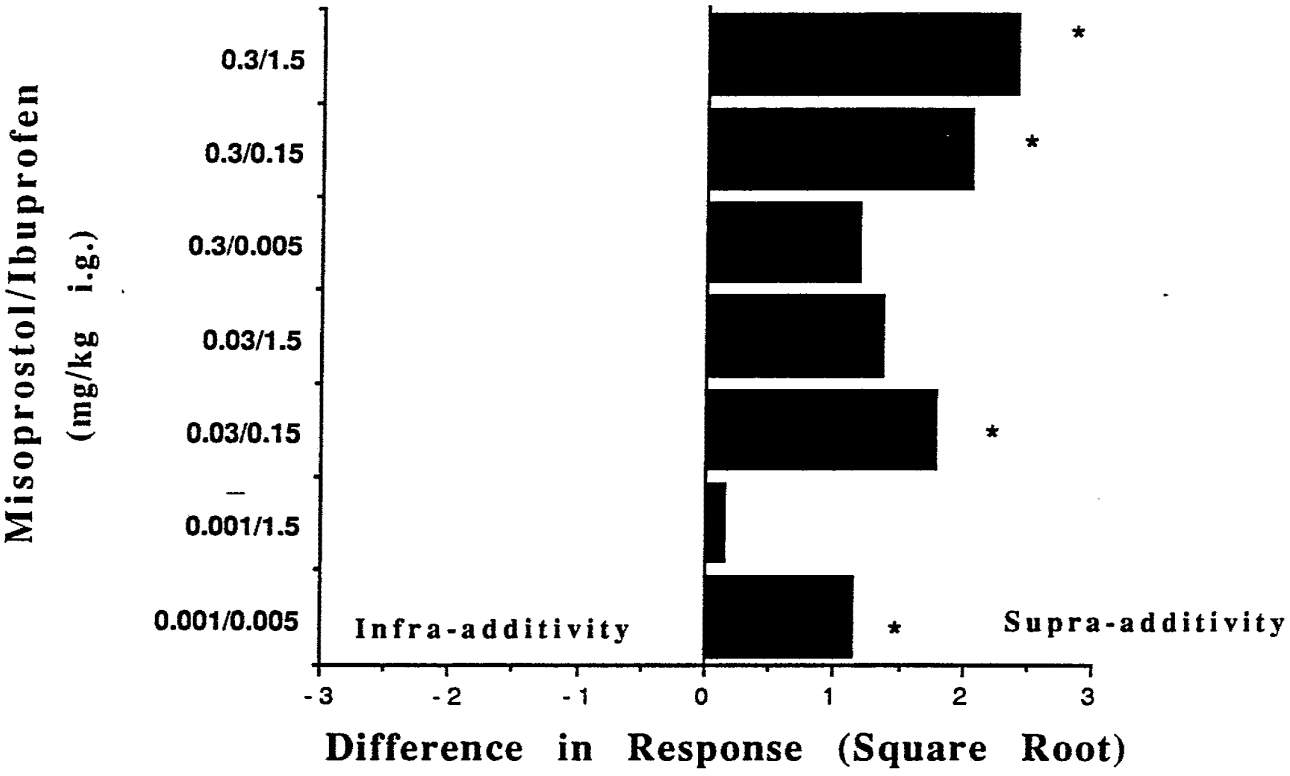


Figure 5

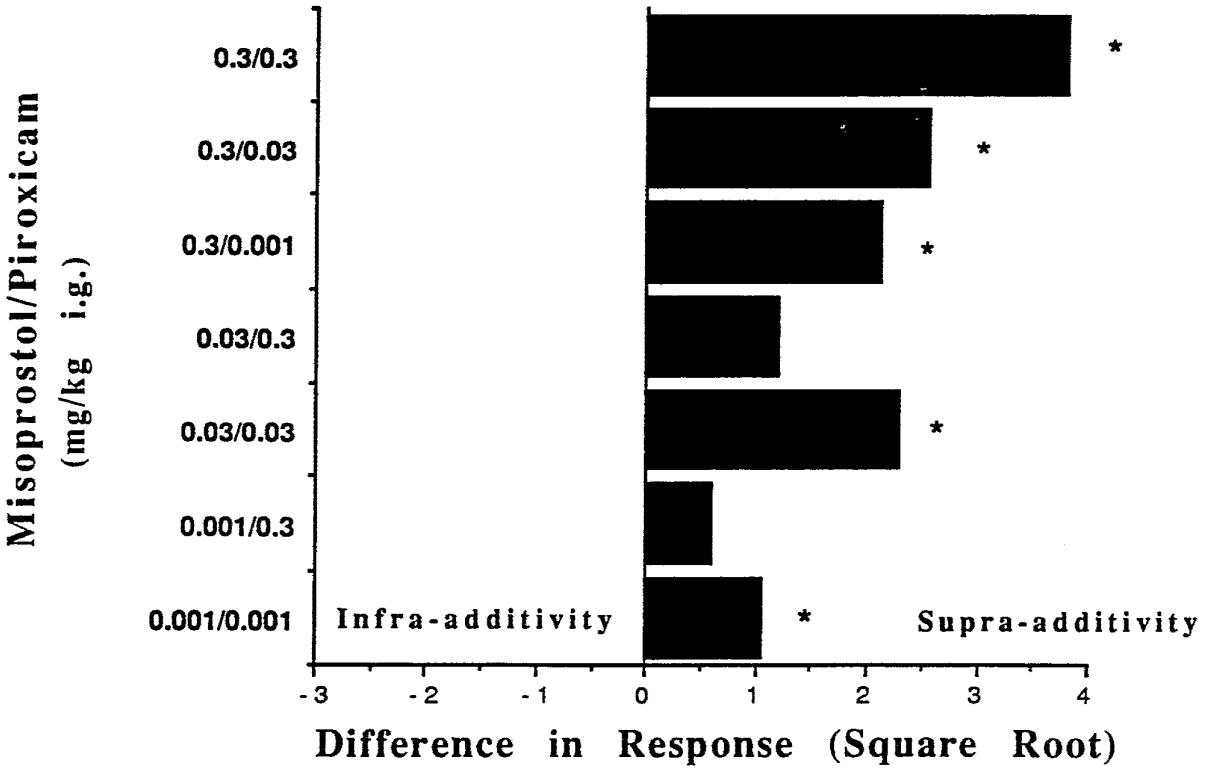
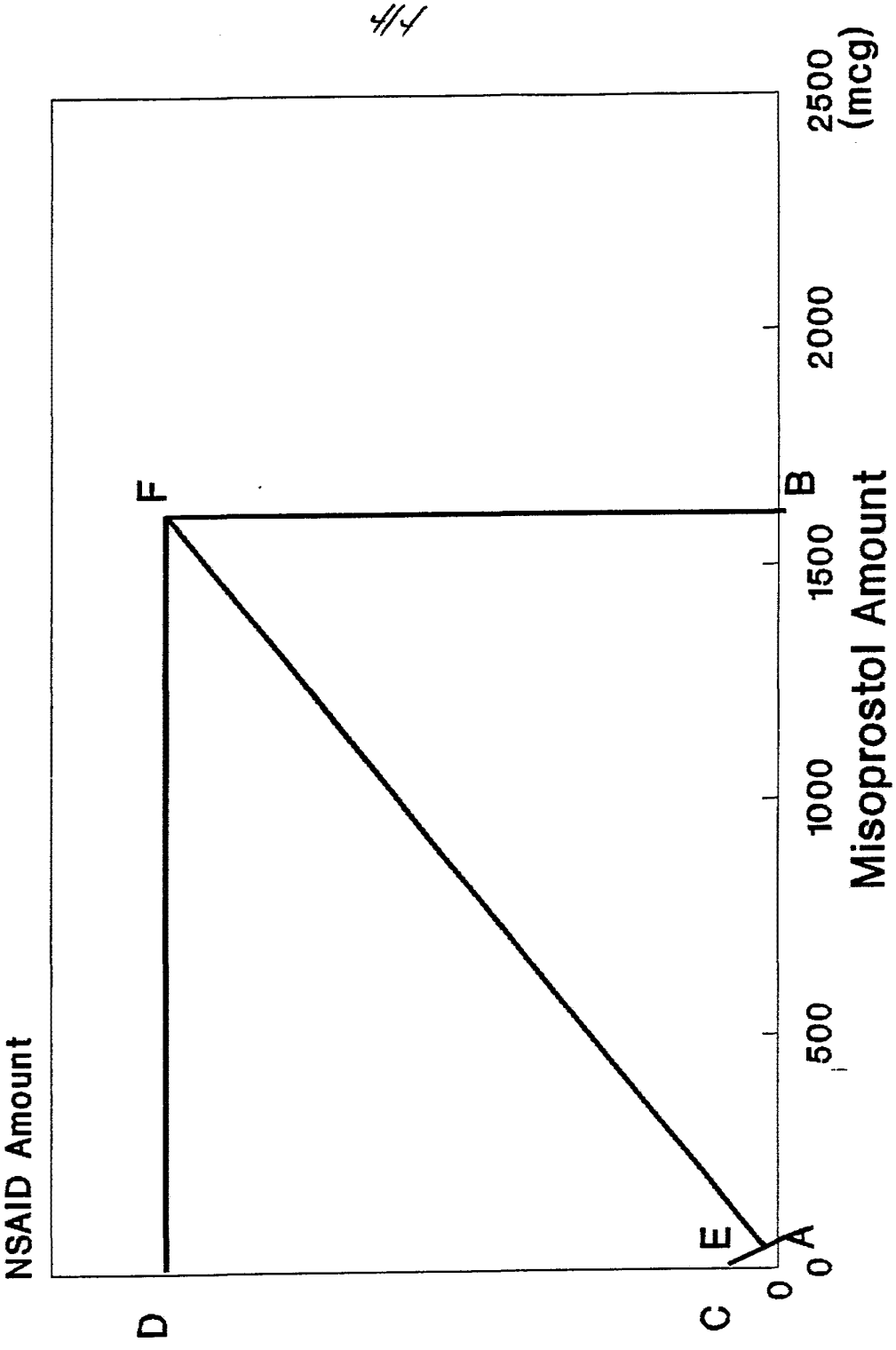


Figure 6

FIGURE 7


NSAID Amount
Misoprostol Amount
0
500
1000
1500
2000
2500
(mcg)
A
B
C
D
E
F

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/02985

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/557 //(A 61 K 31/557 A 61 K 31:19 A 61 K 31:54)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0106649 (THE UPJOHN CO.) 25 April 1984, see page 3, line 34 - page 4, line 4; page 6, table 1; claims 1,2 ---	12-21
A	EP,A,0268388 (GLAXO GROUP LTD) 25 May 1988, see page 3, lines 9-17; page 7, examples A,B; claims 1-5,10,13,14 ---	12-21
A	FORTSCHRITTE DER MEDIZIN, vol. 107, no. 10, 30 March 1989, pages 233-236, S.E. MIEDERER: "Prostaglandine und die Prävention NSAR-induzierter gastraler Läsionen", see pages 234-235 ---	12-21
A	AMERICAN DRUGGIST, vol. 199, no. 2, 1989, page 76, "New drug prevents NSAID-induced ulcers", see page 76 --- -/-	

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
01-08-1991	04 OCT 1991
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,3965143 (G.D. SEARLE & CO.) 22 June 1976, see column 1, lines 1-54	12-21

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. [X] Claim numbers 1-11 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)
Methods for treatment of the human or animal body by means of surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9102985 SA 47309

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 18/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0106649	25-04-84	US-A-	4397865	09-08-83
		JP-A-	59088422	22-05-84
EP-A- 0268388	25-05-88	AU-B-	606082	31-01-91
		AU-A-	8001587	28-04-88
		GB-A,B	2197787	02-06-88
		JP-A-	63115828	20-05-88
		US-A-	4855293	08-08-89
US-A- 3965143	22-06-76	AT-B-	351684	10-08-79
		AU-A-	7947175	30-09-76
		BE-A-	827127	25-09-75
		CA-A-	1040197	10-10-78
		CH-A-	613443	28-09-79
		DE-A,C	2513212	09-10-75
		FR-A,B	2274289	09-01-76
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		JP-A-	50135059	25-10-75
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		SE-A-	7503431	29-09-75
		US-A-	4087621	02-05-78
		US-A-	4060691	29-11-77

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(22) International Filing Date: 11 June 1991 (11.06.91)

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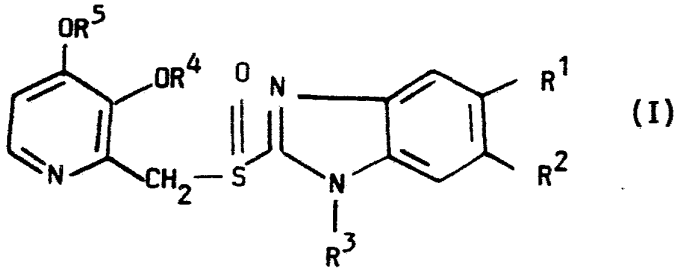
(74) Agents: DANIELSSON, Sten et al.; AB Astra, Patent Department, S-151 85 Södertälje (SE).

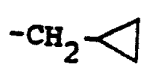
(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).

Published
With international search report.

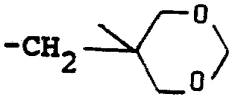
(54) Title: SUBSTITUTED BENZIMIDAZOLES, PROCESS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL USE



(I)



(a)



(b)

(57) Abstract

The novel compounds of formula (I), wherein R^1 and R^2, which are different, is each H, alkyl containing 1-4 carbon atoms or -C(O)-R^6; one of R^1 or R^2 is always selected from the group -C(O)-R^6; wherein R^6 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms, R^3 is the group -CH_2OCOOR^7, wherein R^7 is alkyl containing 1-6 carbon atoms or benzyl; R^4 and R^5 are the same or different and selected from -CH_3, -C_2H_5, (a), (b) and -$CH_2CH_2OCH_3$, or R^4 and R^5 form together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R^4 and R^5 is -$CH_2CH_2CH_2$-, -CH_2CH_2- or -CH_2- as well as pharmaceutical compositions containing such compounds as active ingredient, and the use of the compounds in medicine.

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Substituted benzimidazoles, process for their preparation and their pharmaceutical use

DESCRIPTION

Field of the invention

The object of the present invention is to provide novel compounds, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.

The present invention also relates to the use of the compounds of the invention for inhibiting gastric acid secretion in mammals including man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compounds of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compounds may also be useful in the treatment of diseases related to bone metabolism disorders as well as

the treatment of glaucoma. The invention also relates to pharmaceutical compositions containing the compounds of the invention, as active ingredient. In a further aspect, the invention relates to processes for preparation of such new compounds and to the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

It is a specific primary object of the invention to provide compounds with a high level of biovailability. The compounds of the invention will also exhibit good stability properties at neutral and acidic pH and a good potency in regard to inhibition of gastric acid secretion. The compounds of the invention will not block the uptake of iodine into the thyroid gland. It has earlier been disclosed in several lectures from the company, where the inventors are working that thyroid toxicity depends on if the compounds are lipophilic or not. The inventors have now unexpectedly found that it is not the lipophilicity that is the critical parameter. The claimed compounds, which include rather hydrophilic compounds, do not give any thyroid toxic effect and have at the same time high acid secretion inhibitory effect, good bioavailability and stability.

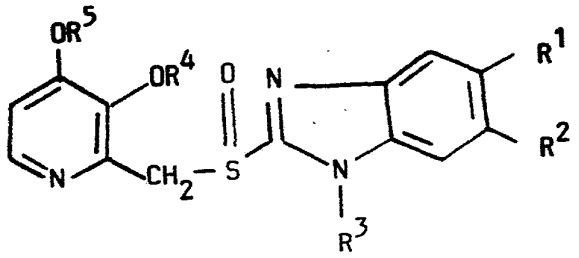
Prior art and background of the invention

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents. Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, BE 898 880, EP 124 495, EP 208 452, EP 221 041, EP 279 149, EP 176 308 and Derwent abstract 87-294449/42. Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory diseases are disclosed in US 4 359 465.

The invention

The compounds of the formula I are effective as inhibitors of gastric acid secretion in mammals including man and in addition do not block the uptake of iodine into the thyroid gland. It has also been found that the compounds of the following formula I show high bioavailability. Further, the compounds of the invention exhibit a high chemical stability in solution at neutral and acidic pH. The high chemical stability also at acidic pH makes the compounds useful for non-enteric coated peroral formulations.

The compounds of the invention are of the following formula I:



I

wherein

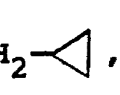
R^1 and R^2, which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^6$, one of R^1 or R^2 is always selected from the group $-C(O)-R^6$;

wherein

R^6 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms

R^3 is the group $-CH_2OCOOR^7$, wherein R^7 is alkyl containing 1-6 carbon atoms or benzyl;

R^4 and R^5 are the same or different and selected from

$-CH_3$, $-C_2H_5$, $-CH_2$  , $-CH_2$  , and $-CH_2CH_2OCH_3$, or R^4 and R^5 form together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R^4 and R^5 is $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

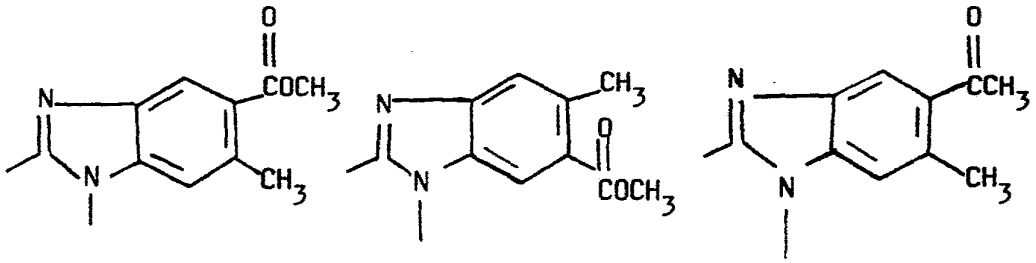
It should be understood that the expressions "alkyl" and "alkoxy" include straight and branched structures.

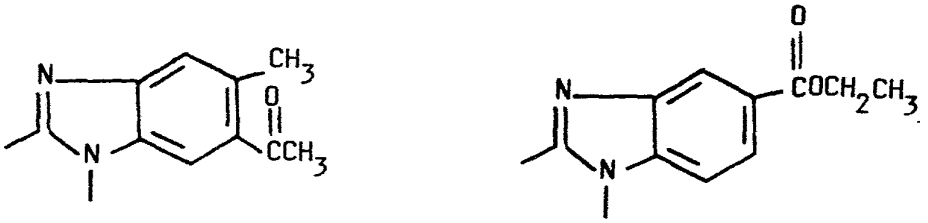
The structural isomers of the invention described in examples 1-6 may be used separately, or in equal or unequal mixtures.

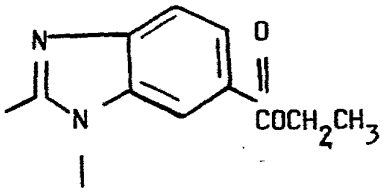
The compounds of the invention of the formula I have an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers) or if they also contain one or more asymmetric carbon atoms, the compounds have two or more diastereomeric forms, each existing in the two enantiomeric forms. Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. It should also be understood that all the diastereomeric forms possible (pure enantiomers or racemic mixtures) are within the scope of the invention.

Preferred groups of compounds of the formula I are:

1. Compounds, wherein R^3 is $-CH_2OCOOCH_2CH_3$.
2. Compounds, wherein R^1 and R^2 are selected from H, methyl or $-C(O)-R^6$, wherein R^6 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.
3. Especially preferred benzimidazole structures are:







4. Especially preferred are compounds, wherein R^4 and R^5 are methyl.

5. Especially preferred specific compounds of the invention are the compounds listed in the following tabulation

R^1	R^2	R^3	R^4	R^5
CH_3	$C(O)OCH_3$	$CH_2OCOOCH_2CH_3$	CH_3	CH_3
$C(O)OCH_3$	CH_3	$CH_2OCOOCH_2CH_3$	CH_3	CH_3
CH_3	$C(O)CH_3$	$CH_2OCOOCH_2CH_3$	CH_3	CH_3
$C(O)CH_3$	CH_3	$CH_2OCOOCH_2CH_3$	CH_3	CH_3

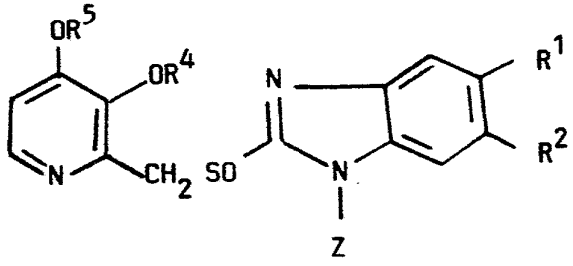
It is believed that compounds of formula I are metabolized

into the corresponding compounds, wherein R^3 is H before exerting their effect.

Preparation

The compounds of the invention may be prepared according to the following methods:

a) Reacting a compound of the formula II



II

wherein R^1, R^2, R^4 and R^5 are as defined under formula I, and Z, is either a metal cation such as Na+, K+, Li+ or Ag+ or a quaternary ammonium ion, such as tetrabutylammonium with alkyl chloromethyl carbonate or benzyl chloromethyl carbonate.

b) Reacting a compound of the formula II, wherein R^1 , R^2, R^4 and R^5 are as defined under formula I and Z is hydroxymethyl with a compound of the formula III,

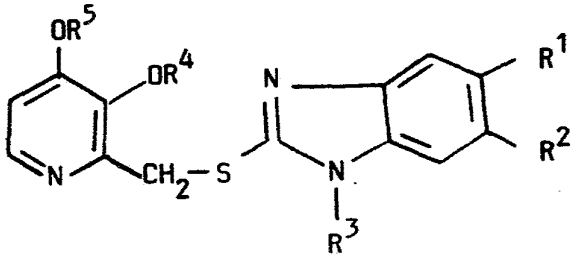
$$X\text{-}C(O)\text{-}O\text{-}R^7 \qquad \text{III}$$

wherein R^7 is as defined above and X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as triethylamine.

The reactions according to a) and b) are suitably carried out under protective gas in absence of water. Suitable solvents are hydrocarbons such as toluene or benzene or halogenated hydrocarbons such as methylene chloride or

chloroform, or acetone, acetonitrile or dimethylformamide. The reactions may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

c) Oxidizing a compound of the formula IV



IV

wherein R^1, R^2, R^3, R^4 and R^5 are as defined under formula I.

This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers, ketones.

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbiotically by using a suitable microorganism. The structural isomers obtained, may be separated by means of crystallization or chromatography.

Racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active

solvent. In the case of racemic diastereomeric mixtures these may be separated into diastereomeric pure enantiomers by means of chromatography or fractional crystallization.

The starting materials utilized in the methods a)-c) are in some cases unknown. These unknown starting materials may, be obtained according to processes known per se.

Alkyl chloromethyl carbonate and benzyl chloromethyl carbonate may be obtained from the pertinent alcohol by treatment with chloromethyl chloroformate in the presence of pyridine.

Intermediates of the formula II, wherein Z is hydroxymethyl are obtained by reaction of the corresponding benzimidazole compound carrying H in the N-1 position with formaldehyde.

Starting materials of the formula III may be obtained by known methods, e.g. from an alcohol HOR^7 by treatment with phosgene or 1,1^1-carbonyldiimidazole or p-nitrophenyl chloroformate.

For clinical use a compound of the invention is formulated into pharmaceutical formulations for oral, rectal, or other modes of administration. The pharmaceutical formulation contains a compound of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form

of dosage units for oral administration a compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopection, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain an active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-

[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

To a suspension of 0.45 g (1.1 mmol) of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole and 0.25 g (1.8 mmol) of potassium carbonate anhydrous in 45 ml of dry acetonitrile, 0.21 g (1.5 mmol) of chloromethyl ethyl carbonate dissolved in 5 ml of acetonitrile was added. The reaction mixture was stirred at room temperature over night. The solvent was then removed in vacuo and the residue was diluted with methylene chloride and water. The organic solvent was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave the crude product, which was chromatographed with silica gel and eluted with ethyl acetate to provide 0.94 g of a yellow oil which slowly crystallized. Recrystallization with ethanol yielded 0.25 g (44 %) of the title compounds as an isomeric mixture.
NMR data for the products are given below.

Example 2. Preparation of 6-carbomethoxy-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was obtained by crystallizing the isomeric mixture given in example 1 from ethanol.
NMR data are given below.

Example 3. Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-acetyl-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

To a magnetically stirred suspension of potassium carbonate

anhydrous (0.48 g, 3.47 mmol) in 80 ml of dry acetonitrile 0.80 g (2.14 mmol) of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and 0.39 g (2.8 mmol) of chloromethyl ethyl carbonate dissolved in 10 ml of acetonitrile was added dropwise. Stirring was continued at room temperature for 20 hours. The solvent was removed in vacuo, the residue diluted with methylene chloride, the methylene chloride solution washed with water and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave the crude product which was chromatographed with silica gel and eluted with ethyl acetate to yield 0.63 g of an almost white crystalline solide. The product was recrystallized from ethyl acetate to give 0.50 g (49 %) of the title compounds as an isomeric mixture.
NMR data for the products are given below.

Example 4. Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was isolated from the isomeric mixture given in example 3 by chromatography on a silica column with methylene chloride - acetonitrile (ratio 6:4) as eluent. The title compound was crystallized from ethanol.
NMR data are given below.

Example 5. Preparation of 6-acetyl-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was isolated from the isomeric mixture given in example 3 by chromatography on a silica column with methylene chloride-acetonitrile (ratio 6:4) as eluent. The title compound was crystallized from ethanol.
NMR data are given below.

Example 6 Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

To a suspension of 0.28 g (0.72 mmol) 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole and 0.16 g (1.2 mmol) anhydrous potassium carbonate in 20 ml of dry acetonitrile 0.16 g (1.2 mmol) chloromethyl ethyl carbonate dissolved in 2 ml dry acetonitrile was added. The mixture was stirred at ambient temperature over night. The solvent was evaporated off and the crude product was chromatographed on a silica column using ethyl acetate as eluent. Crystallizing from ethanol gave the title compounds as an isomeric mixture, (0.13 g, 37%).
NMR data for the products are given below.

Table 1

Ex.	Solvent	NMR data δ ppm
1	$CDCl_3$ (300 MHz)	1.20-1.30 (m, 3H), 2.70 (s,1.8H), 2.75 (s, 1.2H), 3.85-3.95 (m,9H), 4.15-4.25 (m,2H), 4.85-5.05 (m,2H), 6.40-6.55 (m,2H), 6.75 (d,1H), 7.45 (s, 0.6H), 7.65 (s, 0.4 H), 8.10 (d, 1H), 8.20 (s, 0.4 H), 8.40 (s, 0.6 H).
2	$CDCl_3$ (300 MHz)	1.30 (t, 3H), 2.70 (s, 3H) 3.90 (s,3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.25 (q, 2H), 4.95 (d, 1H), 5.05 (d, 1H), 6.50 (m, 2H), 6.75 (d, 1H), 7.65 (s, 1H), 8.10 (d, 1H), 8.20 (s,

			1H)
	3	$CDCl_3$ (300 MHz)	1.30 (t, 3H) 2.60-2.70 (m, 6H), 3.85-3.90 (m, 6H), 4.25 (q,2H), 4.85-5.05 (m, 2H), 6.75 (d,1H), 7.45 (s, 0.7 H), 7.60 (s, 0.3H), 8.05 (s, 0.3H), 8.10 (d, 1H), 8.20 (s, 0.7H)
	4	$CDCl_3$ (300 MHz)	1.30 (t, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.20 (q, 2H), 4.90 (d, 1H), 5.05 (d, 1H), 6.50 (m, 2H), 6.80 (d, 1H), 7.50 (s, 1H), 8.15 (d, 1H), 8.20 (s, 1H)
	5	$CDCl_3$ (300 MHz)	1.30 (t, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3 H), 4.25 (q, 2H), 4.90 (d, 1H), 5.05 (d, 1H), 6.55 (m, 2H), 6.80 (d, 1H), 7.60 (s, 1H), 8.05 (s, 1 H), 8.15 (d, 1H)
	6	$CDCl_3$ (300 MHz)	1.30 (m, 3H), 1.45 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.25 (m, 2H), 4.45 (m, 2H), 5.00 (m, 2H), 6.55 (m, 2H), 6.80 (d, 1H), 7.70 (d, 0.55H), 7.80 (d, 0.45H), 8.10 (m, 2H), 8.35 (s, 0,45H), 8.50 (d, 0.55H).

Preparation of intermediates

Example I 1

Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-carbomethoxy-6-methyl-2-mercapto-1H-benzimidazole (0.67 g, 0.003 mol) and NaOH (0.12 g, 0.003 mol) in H_2O (0.6 ml) were dissolved in CH_3OH (15 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride, (≈0.0036 mol) as a crude material in CH_3OH (10 ml) and NaOH (0.144 g, 0.0036 mol) in H_2O (0.72 ml) were added. The mixture was heated to reflux and the reflux was continued for 1 hour. CH_3OH was evaporated off and the crude material was purified by chromatography on a silica column using CH_2Cl_2-CH_3OH (98-2) as eluent, giving (1.03 g, 92%) of the pure title compound.

NMR data are given below.

Example I 2

Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (1.03 g, 0.00276 mol) was dissolved in CH_2Cl_2 (30 ml). $NaHCO_3$ (0.46 g, 0.0055 mol) in H_2O (10 ml) was added and the mixture was cooled to +2°C. m-chloroperbenzoic acid 69.5% (0.62 g, 0.0025 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at +2°C for 15 min. After separation the organic layer was extracted with an aqueous 0.2 M NaOH solution (3x15 ml, 0.009 mol). After separation the aqueous solutions were combined and neutralized with methyl formate (0.56 ml, 0.009 mol) in the

presence of CH_2Cl_2 (25 ml). After separation the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (10 ml) giving the title compound (0.68 g, 70 %).

NMR data are given below.

Example I 3

Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-acetyl-6-methyl-2-mercapto-1H-benzimidazole (4.2 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in H_2O (1 ml) were dissolved in 60 ml ethanol. 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (≈17 mmol) as a crude material was added and the mixture was heated to boiling. NaOH (0.7 g, 17 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Crystallizing from acetonitrile gave the title compound, (3.75 g, 62%).

NMR data are given below.

Example I 4

Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.75 g, 10 mmol) was dissolved in CH_2Cl_2 (70 ml). $NaHCO_3$ (1.76 g, 21 mmol) in H_2O (25 ml) was added and the mixture was cooled to ≈+3°C. m-Chloroperbenzoic acid 69.5% (2.43 g, 9.8 mmol) dissolved

in CH_2Cl_2 (20 ml) was added dropwise under stirring. Stirring was continued for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN giving the title compound (2.25 g, 60%).

NMR data are given below.

Example I 5

Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-carbethoxy-2-mercapto-1H-benzimidazole (2.0 g, 9 mmol) and NaOH (0.36 g, 9 mmol) in H_2O (1 ml) were dissolved in ethanol (30 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (≈6.6 mmol) as a crude material were added and the mixture was heated to boiling. NaOH (0.26 g, 6.6 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. Crystallizing from CH_3CN gave the desired product (1.75 g, 71 %).

NMR data are given below.

Example I 6

Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (95.2% pure) (1.4 g, 0.0036 mol) was dissolved in CH_2Cl_2 (30 ml). $NaHCO_3$ (0.6 g, 0.0072 mol in H_2O (10 ml) was added and the mixture was cooled to +2°C.

m-Chloroperbenzoic acid 69.5 % (0.87 g, 0.0035 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at +2°C for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (15 ml) giving the title compound (0.76 g, 54 %).

NMR data are given below.

Table 2

Ex	Solvent	NMR data δ ppm
I 1	$CDCl_3$ (300 MHz)	2.70 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 4.40 (s, 2H), 6.90 (d, 1H), 7.35 (s, 1H), 8.20 (s, 1H), 8.25 (d,1H).
I 2	$CDCl_3$ (500 MHz)	2.70 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.8 (d, 1H), 7.30 (b, 1H), 8.20 (d, 1H), 8.35 (b, 1H).
I 3	$CDCl_3$ (300 MHz)	2.60 (s, 3H), 2.65 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.35 (s, 2H) 6.85 (d, 1H), 7.25 (s,0.6H), 7.40 (s, 0.4H), 7.85 (s, 0.4H), 8.05 (s, 0.6H), 8.30 (m, 1H)
I 4	$CDCl_3$ (300 MHz)	2.60 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.80 (d, 1H), 7.30 (b, 1H), 8.15 (d, 1H), 8.20 (b, 1H)

I 5	$CDCl_3$ (300 MHz)	1.40 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.40 (m, 4H), 6.90 (dd, 1H), 7.45 (d, 0.4H), 7.60 (d, 0.6H), 7.90 (m, 1H), 8.20 (s, 0.6H), 8.25 (m, 1H), 8.25 (s, 0.4H)
I 6	$CDCl_3$ (300 MHz)	1.45 (t, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.40 (q, 2H), 4.65 (d, 1H), 4.40 (d, 1H), 6.80 (d, 1H), 7.50 7.80 (b, 1H) 8.05 (d, 1H), 8.20 (d, 1H), 8.25, 8.55 (b, 1H)

The best mode of carrying out the invention known at present is to use the compound mixture according to Example 3 and the compound according to Example 4.

Table 3

Examples of compounds included in the formula I are given in the following table.

Example	R^1	R^2	R^3	R^4	R^5	Yield %	Ident. data	Remarks
1	$C(O)OCH_3$ CH_3	CH_3 $C(O)OCH_3$	$CH_2OCOOC_2H_5$	CH_3	CH_3	44	NMR	Isomeric mixture
2	CH_3	$C(O)OCH_3$	$CH_2OCOOC_2H_5$	CH_3	CH_3		NMR	Isolated isomer
3	$C(O)CH_3$ CH_3	CH_3 $C(O)CH_3$	$CH_2OCOOC_2H_5$	CH_3	CH_3	49	NMR	Isomeric mixture
4	$C(O)CH_3$	CH_3	$CH_2OCOOC_2H_5$	CH_3	CH_3		NMR	Isolated isomer
5	CH_3	$C(O)CH_3$	$CH_2OCOOC_2H_5$	CH_3	CH_3		NMR	Isolated isomer
6	$C(O)OCH_2CH_3$ H	H $C(O)OCH_2CH_3$	$CH_2OCOOC_2H_5$	CH_3	CH_3	37	NMR	Isomeric mixture

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

A compound according to Example 4	1.0	g
Sugar, powder	30.0	g
Saccharine	0.6	g
Glycerol	5.0	g
Tween	1.0	g
Flavouring agent	0.05	g
Ethanol 96%	5.0	g
Distilled water q.s. to a final volume of	100	ml

A solution of the compound mixture according to Example in ethanol and Tween was prepared. Sugar and saccharine were dissolved in 60 g of warm water. After cooling the solution of the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Tablets

A tablet containing 50 mg of active compound was prepared from the following ingredients:

I Compound mixture according to Example 3	500	g
Lactose	700	g
Methyl cellulose	6	g
Polyvinylpyrrolidone cross-linked	50	g
Magnesium stearate	15	g
Sodium carbonate	6	g
Distilled water	q.s.	

II	Hydroxypropyl methylcellulose	36 g
	Polyethylene glyco	19 g
	Colour Titanium dioxide	4 g
	Purified water	313 g

I Compound mixture according to Example 3, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of hydroxypropyl methylcellulose and polyethylene glycol in purified water was prepared. After dispersion of titanium dioxide the solution was sprayed onto the tablets I in an Accela Cota^{R}, Manesty coating equipment. A final tablet weight of 125 mg was obtained.

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

A compound according to Example 4	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Purified water	q.s.

The active compound mixture was mixed with the dry ingredients and granulated with a solution of disodium

hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 600 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:
Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	600 g
Ethanol	200 g

The final coated pellets were filled into capsules.

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound mixture according to Example 4	4 g
Witepsol H-15	180 g

The active compound mixture was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Biological Effects

Biovailability

Bioavailability, is assessed by calculating the quotient between the areas under plasma concentration (AUC) curve of a compound of the formula I wherein R^3 is hydrogen (herein defined as compound A), following 1) intraduodenal (id) or oral (po) administration of the corresponding compound according to the invention and 2) intravenous (iv) administration of compound A, from the rat and the dog. Low, therapeutically relevant doses, were used. Data are provided in Table 4.

Potency for inhibition of acid secretion

The potency for inhibition of acid secretion is measured in the female rat orally and in the dog both intraduodenally and orally.

Potency data are provided in Table 4.

Effects on the uptake of iodine into the thyroid gland.

The effect of a compound within the invention of the formula I on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of ^{125}I in the thyroid gland of the corresponding compound of the formula I, wherein R^3 is hydrogen, that is a metabolized compound of the formula I.

Biological Tests

Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen), for collection of gastric secretions. A fourteen days recovery period after surgery is allowed before testing is commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion is stimulated with infusion during 2.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substances or vehicle are given orally 120 min before starting the stimulation, in a volume of 5 ml/kg. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output is calculated as the product of titrant volume and concentration. Further calculations are based on group mean responses from 4-7 rats. Percentage inhibition is calculated from absolute rates of acid output. ED_{50}- values are obtained from graphical interpolation on log dose-response curves, or estimated from single-dose experiments assuming a similar slope for all dose-response curves. The results are based on gastric acid secretion during the third hour after drug/vehicle administration.

Bioavailability in the Male Rat.

Male adult rats of the Sprague-Dawley strain were used. One day, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein.

(Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substances. The same dose (4 µmol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until analysis of the test compound.

The area under the blood concentration vs time curve, AUC, for the compound A, determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) of the compound A following intraduodenal administration of compounds of the invention of formula I was calculated as

$$F(\%) = \frac{AUC(\text{Compound A})_{id(\text{compound of the invention})}}{AUC(\text{Compound A})_{iv(\text{Compound A})}} \times 100$$

Inhibition of Gastric Acid Secretion and Bioavailability in the Conscious Dog

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhain-pouch for the collection of gastric secretions.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given orally, id or iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenhain-pouch dog.

The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED_{50}-values were obtained by graphical interpolation on log dose - response curves, or estimated from single-dose experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

Blood samples for the analysis of test compound concentration in plasma were taken at intervals up to 3 h after dosing. Plasma was separated and frozen within 30 min after collection and later analyzed. AUC (area under the plasma concentration - time curve) from time zero to 3 h after dose for compound A, was calculated by the linear trapezoidal rule. The systemic bioavailability (F%) of the

compound A after oral or id administration of compounds of the invention was calculated as described above in the rat model.

Effect on the accumulation of ^{125}I in the thyroid gland

The accumulation of ^{125}I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24 hours before the test. The experimental protocol of Searle, CE et al. (Biochem J 1950; 47:77-81) was followed.

Test substances, suspended in 0.5% buffered (pH 9) methocel, were administerd by oral gavage in a volume of 5 ml/kg body weight. After 1 hour, ^{125}I (300kBq/kg, 3ml/kg) was administered by intraperitoneal injection. Four hours after ^{125}I-administration, the animals were killed by CO_2-asphyxiation and bled. The thyroid gland together with a piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula 100 (1-T/P), where T and P is the mean radioactivity of thyroid glands from animals treated with test agent and placebo (buffered methocel), respectively. The statistical significance for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). $P<0.05$ was accepted as significant.

Chemical Stability

The chemical stability of the compounds of the invention has been followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 5 show the half life (t 1/2) at pH 7, that is the time period after which half the amount of the

original compound remains unchanged, and $t_{10\%}$ at pH 2, that is the time period after which 10% of the original compound has decomposed.

Results of biological and stability tests

Table 4 and 5 give a summary of the test data available for the compounds of the invention.

Table 4, Biological Test Data

Test compound Example no.	Inhibition of acid secretion, oral administration ED_{50} µmol/kg		Inhibition of acid secretion, id administration Dog, ED_{50} µmol/kg	Biovailability F%			Per cent inhibition of 400 µmol/kg, or the uptake of ^{125}I in the thyroid gland
	Dog	Rat		Dog		Rat	
				oral adm	id adm	id adm	
1	1.0[b]		1.3[a]	51[b]		106	0
2							0
3	1.5[b]	0.9	1.3[a] 0.8[b]	51[b]	66[b]	99	-7
4	2.2[b]			35[b]			-7
5	1.5[b]			50[b]			-7
6							-6

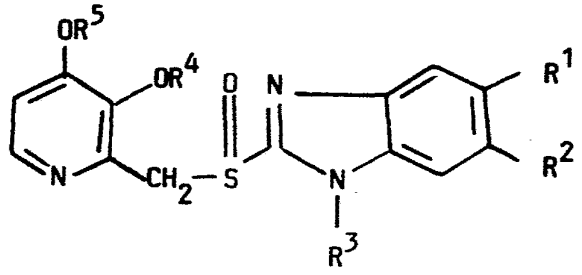
a) gastric fistula dog
b) Heidenhain pouch dog

Table 5, Stability Data

Test compound Example No.	Chemical stability at pH 7 t 1/2 (h)	pH 2 t 10% (h)
1	87	9.5
2	50	6.5
3	51	7.5
4	82	13
5	60	7
6	63	13

CLAIMS:

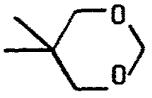
1. Compounds of the formula I



wherein
R^1 and R^2, which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^6$; one of R^1 or R^2 is always selected from the group $-C(O)-R^6$;

wherein
R^6 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms,

R^3 is the group $-CH_2OCOOR^7$, wherein R^7 is alkyl containing 1-6 carbon atoms or benzyl;

R^4 and R^5 are the same or different and selected from $-CH_3$, $-C_2H_5$, $-CH_2$-  , $-CH_2$-  and $-CH_2CH_2OCH_3$, or R^4 and R^5 form together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R^4 and R^5 is $-CH_2CH_2-CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

2. Compounds according to formula I of claim 1, namely a mixture of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-[[(3,4-

dimethoxy-2-pyridinyl)methyl]sulfinyl]-H-benzimidazole-1-ylmethyl ethyl carbonate.

3. Compounds according to formula I of claim 1, namely mixture of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-acetyl-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

4. A compound according to claim 1, namely 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

5. A compound according to claim 1, namely 6-carbomethoxy-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

6. A compound according to claim 1, namely 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

7. A compound according to claim 1, namely 6-acetyl-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sufinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

8. A compound according to claim 1, wherein R^3 is the group $CH_2OCOOCH_2CH_3$.

9. A compound according to claim 1, wherein R^1 and R^2 is each H, methyl or $-C(O)R^6$, wherein R^6 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.

10. A pharmaceutical composition containing as active ingredient a compound according to claim 1.

11. A compound as defined in claim 1 for use in therapy.

12. A compound as defined in claim 1 for use in inhibiting gastric acid secretion in mammals including man.

13. A compound as defined in claim 1 for use in the treatment of gastrointestinal inflammatory deseases in mammals including man.

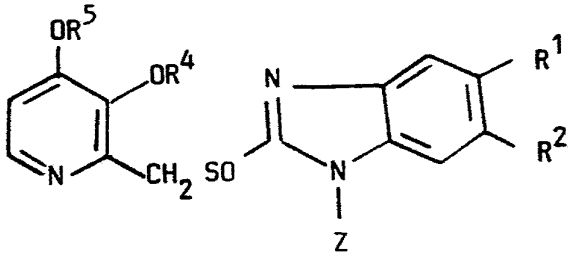
14. A method for inhibiting gastric acid secretion by administering to mammals including man a compound as defined in claim 1.

15. A method for the treatment of gastrointestinal infammatory diseases in mammals including man by administering a compound as defined in claim 1.

16. Use of a compound according to claim 1 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals including man.

17. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases in mammals including man.

18. A process for the preparation of a compound of the formula I according to claim 1, by
a) reacting a compound of the formula II



II

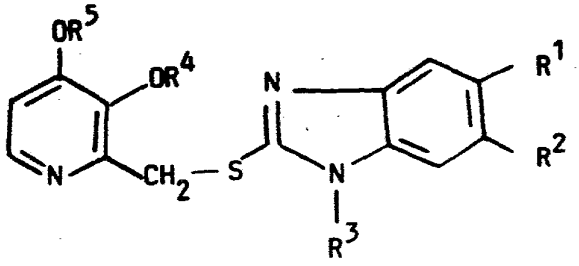
wherein R^1, R^2, R^4 and R^5 are as defined under formula I and Z is either a metal cation such as Na+, K+, Li+ or Ag+ or a quaternary ammonium ion, such as tetrabutylammonium with alkyl chloromethyl carbonate or benzyl chloromethyl carbonate or;

b) reacting a compound of the formula II, wherein R^1, R^2, R^4 and R^5 are as defined under formula I and Z is hydroxymethyl with a compound of the formula III

$$X\text{-}C(O)\text{-}O\text{-}R^7$$

wherein R^7 is as defined above and X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group in the presence of a suitable base such as triethylamine or;

c) oxidizing a compound of the formula IV



wherein R^1, R^2, R^3, R^4 and R^5 are as defined under formula I.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00415

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 401/12, A 61 K 31/415, 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP, A, 0221041 (AKTIEBOLAGET HÄSSLE) 6 May 1987, see the whole document --	1-13,16-18
A	EP, A, 0176308 (THE UPJOHN COMPANY) 2 April 1986, see the whole document --	1-13,16-18

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th September 1991	1991 -09- 19
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Göran Karlsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. [X] Claim numbers 14-15, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00415

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-07-31
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0221041	87-05-06	AU-B-	598491	90-06-28
		AU-D-	6542986	87-05-19
		EP-A-	0233284	87-08-26
		JP-T-	63501151	88-04-28
		US-A-	5021433	91-06-04
		WO-A-	87/02668	87-05-07
EP-A- 0176308	86-04-02	AU-B-	568441	87-12-24
		AU-D-	4669085	86-04-10
		JP-A-	61078784	86-04-22
		US-A-	4873337	89-10-10

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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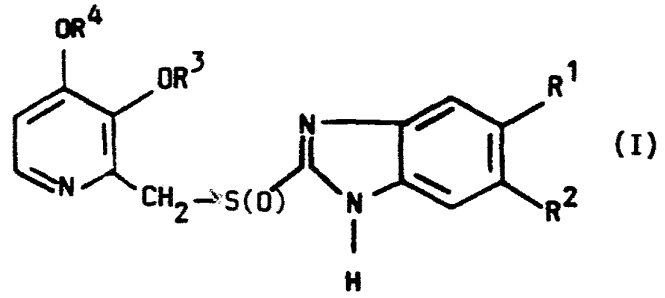

(57) Abstract

The novel compounds of formula (I) and physiologically acceptable salts thereof, wherein R^1 and R^2, which are different, is each H, alkyl containing 1-4 carbon atoms or -C(O)-R^5; wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms and one of R^1, or R^2 is always selected from the group -C(O)-R^5; R^3 and R^4 are the same or different and selected from $-CH_3$, $-C_2H_5$, (a), (b), and $-CH_2CH_2OCH_3$ or R^3 and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring, wherein the part constituted by R^3 and R^4 is $-CH_2CH_2CH_2-$, or $-CH_2-CH_2-$ or $-CH_2-$; as well as intermediates, pharmaceutical compositions containing such compounds as active ingredient and use of the compounds in medicine.

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Dialkoxy-pyridinyl-benzimidazole derivatives, process for their preparation and their pharmaceutical use

DESCRIPTION

Field of the invention

The object of the present invention is to provide novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.

The present invention also relates to the use of the compounds of the invention, and therapeutically acceptable salts thereof, for inhibiting gastric acid secretion in mammals including man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome. Furthermore, the compound may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compounds of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compounds may also be useful in the treatment of diseases related to bone metabolism disorders as well as

the treatment of glaucoma. The invention also relates to pharmaceutical compositions containing the compounds of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to processes for preparation of such new compounds, to novel intermediates in the preparation of the compounds of the invention, and to the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

It is a specific primary object of the invention to provide compounds with a high level of bioavailability. The compounds of the invention will also exhibit high stability properties at neutral pH and a good potency in regard to inhibition of gastric acid secretion. In addition the compounds of the invention will not block the uptake of iodine into the thyroid gland. It has earlier been disclosed in several lectures from the company, where the inventors are working that thyroid toxicity depends on if the compounds are lipophilic or not. The inventors have now unexpectedly found that it is not the lipophilicity that is the critical parameter. The claimed compounds, which include rather hydrophilic compounds, do not give any thyroid toxic effect and have at the same time high acid secretion inhibitory effect, good bioavailability and stability.

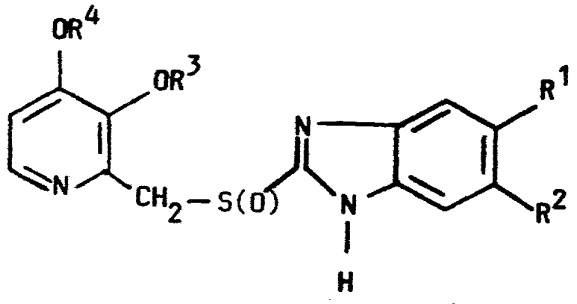
Prior art and background of the invention

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents. Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, EP 124 495, BE 898 880, EP 208 452 and Derwent abstract 87-294449/42. Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory diseases are disclosed in US 4 359 465.

The invention

It has been found that the compounds of the following formula I show high bioavailability. The compounds of the formula I also are effective as inhibitors of gastric acid secretion in mammals and man and do not block the uptake of iodine into the thyroid gland. The compounds of the invention exhibit a high chemical stability in solution at neutral pH.

The compounds of the invention are of the following formula I:



I

and physiologically acceptable salts thereof

wherein R^1 and R^2, which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^5$; wherein one of R^1 or R^2 is always selected from the group $-C(O)-R^5$; and wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms;

R^3 and R^4 are the same or different and selected from $-CH_3$, $-C_2H_5$, $-CH_2$-cyclopropyl, $-CH_2$-(1,3-dioxolan-2-yl) and $-CH_2CH_2OCH_3$ or R^3 and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring, wherein the part constituted by R^3 and R^4 is $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

It should be understood that the expressions "alkyl" and "alkoxy" include straight and branched structures.

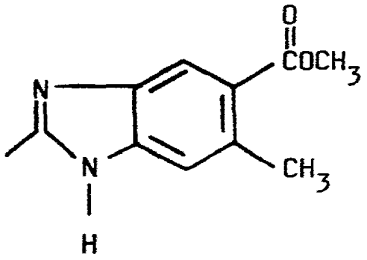
The compounds of the invention of the formula I have an asymmetric centre in the sulfur atom, i.e. exist as two optical isomers (enantiomers), or if they also contain one or more asymmetric carbon atoms the compounds have two or more diastereomeric forms, each existing in two enantiomeric forms.

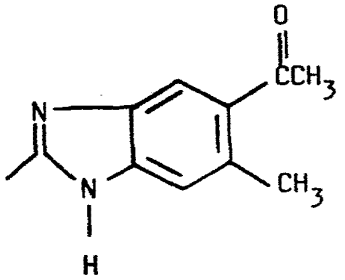
Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. It should be understood that all the diasteromeric forms possible (pure enantiomers or racemic mixtures) are within the scope of the invention.

Preferred groups of compounds of the formula I are:

1. Compounds, wherein R^1 and R^2 are selected from H methyl or $-C(O)R^5$, wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.

2. Especially preferred benzimidazole structures are

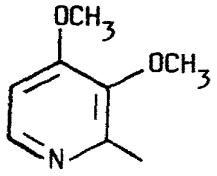
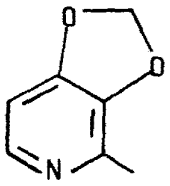
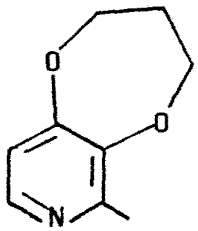




3. Compounds wherein R^3 and R^4 are CH_3.

4. Compounds wherein R^3 and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring wherein the part constituted by R^3 and R^4 is $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

5. Especially preferred pyridine structures are

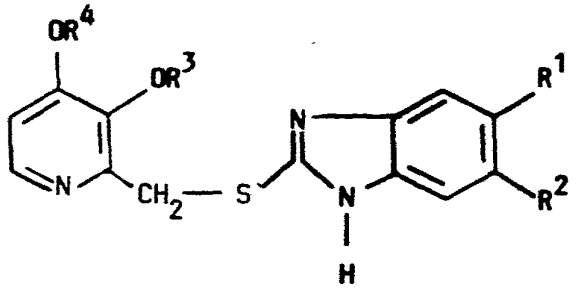
6. Further especially preferred specific compounds of the invention are as listed in the following tabulation.

R^1	R^2	R^3	R^4
$C(O)OCH_3$	CH_3	CH_3	CH_3
$C(O)CH_3$	CH_3	CH_3	CH_3
$C(O)OCH_3$	CH_3	$-CH_2-$	
$C(O)CH_3$	CH_3	$-CH_2CH_2CH_2-$	

Preparation

The compounds of the invention may be prepared according to the following method:

Oxidizing a compound of the formula II



II

wherein R^1, R^2, R^3 and R^4 are as defined under formula I. This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers, ketones.

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbiotically by using a suitable microorganism.

Depending on the process conditions and the starting materials, the compounds of the invention are obtained either in neutral or salt form. Both the neutral compounds and the salts of these are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates.

Alkaline salts of the compounds, of the invention are exemplified by their salts with Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, and $N^+(R)_4$, where R is (1-4 C)alkyl. Particularly preferred are the Na^+, Ca^{2+} and Mg^{2+} salts. Especially preferred are the Na^+ and Mg^{2+} salts. Such salts may be prepared by

reacting a compound with a base capable of releasing the desired cation.

Examples of bases capable of releasing such cations, and examples of reaction conditions are given below.

a) Salts wherein the cation is Li^+, Na^+ or K^+ are prepared by treating a compound of the invention with LiOH, NaOH or KOH in an aqueous or nonaqueous medium or with LiOR, $LiNH_2$, $LiNR_2$, NaOR, $NaNH_2$, $NaNR_2$, KOR, KNH_2 or KNR_2, wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous medium.

b) Salts wherein the cation is Mg^{2+} or Ca^{2+}, are prepared by treating a compound of the invention with $Mg(OR)_2$, $Ca(OR)_2$ or CaH_2; wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran.

Racemates obtained can be separated into the pure enantiomers. This may be done according to known methods, e.g. from racemic diastereomeric salts by means of chromatography or fractional crystallization.

The starting materials described in the intermediate examples may be obtained according to processes known per se.

For clinical use a compound of the invention is formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administration. The pharmaceutical formulation contains a compound of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the

invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration a compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of

an active compound. Hard gelatine capsules may also contain an active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain an active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains an active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or

vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1

Preparation of 5-carbomethoxy-6-methyl-2-[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

5-Carbomethoxy-6-methyl-2-[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]]-1H-benzimidazole (0.42 g, 1.0 mmol) was dissolved in methylene chloride (30 ml). $NaHCO_3$ (0.17 g, 2.0 mmol) dissolved in water (5 ml) was added and the mixture was cooled to +2°C m-chloroperbenzoic acid, 71% (0.19, 0.80 mmol) dissolved in methylene chloride (5 ml) was added dropwise with stirring. Stirring was continued at +2° for 15 min. After separation the organic layer was washed with water, dried with Na_2SO_4 and evaporated. To the oily residue acetonitrile (1 ml) was added and after cooling the desired product was filtered off as white crystals (0.15 g, 44%).

NMR data are given below.

Example 2

Preparation of 5-acetyl-6-methyl-2-[[(3,4-ethylendioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

5-Acetyl-6-methyl-2-[[(3,4-ethylendioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (0.17 g, 0.49 mmol) was dissolved in methylene chloride (5 ml). $NaHCO_3$ (0.082 g, 0.97 mmol) dissolved in water (2 ml) was added and the mixture was cooled to +2°C. m-Chloroperbenzoic acid, 69,5% (0.11 g, 0.44 mmol) dissolved in methylene chloride (2 ml) was added dropwise with stirring.

Stirring was continued at +2°C for 15 min. After separation the organic layer was extracted with an aqueous 0.20 M NaOH solution (3x2.5 ml, 1.5 mmol). Methyl formate (0.093 ml, 1.5 mmol) was added to the combined aqueous solutions and after 15 minutes the solution was extracted with methylene chloride. The organic solution was dried over Na_2SO_4 and evaporated leaving a white crystalline product which was washed with ether. In this way the desired compound was obtained (0.050 g, 30%).

NMR data are given below.

Example 3

Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (1.03 g, 0.00276 mol) was dissolved in CH_2Cl_2 (30 ml). $NaHCO_3$ (0.46 g, 0.0055 mol) in H_2O (10 ml) was added and the mixture was cooled to +2°C. m-chloroperbenzoic acid 69.5% (0.62 g, 0.0025 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at +2°C for 15 min. After separation the organic layer was extracted with an aqueous 0.2 M NaOH solution (3x15 ml, 0.009 mol). After

separation the aqueous solutions were combined and neutralized with methyl formate (0.56 ml, 0.009 mol) in the presence of CH_2Cl_2 (25 ml). After separation the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (10 ml) giving the title compound (0.68 g, 70 %).

NMR data are given below.

Example 4

Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.75 g, 10 mmol) was dissolved in CH_2Cl_2 (70 ml). $NaHCO_3$ (1.76 g, 21 mmol) in H_2O (25 ml) was added and the mixture was cooled to ≈+3°C. m-Chloroperbenzoic acid 69.5% (2.43 g, 9.8 mmol) dissolved in CH_2Cl_2 (20 ml) was added dropwise under stirring. Stirring was continued for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN giving the title compound (2.25 g, 60%).

NMR data are given below.

Example 5

Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (95.2% pure) (1.4 g, 0.0036 mol) was dissolved in CH_2Cl_2 (30 ml). $NaHCO_3$ (0.6 g, 0.0072 mol in H_2O (10 ml) was added and the mixture was cooled to +2°C. m-Chloroperbenzoic acid 69.5 % (0.87 g, 0.0035 mol)

dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at +2°C for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (15 ml) giving the title compound (0.76 g, 54 %).

NMR data are given below.

Example 6

Preparation of 5-acetyl-6-methyl-2-[[(3,4-propylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

The compound was prepared from 5-acetyl-6-methyl-2-[[(3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole and m-chloroperbenzoic acid on a 0.01 mmol scale according to standard procedures.

NMR data are given below.

Example 7

5-Acetyl-6-methyl-2-[[(3,4-methylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

5-Acetyl-6-methyl-2-[[(3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (140 mg, 0,41 mmol) was dissolved in methylene chloride (20 ml) and sodium hydrogen carbonate (5 ml,1M). The mixture was stirred at ambient temperature and MCPBA (100 mg, 0.41 mmol, 70%) dissolved in methylene chloride (10 ml) was added portionwise. After 10 min sodium thiosulphate (100 mg) was added whereupon the phases were separated. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was chromatographed on

silica (CH_2Cl_2/MeOH/NH_3, 97.5:2.5:sat.) Yield: 90 mg (61%) of the title compound. Mp: 178-180°C (dec., uncorr.).

NMR data are given below.

Example 8

Preparation of 5-acetyl-6-methyl-2-[[(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

A stirred mixture of 5-acetyl-6-methyl-2-[[(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]thio]-1H-benzimidazole (87 mg, 0.19 mmol) in 20 ml CH_2Cl_2 and $NaHCO_3$ (32 mg, 0.38 mmol) in 5 ml H_2O was cooled to 0°C and treated with 3-chloro-perbenzoic acid (47 mg 70%, 0.19 mmol). After reacting for 10 min the layers were separated (the aqueous layer was washed once more with 5 ml CH_2Cl_2) and the organic layer extracted with 10 ml H_2O containing NaOH (15 mg, 38 mmol). The alkaline aqueous layer was collected and treated with several portions of methyl formate (each 23 µl, 38 mmol) until the solution turned opaque. The aqueous layer was extracted with 25 + 10 ml CH_2Cl_2. The two latter organic layers were combined, dried over $MgSO_4$ and evaporated. The residue was chromatographed (SiO_2, CH_2Cl_2/MeOH saturated with $NH_{3(g)}$, 93/7) yielding 40 mg (44%) pure solfoxide.

NMR data are given below.

Example 9

Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, sodium salt

5-Acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (0.50 g, 1.3 mmol) dissolved in dichloromethane and sodium hydroxide (51

mg, 1.3 mmol) dissolved in water (6 ml) were transferred to a seporatory funnel. The mixture was shaken to equilibrium whereupon the solvent phases were separated. The aqueous solution was washed with dichloromethane and then freeze dried.

NMR data are given below.

Example 10

Preparation of 5-acetyl-6-methyl-2-[[(4cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Acetyl-6-methyl-2-[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (40 mg, 0.10 mmol) was dissolved in methylene chloride (10 ml) and sodium hydrogen carbonate (3 ml,1M). The mixture was stirred at ambient temperature and MCPBA (25 mg, 0.10 mmol, 70 %) dissolved in methylene chloride (5 ml) was added portionwise. After 10 min sodium thiosulphate (30 mg) was added whereupon the phases were separated. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (CH_2Cl_2/MeOH/NH_3, 97.5:2.5:sat.) Yield 30 mg (73 %) of the title compound.

Table 1

Ex	Solvent	NMR data δ ppm
1	$CDCl_3$ (300 MHz)	0.30-0.35 (m, 2H), 0.60-067 (m, 2H), 1.2-1.3 (m, 1H) 2.67 (s, 3H), 3.83 (d, 2H), 3.86 (s, 3H), 3.90 (s, 3H), 4.72 (d, 1H), 4.86 (d, 1H), 6.71 (d, 1H), 7.35 (b, 1H), 8.09 (d, 1H), 8.24 (b, 1H),

2	$CDCl_3$ (500 MHz)	2.65 (s, 3H), 2.66 (s, 3H), 3.9-4.2 (m, 4H), 4.70 (d, 1H), 4.82 (d, 1H), 6.75 (d, 1H), 7.3 (b, 1H), 7.92 (d, 1H), 8.2 (b, 1H),
3	$CDCl_3$ (500 MHz)	2.70 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.8 (d, 1H), 7.30 (b, 1H), 8.20 (d, 1H), 8.35 (b, 1H).
4	$CDCl_3$ (300 MHz)	2.60 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.80 (d, 1H), 7.30 (b, 1H), 8.15 (d, 1H), 8.20 (b, 1H)
5	$CDCl_3$ (300 MHz)	1.45 (t, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.40 (q, 2H), 4.65 (d, 1H), 4.40 (d, 1H), 6.80 (d, 1H), 7.50 7.80 (b, 1H) 8.05 (d, 1H), 8.20 (d, 1H), 8.25, 8.55 (b, 1H)
6	$CDCl_3$ (500 MHz)	2.16 (m, 2H), 2.64 (s, 3H), 2.66 (s, 3H), 4.23 (t, 2H), 4.30 (t, 2H), 4.68 (d, 1H), 4.88 (d, 1H), 6.83 (d, 1H), 7.3-7.5 (b, 1H), 8.01 (d, 1H), 8.1-8.2 (b, 1H).
7	$CDCl_3$ (300 MHz)	2.66 (s, 6H), 4.54 (d, 1H), 4.75 (d, 1H), 5.80 (s, 1H), 5.87 (s, 1H), 6.77 (d, 1H), 7.93 (br. 1H), 8.07 (d, 1H), 8.12 (br. 1H)

8	$CDCl_3$ (300 MHz)	0.91 (s, 3H), 2.63 (s, 3H), 2.64 (s, 3H), 3.49 (d, 2H), 3.84 (s, 3H), 3.94 (d, 2H), 4.15 (m, 2H), 4.66 (d, 1H), 4.73 (d, 1H), 4.86 (d, 1H), 5.02 (d, 1H), 6.89 (d, 1H), 7.33 (s, 1H), 8.08 (s, 1H), 8.14 (d, 1H)
9	D_2O (protons in water were set to 4.82 ppm) (300 MHz)	2.66 (s, 3H), 2.81 (s, 3H), 3.81 (s, 3H), 4.02 (s, 3H), 4.73 (d, 1H), 4.91 (d, 1H), 7.16 (d, 1H), 7.62 (s, 1H), 8.23 (d, 1H), 8.30 (s, 1H)
10	$CDCl_3$ (300 MHz)	0.33 (m, 2H), 0.65 (m, 2H), 1.24 (m, 1H), 2.63 (s, 3H), 2.64 (s, 3H), 3.84 (d, 2H), 3.88 (s, 3H), 4.73 (d, 1H), 4.83 (d, 1H), 6.73 (d, 1H), 7,35 (s, 1H), 8.08 (s, 1H), 8.11 (d, 1H)

Example of intermediates

Example I 1

Preparation of 5-carbomethoxy-6-methyl-2-[[(4-cyclopropyl-methoxy-3-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole.

To a solution of 5-carbomethoxy-6-methyl-2-mercapto-1H-benzimidazole (0.58 g, 2.6 mmol) in methanol (25 ml) aqueous NaOH (1.0 ml 5M, 5.0 mmol) and 4-cyclopropylmethoxy-3-methoxy-2-chloromethyl pyridine hydrochloride (prepared according to processes known per se.) (0.63 g, 2.4 mmol) dissolved in methanol (25 ml were added in the given order. The mixture was refluxed for one hour whereupon the solution

was evaporated. The residue was partitioned between methylene chloride and water. After separation the organic solution was dried over Na_2SO_4 and evaporated giving a yellow syrup (1.0 g, 100%).

NMR data are given below.

Example I 2

5-Acetyl-6-methyl-2-[[(3,4-ethylendioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

To a solution of 5-acetyl-6-methyl-2-mercapto-1H-benzimidazole (0.14 g, 0.66 mmol) in methanol (2 ml) aqueous NaOH (0.25 ml 5M, 1.25 mmol) and 3,4-ethylendioxy-2-chloromethyl pyridine hydrochloride (0.13 g, 0.60 mmol) dissolved in methanol (2 ml) were added in the given order. The mixture was refluxed for one hour whereupon the solution was evaporated. The residue was partitioned between methylene chloride and water. After separation the organic solution was dried over Na_2SO_4 and evaporated giving a yellow syrup (0.17 g, 81%).

NMR data are given below.

Example I 3

Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Carbomethoxy-6-methyl-2-mercapto-1H-benzimidazole (0.67 g, 0.003 mol) and NaOH (0.12 g, 0.003 mol) in H_2O (0.6 ml) were dissolved in CH_3OH (15 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride, (≈0.0036 mol) as a crude material in CH_3OH (10 ml) and NaOH (0.144 g, 0.0036 mol) in H_2O (0.72 ml) were added. The mixture was heated to reflux

and the reflux was continued for 1 hour. CH_3OH was evaporated off and the crude material was purified by chromatography on a silica column using CH_2Cl_2-CH_3OH (98-2) as eluent, giving (1.03 g, 92%) of the pure title compound. NMR data are given below.

Example I 4

Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Acetyl-6-methyl-2-mercapto-1H-benzimidazole (4.2 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in H_2O (1 ml) were dissolved in 60 ml ethanol. 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (≈17 mmol) as a crude material was added and the mixture was heated to boiling. NaOH (0.7 g, 17 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Crystallizing from acetonitrile gave the title compound, (3.75 g, 62%).
NMR data are given below.

Example I 5

Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Carbethoxy-2-mercapto-1H-benzimidazole (2.0 g, 9 mmol) and NaOH (0.36 g, 9 mmol) in H_2O (1 ml) were dissolved in ethanol (30 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (≈6.6 mmol) as a crude material were added and the mixture was heated to boiling. NaOH (0.26 g, 6.6 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase

was dried over Na_2SO_4 and the solvent removed under reduced pressure. Crystallizing from CH_3CN gave the desired product (1.75 g, 71%).
NMR data are given below.

Example I 6

Preparation of 5-acetyl-6-methyl-2-[[(3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

The compound was prepared from 5-acetyl-2-mercapto-6-methyl-1H-benzimidazole and 2-chloromethyl-3,4-propylenedixoxy-pyridine on a 0.01 mmol scale according to standard procudures.
NMR data are given below.

Example I 7

Preparation of 5-acetyl-6-methyl-2-[[(3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

2-Chloromethyl-3,4-methylenedioxypyridine (90 mg, 0.52 mmol) and 5-acetyl-6-methyl-2-mercaptobenzimidazole (214 mg, 1.04 mmol) were dissolved in ethanol (15 ml). The pH value of the solution was adjusted to 9 (0.2M NaOH) whereupon the solution was refluxed for 10 min. After concentration of the reaction mixture at reduced pressure the residue was taken up in methylene chloride (10 ml) and brine (2 ml). The phases were separated and the organic phase was dried over sodium sulphate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica (ethyl acetate). Yield: 140 mg (79%) of the title compound. Mp: 141-143°C (uncorr.)
NMR data are given below.

Example I 8

Preparation of 5-acetyl-6-methyl-2-[[(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]-thio]-1H-benzimidazole

A solution of 2-(hydroxymethyl)-3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine (0.34 g, 1.3 mmol) in 10 ml CH_2Cl_2 was cooled to 0°C and treated with $SOCl_2$ (0.12 ml, 1.7 mmol). The solution was allowed to warm to room temperature and reacted for 1 h. Evaporation of the solvent furnished a quantitative yield of the corresponding chloromethyl derivative as the hydrochloride. DI-MS, m/z (%): 289 and 287 (11 and 38). A suspension of 5-acetyl-2-mercapto-6-methyl-1H-benzimidazole (0.29 g, 1.4 mmol) in 10 ml MeOH was treated with a solution of NaOH (0.10 g, 2.6 mmol) in 1.5 ml H_2O. The formed solution was treated with the prepared chloromethyl compound and reacted for 21 h at room temperature. The solvent was evaporated and the residue taken up in 20 ml 2.5% NaOH. The aqueous layer was extracted with 50 + 25 ml CH_2Cl_2, the organic layers combined, dried over $MgSO_4$, and evaporated leaving 0.49 g (82%) title compound as a tanned foam.
NMR data are given below.

Example I 9

Preparation of 5-acetyl-6-methyl-2-[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

2-Chloromethyl-4-cyclopropylmethoxy-3-methoxypyridine (50 mg, 0.22 mmol) and 5-acetyl-6-methyl-2-mercaptobenzimidazole (50 mg, 0.24 mmol) were dissolved in ethanol (15 ml). The pH value of the solution was adjusted to 9 (0.2M NaOH) whereupon the solution was refluxed for 10 min. After concentration of the reaction mixture at reduced pressure the residue was taken up in methylene chloride (10 ml) and

brine (2 ml). The phases were separated and the organic phase was dried over sodium sulphate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica (ethyl acetate). Yield: 40 mg (46%) of the title compound.
NMR data are given below.

Example I 10

Preparation of 4-chloro-3-hydroxyethoxy-2-methylpyridine

A solution of 4-chloro-3-methoxyethoxy-2-methylpyridine (2.78 g, 0.014 mol) in dry $CDCl_3$ (≈14 ml) under Ar was treated with TMSI (5.10 ml, 0.036 mol) for 23 h at room temperature. The reaction mixture was partitioned between 100 ml CH_2Cl_2 and 100 ml 1M HCl. The aqueous layer was collected, washed once more with 50 ml CH_2Cl_2, and then treated with Na_2CO_3 until the pH was ≈10. The aqueous layer was extracted with 100 + 50 ml CH_2Cl_2. The two latter organic layers were combined, dried over $MgSO_4$ and evaporated leaving 2.31 g enriched product.

Chromatography (silica gel, diethyl ether followed by diethyl ether/MeOH;95/5) afforded 1.06 g (40%) pure product.
NMR data are given below.

Example I 11

Preparation of 3,4-ethylenedioxy-2-methylpyridine

A mixture of 4-chloro-3-hydroxyethoxy-2-methylpyridine (1.03g, 0.0055 mol) and NaH (55% in oil, 599 mg, 0.0138 mol) in 600 ml THF was refluxed for 15 h. Excess NaH was destroyed with 3 ml of H_2O. The solvent was evaporated and the residue partitioned between 100 ml 1M HCl and 100 ml CH_2Cl_2. The aqueous layer was collected, washed once more with 100 ml CH_2Cl_2 and then treated with Na_2CO_3 until the pH

was ≈10. The aqueous layer was extracted with 150 + 100 ml CH_2Cl_2. The two latter organic layers were combined, dried over $MgSO_4$, and evaporated leaving 720 mg enriched product. Chromatography (silica gel, diethyl ether) furnished 0.49 g (59%) pure product.
NMR data are given below.

Example I 12

Preparation of 3,4-ethylenedioxy-2-hydroxymethyl-pyridine

The title compound was prepared on a 3.2 mmol scale according to standard procedures yielding 395 mg (77%) pure product.

NMR data for the intermediate are given below.

Example I 13

Preparation of 3-(3-hydroxy-1-propoxy)-2-methyl-4-pyrone

A suspension of 3-hydroxy-2-methyl-4-pyrone (25 g, 200 mmol), 3-bromo-1-propanol (70 g, 500 mmol) and K_2CO_3 (111 g 800 mmol) in 600 ml acetone was stirred for three days. The solvent was evaporated and the residue partitioned between 300 ml methylene chloride and 500 ml 2.5% NaOH. The aqueous layer was separated and extracted with 2x300 ml methylene chloride. The organic phases were combined, dried over Na_2SO_4 and evaporated at 50°C. Eight grams of the residue (24 g) was chromatographed on silica gel with methanol/methylene chloride (5:95) as eluent which afforded 2.7 g (22%) of the desired product as an oil.
NMR data are given below.

Example I 14

Preparation of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyrone

A mixture of 3-(3-hydroxy-1-propoxy)-2-methyl-4-pyrone (1.4 g, 7.6 mmol), 85% KOH (0.55 g, 8.4 mmol) and methyliodide (11 g, 76 mmol) was stirred at room temperature for one day. The red solution was partitioned between methylene chloride and half saturated aqueous ammoniumchloride solution. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel with methanol/methylene chloride (3:97) as eluent. Removing the eluent by film evaporation afforded 0.31 g (20%) of the desired product as an oil.
NMR data are given below.

Example I 15

Preparation of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyridone

A solution of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyrone (0.31 g, 1.7 mmol) in 50 ml concentrated aqueous NH_3 was heated to 120°C for 2 h in an autoclave. The reaction mixture was transferred to a round bottomed flask and evaporation off the solvent afforded 0.32 g (100%) product as a yellow oil.
NMR data are given below.

Example I 16

Preparation of 4-chloro-3-(3-methoxy-1-propoxy)-2-methyl-pyridine

A solution of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyridone (0.32 g, 1.6 mmol) in 50 ml $POCl_3$ was refluxed for 14 h. The $POCl_3$ was evaporated off and the residue was partitioned between methylene chloride and water. The aqueous layer was separated, treated with K_2CO_3 until pH=10 and extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by chromatography

on silica gel with methanol/methylene chloride (3:97) as eluent. Evaporation off the solvent afforded 0.12 g (34%) product as a red oil.
NMR data are given below.

Example I 17

Preparation of 4-chloro-3-(3-hydroxy-1-propoxy)-2-methyl-pyridine

To a solution of 4-chloro-3-(3-methoxy-1-propoxy)-2-methyl-pyridine (120 mg, 0.56 mmol) in 2 ml of $CDCl_3$ was added trimethylsilyl iodide (0.16 ml, 1.3 mmol), this was done in a NMR tube. The reaction was complete after four days as indicated by the absence of a signal for the OCH_3 protons at 3.3 ppm in the NMR spectrum. The solution was poured over 10 ml of 1 M HCl whereupon the mixture was stirred for 5 minutes with 10 ml of methylene chloride. The aqueous layer was separated, treated with K_2CO_3 until pH=10 and extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and evaporated. This afforded 0.049 g (43%) of the desired product as a yellow oily film.
NMR data are given below.

Example I 18

Preparation of 2-methyl-3,4-propylenedioxy-pyridine

A solution of 4-chloro-3-(3-hydroxy-1-propoxy)-2-methyl-pyridine (49 mg, 0.24 mmol) in 3 ml of DMSO was heated for 2 h at 70°C with 55% NaH (32 mg, 0.73 mmol). The mixture was cooled, diluted with water and extracted with methylene chloride. The organic solution was evaporated and the residue was chromatographed on silica gel with methylene chloride as eluent. The solvent was evaporated which afforded 22 mg (55%) of a yellow oil.
NMR data are given below.

Example I 19

Preparation of 2-hydroxymethyl-3,4-propylene-dioxypyridine

The title compound was prepared from 2-methyl-3,4-propylenedioxypyridine on a 0.01 mmol scale according to standard procedures yielding 3 mg (11%) product. NMR data are given below.

Example I 20

Preparation of 2-chloromethyl-3,4-propylene-dioxypyridine

The title compound was prepared from 2-hydroxymethyl-3,4-propylenedioxypyridine in a quantitative yield on a 0.01 mmol scale according to standard procedures. The compound was used in the synthesis without purification and characterisation.

Example I 21

Preparation of 2-methyl-3,4-methylenedioxypyridine

2-Methyl-3-hydroxy-4-pyridone (1.25 g, 10 mmol) was dissolved in dry DMSO (20 ml). Dibromomethane (3.5 g, 20 mmol) was added followed by sodium hydride (1 g, >20 mmol, 50-60% in oil). The mixture was left at ambient temperature under stirring for 3 days whereupon it was poured into brine (50 ml). The water-DMSO solution was extracted with methylene chloride (3x50 ml) and the collected extracts were used directly in the next step. A sample for NMR analysis was withdrawn.

NMR data are given below.

Example I 22

Preparation of 2-methyl-3,4-methylenedioxypyridine-N-oxide

To the methylene chloride solution of 2-methyl-3,4-methylenedioxypyridine from example I 21 sodium hydrogen carbonate (1M, 50 ml) and MCPBA (4 g, 70%) were added. The mixture was stirred at ambient temperature for 15 min whereupon the excess of MCPBA was destroyed with addition of sodium thiosulphate (1 g). The organic phase was separated and the aqueous phase was extracted with methylene chloride (3x50 ml). The collected organic phases were concentrated under reduced pressure and chromatographed on silica (CH_2Cl_2/MeOH, 90:10). Yield: 120 mg (7,8%) of the title compound.
NMR data are given below.

Example I 23

Preparation of 2-hydroxymethyl-3,4-methylenedioxypyridine

2-Methyl-3,4-methylenedioxypyridine-N-oxide (120 mg, 0.78 mmol) was dissolved in acetic anhydride (10 ml) and the solution was heated at 110 °C for 15 min, whereupon the mixture was concentrated under reduced pressure. The residue was dissolved in methanol (20 ml) and sodium hydroxide (3 drops, 6M) was added. After 30 min at ambient temperature the mixture was neutralised with acetic acid (pH 6) and concentrated under reduced pressure. The residue was chromatographed on silica (hexane/ethyl acetate, 1:1). Yield: 90 mg (75%) of the title compound.

NMR data are given below.

Example I 24

Preparation of 2-chloromethyl-3,4-methylenedioxypyridine

2-Hydroxymethyl-3,4-methylenedioxypyridine (90 mg, 0.59 mmol) was dissolved in methylene chloride (10 ml) and thionyl chloride (240 mg, 2 mmol) was added. After 10 min at ambient temperature the mixture was hydrolysed with sodium hydrogen carbonate and the phases were separated. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. Yield: 90 mg (88%) of the title compound (crude).

NMR data are given below.

Example I 25

Preparation of 3-methoxy-2-methyl-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine-N-oxide

A deareated solution of 5-(hydroxymethyl)-5-methyl-1,3-dioxane (1.19 g, 9 mmol) in 125 ml dry THF was treated with NaH (0.79 g 55% dispersion in oil, 18 mmol) for 20 min. 4-Chloro-3-methoxy-2-methylpyridine-N-oxide (1.04 g, 6 mmol) was added and the mixture was refluxed for 26 h. Excess NaH was quenched with 10 ml of H_2O and the solvent evaporated. The residue was partitioned between 150 ml CH_2Cl_2 and 50 ml 5% Na_2CO_3. The organic layer was passed through a phase separation paper and evaporated leaving 1.83 g enriched product. Chromatography ($SiO_2CH_2Cl_2$/MeOH, 95/5) afforded 0.39 g (24%) pure title compound as a tanned oil.

NMR data are given below.

Example I 26

Preparation of 2-(hydroxymethyl)-3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine

A solution of 3-methoxy-2-methyl-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine-N-oxide (0.39 g, 1.5 mmol) in 4.5 ml $(CH_3CO)_2O$ was heated to 100°C for 4 h. Excess $(CH_3CO)_2O$ was azeotroped off 4 times with 75 ml portions of abs. EtOH leaving 0.42 g (90%) crude 3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)-methyl acetate.

The crude acetate was treated with 20 ml 2M NaOH for 1 h at 100 °C. The aqueous layer was extracted with 75 + 50 + 25 ml CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and evaporated leaving 0.34 g (97%) product pure enough for further use.

NMR data are given below.

Table 2

Ex	Solvent	NMR data δ ppm
I 1	$CDCl_3$ (300 MHz)	0.37-0.42 (m, 2H), 0.67-0.73 (m, 2H), 1.25-1.40 (m, 1H) 2.69 (s, 3H), 3.90 (s, 3H), 3.94 (d, 2H), 3.98 (s, 3H), 4.40 (s, 2H) 6.81 (d, 1H), 7.3 (b, 1H), 8.2 (b, 1H), 8.22 (d, 1H),
I 2	$CDCl_3$ (500 MHz)	2.64 (s, 3H), 2.66 (s, 3H), 4.35 (s, 2H), 4.40 (s, 4H), 6.85 (d, 1H), 7.30 (s, 1H), 8.06 (d, 1H), 8.08 (s, 1H).
I 3	$CDCl_3$ (300 MHz)	2.70 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 4.40 (s, 2H), 6.90 (d, 1H), 7.35 (s, 1H), 8.20 (s, 1H), 8.25 (d, 1H)

I 4	$CDCl_3$ (300 MHz)	2.60 (s, 3H), 2.65 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.35 (s, 2H), 6.85 (d, 1H), 7.25 (s, 0.6H), 7.40 (s, 0.4H), 7.85 (s, 0.4H), 8.05 (s, 0.6H), 8.30 (m, 1H)
I 5	$CDCl_3$ (300 MHz)	1.40 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.40 (m, 4H), 6.90 (dd, 1H), 7.45 (d, 0.4H), 7.60 (d, 0.6H), 7.90 (m, 1H), 8.20 (s, 0.6H), 8.25 (m, 1H), 8.25 (s, 0.4H)
I 6	$CDCl_3$ (500 MHz)	2.32 (p, 2H), 2.64 (s, 3H), 2.66 (s, 3H), 4.37-4.43 (m, 4H), 4.39 (s, 2H), 6.88-6.90 (m, 1H), 7.29 (s, 0.6H), 7.42 (s, 0.4H), 7.85 (s, 0.4H), 8.07 (s, 0.6H), 8.11 (m, 1H)
I 7	$CDCl_3$ (300 MHz)	2.648 (s, 3H), 2.652 (s, 3H), 4.32 (s, 2H), 6.14 (s. 2H), 6.85 (d, 1H), 7.34 (br. 1H), 8.00 (br. 1H), 8.20 (d, 1H)
I 8	$CDCl_3$ (300 MHz)	0.98 (s, 3H), 2.65 (coinciding s, 6H), 3.53 (d, 2H), 3.95 (s, 3H), 4.00 (d, 2H), 4.25 (s, 2H), 4.39 (s, 2H), 4.69 (m, 1H), 5.06 (m, 1H), 6.9-7.0 (2 d, 1H), 7.3-7.5 (several b, 1H), 7.8-8.1 (several b, 1H), 8.2-8.3 (2 d, 1H), 13.2 (b. 1H)
I 9	$CDCl_3$ (300 MHz)	0.38 (m, 2H), 0.69 (m, 2H), 1.31 (m,1H), 2.63 (s, 3H), 2.636 (s, 3H), 3.93 (d, 2H), 3.98 (s, 3H),

		4.40 (s, 2H), 6.81 (d, 1H), 7.33 (s, 1H), 7.98 (s, 1H), 8.22 (d, 1H)
I 10	$CDCl_3$ (500 MHz)	2.57 (s, 3H), 2.70 (t, 1H) 3.99 (dt, 2H), 4.09 (t, 2H), 7.19 (d, 1H), 8.16 (d, 1H)
I 11	$CDCl_3$ (500 MHz)	2.41 (s, 3H), 4.30 (s, 4H), 6.65 (d, 1H), 7.90 (d, 1H),
I 12	$CDCl_3$ (500 MHz)	4.11 (b, 1H), 4.33 (m, 4H), 4.69 (b, 2H), 6.76 (d, 1H), 7.99 (d, 1H)
I 13	$CDCl_3$ (300 MHz)	1.85 (p, 2H), 2.30 (s, 3H), 3.85 (q, 2H), 4.00 (t, 2H), 4.35 (t, 1H), 6.35 (d, 1H), 7.65 (d, 1H)
I 14	$CDCl_3$ (300 MHz)	2.00 (p, 2H), 2.32 (s, 3H), 3.35 (s, 3H), 3.56 (t, 2H), 4.13 (t, 2H), 6.33 (d, 1H), 7.59 (d, 1H)
I 15	$CDCl_3$ (300 MHz)	1.98 (p, 2H), 2.45 (s, 3H), 3.38 (s, 3H), 3.61 (t, 2H), 4.08 (t, 2H), 6.53 (d, 1H), 7.63 (d, 1H)
I 16	$CDCl_3$ (300 MHz)	2.09 (p, 2H), 2.54 (s, 3H), 3.38 (s, 3H), 3.63 (t, 2H), 4.04 (t, 2H), 7.16 (d, 1H), 8.13 (d, 1H)
I 17	$CDCl_3$ (500 MHz)	2.10 (p, 2H), 2.56 (s, 3H), 3.96 (t, 2H), 4.10 (t, 2H), 7.18 (d, 1H), 8.15 (d, 1H)
I 18	$CDCl_3$ (300 MHz)	2.25 (p, 2H), 2.45 (s, 3H), 4.28 (t, 2H), 4.34 (t, 2H), 6.70 (d, 1H), 7.96 (d, 1H)

I 19	$CDCl_3$ (500 MHz)	2.27 (p, 2H), 4.30 (t, 2H), 4.37 (t, 2H), 4.71 (d, 2H), 6.80 (d, 2H), 8.05 (d, 1H)
I 21	$CDCl_3$ (500 MHZ)	2.34 (s, 3H), 5.92 (s, 2H), 6.61 (d, 1H), 7.93 (d, 1H)
I 22	$CDCl_3$ (500 MHz)	2.42 (s, 3H), 6.12 (s, 2H), 6.59 (d, 1H), 7.90 (d, 1H)
I 23	$CDCl_3$ (300 MHz)	4.73 (s, 2H), 6.05 (s, 2H), 6.76 (d, 1H), 8.09 (d, 1H)
I 24	$CDCl_3$ (300 MHz)	4.65 (s, 2H), 6.10 (s, 2H), 6.78 (d, 1H), 8.13 (d, 1H)
I 25	$CDCl_3$ (300 MHz)	0.97 (s, 3H), 2.50 (s, 3H), 3.52 (d, 2H), 3.85 (s, 3H), 3.98 (d, 2H), 4.18 (s, 2H), 4.67 (d, 1H), 5.02 (d, 1H), 6.77 (d, 1H), 8.08 (d, 1H)
I 26	$CDCl_3$ (300 MHz)	0.98 (s, 3H), 3.52 (d, 2H), 3.86 (s, 3H), 4.00 (d, 2H), 4.09 (m, 1H), 4.20 (s, 2H), 4.68 (d, 1H), 4.75 (d, 2H), 5.02 (d, 1H), 6.88 (d, 1H), 8.20 (d, 1H)

The best mode of carrying out the invention known at present is to use the compound according to Example 4 or its salt according to Example 9.

Table 3

Examples of compounds included in the formula I are given in the following table

Ex.	R^1	R^2	R^3	R^4	Yield%	Ident.data
1	$C(O)-OCH_3$	CH_3	CH_3	CH_2	44	NMR
2	$C(O)CH_3$	CH_3	$-CH_2CH_2-$		30	NMR
3.	$C(O)-OCH_3$	CH_3	CH_3	CH_3	70	NMR
4.	$C(O)CH_3$	CH_3	CH_3	CH_3	60	NMR
5.	$C(O)OCH_2CH_3$	H	CH_3	CH_3	54	NMR
6.	$C(O)CH_3$	CH_3	$-CH_2CH_2CH_2-$			NMR
7.	$C(O)CH_3$	CH_3	$-CH_2-$		61	NMR
8.	$C(O)CH_3$	CH_3	CH_3	CH_2	44	NMR
9.	$C(O)CH_3$	CH_3	CH_3	CH_3	sodium salt	NMR
10.	$C(O)CH_3$	CH_3	CH_3	CH_2	73	NMR

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 4	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	15.0 g
Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 4 as Mg salt	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate15 g Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to example 1, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota®, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 9	4 g
Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to Example 4	300 g
Lactose	700 g
Microcrystalline cellulose	40 g

Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 4	4 g
Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat

sealed. Each suppository contained 40 mg of active compound.

Biological Effects

Bioavailability

Biovailability is assessed by calculating the quotient between the area under plasma concentration (AUC) curve following introduodenal (id) administration and intravenous (iv) administration from the rat.

Potency for inhibition of acid secretion

The potency for inhibition of acid secretion is measured in the dog, intravenously (iv) and in the female rat, intravenously (iv).

Effects on the uptake of iodine into the thyroid gland

The effect of a compound within the invention of the formula I on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of ^{125}I in the thyroid gland.

Biological tests

Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen) for collection of gastric secretions. A fourteen days recovery period after surgery is allowed before testing is commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through

the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion is stimulated with infusion during 3.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substances or vehicle are given iv at 90 min after starting the stimulation, in a volume of 1 ml/kg. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output is calculated as the product of titrant volume and concentration. Further calculations are based on group mean responses from 4-7 rats. The acid output during the periods after administration of test substances or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. ED_{50}-values are obtained from graphical interpolation on log dose-response curves, or estimated from single-dose experiments assuming a similar slope for all dose-response curves. The results are based on gastric acid secretion during the second hour after drug/vehicle administration.

Bioavailability in the Male Rat.

Male adult rats of the Sprague-Dawley strain were used. One day, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein. (Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substances. The same dose (4 µmol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until analysis of the test compound.

The area under the blood concentration vs time curve, AUC, was determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase.

The systemic bioavailability (F%) following intraduodenal administration was calculated as

$$F(\%) = \frac{AUC_{id}}{AUC_{iv}} \times 100$$

Inhibition of Gastric Acid Secretion in the Conscious Dog.

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a Heidenhain-pouch for the collection of gastric secretions.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or

vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED_{50}-values were obtained by graphical interpolation on log dose - response curves, or estimated from single-dose experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

Effect on the accumulation of ^{125}I in the thyroid gland

The accumulation of ^{125}I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24 hours before the test. The experimental protocol of Searle, CE et al. (Biochem J 1950, 47:77-81) was followed.

Test substances suspended in 0.5% buffered (pH 9) methocel, were administered by oral gavage in a volume of 5 ml/kg body weight. After 1 hour, ^{125}I (300 kBqkg, 3 ml/kg) was administered by intraperitoneal injection. Four hours after ^{125}I-administration, the animals were killed by CO_2-asphyxiation and bled. The thyroid gland together with a piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula 100 (1-T/P), where T and P is the mean radioactivety of thyroid glands from animals treated with test agent and placebo (buffered methocel), respectively. The statistical significane for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). $P<0.05$ was accepted as significant.

Chemical Stability

The chemical stability of a compound of the invention is followed kinetically at low cencentration at 37°C in aqueous buffer solution at different pH values. The results in Table 4 show the half life (t 1/2) at pH 7, that is the time period after which half the amount of the original compound remains unchanged.

Results of biological and stability tests

Table 4 gives a summary of the test data available for the compounds of the invention.

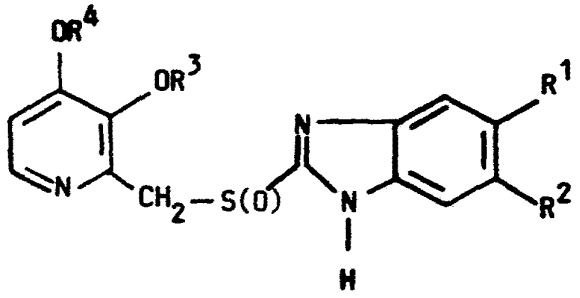
Table 4, Biological Test Data and Stability Data

Test compound Example No.	Inhibition of acid secretion iv administration ED_{50} µmol/kg		Bioavailability F%, Rat	Per cent inhibition of 400 µmol/kg on the uptake of ^{125}I in the thyroid gland	Chemical stability a pH 7 half-life (t 1/2) min
	Dog	Rat			
2		a)			
3	0.5			0	480
4	0.74	0.9	> 100	-7	470
5				-6	270

a) 1 µmol/kg gave 14% inhibition

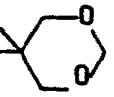
CLAIMS

1. **Compounds of the formula I**



and physiologically salts thereof wherein R^1 and R^2, which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^5$;

wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms and one of R^1, or R^2 is always selected from the group $-C(O)-R^5$;

R^3 and R^4 are the same or different and selected from $-CH_3$, C_2H_5, $-CH_2$-  , $-CH_2$-  and $-CH_2CH_2OCH_3$ or R^3 and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring, wherein the part constituted by R^3 and R^4 is $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

2. A compound according to formula I of claim 1, namely 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

3. A compound according to formula I of claim 1, namely 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

4. A compound according to formula I of claim 1, namely 5-

acetyl-6-methyl-2-[[(3,4-propylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

5. A compound according to formula I of claim 1, namely 5-acetyl-6-methyl-2-[[(3,4-methylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

6. The sodium salt of a compound according to claim 1.

7. The sodium salt of the compound according to claim 3.

8. The magnesium salt of a compound according to claim 1.

9. A pharmaceutical composition containing as active ingredient a compound according to claim 1.

10. A compound as defined in claim 1 for use in therapy.

11. A compound as defined in claim 1 for use in inhibiting gastric acid secretion in mammals including man.

12. A compound as defined in claim 1 for use in the treatment of gastrointestinal inflammatory diseases in mammals including man.

13. A method for inhibitning gastric acid secretion by administering to mammals including man a compound as defined in claim 1.

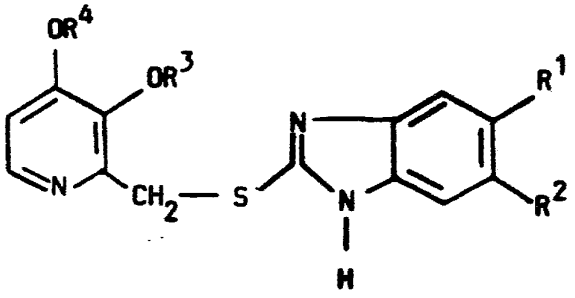
14. A method for the treatment of gastrointestinal inflammatory diseases in mammals including man by administering a compound as defined in claim 1.

15. Use of a compound according to claim 1 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals including man.

16. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases in mammals including man.

17. A process for the preparation of a compound of the formula I according to claim 1, by

a) oxidizing a compound of the formula II



II

wherein R^1, R^2, R^3 and R^4 are as defined under formula I.

18. The new intermediates 2-methyl-3,4-propylenedioxy-pyridine, 2-hydroxymethyl-3,4-propylene-dioxy-pyridine, 2-methyl-3,4-methylenedioxy-pyridine, 2-hydroxymethyl-3,4-methylene-dioxypyridine, 5-acetyl-6-methyl-2-[[(3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole and 5-acetyl-6-methyl-2-[[(3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole for use in the preparation of a compound of formula I according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00416

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 401/12, A 61 K 31/415, 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US, A, 4359465 (THE UPJOHN COMPANY) 16 November 1982, see the whole document --	1-12,15-17
A	US, A, 4255431 (AKTIEBOLAGET HÄSSLE) 10 March 1981, see the whole document --	1-12,15-17
A	EP, A, 0197013 (AKTIEBOLAGET HÄSSLE) 8 October 1986, see the whole document --	1-12,15-17
A	EP, A, 0208452 (TAKEDA CHEMICAL INDUSTRIES, LTD) 14 January 1987, see the whole document --	1-12,15-17

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* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11th September 1991	1991 -09- 19
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Göran Karlsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. [X] Claim numbers 13-14 because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 91/00416

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-07-31
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP-A-B- 0045200	82-02-03
		JP-B- 1060008	89-12-20
		JP-C- 1574094	90-08-20
		JP-A- 57053406	82-03-30
US-A- 4255431	81-03-10	AT-B- 374471	84-04-25
		AT-B- 374472	84-04-25
		AT-B- 374473	84-04-25
		AT-B- 375365	84-07-25
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EP-A- 0208452	87-01-14	JP-A- 62116576	87-05-28
		US-A- 4738975	88-04-19

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(74) Agent: BARON, Ronald, J.; Hoffmann & Baron, 350 Jericho Turnpike, Jericho, NY 11753 (US).

(81) Designated States: AU, BR, CA, CS, FI, HU, JP, KR, NO, PL, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

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(54) Title: ULCER PREVENTION AND TREATMENT COMPOSITION AND METHOD

(57) Abstract

Anti-ulcer compositions are disclosed having therapeutic agents dispersed in a soluble matrix formed by melt spinning the therapeutic agent with a carrier and hydrogel. Methods of treating ulcer-bearing tissue and preparing the matrix are also disclosed. One embodiment includes use of gastric irritating bio-affecting agents in which case the composition is preventative as well as therapeutic.

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ULCER PREVENTION AND TREATMENT COMPOSITION AND METHOD

BACKGROUND OF THE INVENTION

This is a Continuation-in-Part application of co-pending U.S. application Serial No. 808,599 which was filed on December 17, 1991.

The present invention relates to ulcer treatments. In particular, the present invention relates to the use of dosage forms containing anti-ulcer agents dispersed in a soluble matrix.

Sucralfate is a therapeutic compound useful for treatment of various gastrointestinal disorders. Sucralfate accelerates the healing of gastric and duodenal ulcers and also finds use as a symptomatic treatment for disturbances such as dyspepsia and reflux.

Sucralfate displays its action in the acid medium of the digestive tract where it lines ulcerated mucous membranes of the stomach and duodenum with a protective coating. The preferential binding affinity of sucralfate for ulcerated areas of mucous membrane results in increased protection and accelerated healing of ulcers as well as regeneration of the mucous membrane.

Although sucralfate is usually taken orally in the form of tablets, other dosage forms are known. For example, U.S. Patent No. 4,885,281 discloses an aqueous suspension containing sucralfate, xanthum gum and a "peptiser". Peptisers such as salts of inorganic or organic acids are added to ensure that the xanthan gum does not separate out of the suspension by gel formation.

Belgium Patent No. 900,605 discloses a composition of sucralfate and a nonsteroidal anti-inflammatory product. The compositions were prepared for administering to mammalian test specimens by suspending the active substances in an aqueous medium containing 0.5% sodium CMC (carboxymethylcellulose).

The preparation of melt-spun medicament-containing products is known. For example, commonly-assigned U.S. Patent No. 4,855,326, which is incorporated by reference herein, discloses combining a medicament with a melt-spinnable carrier agent, preferably a mixture of sucrose and lactose, and then melt-spinning the mixture to form a spun product.

Similarly, commonly-assigned U.S. Patent No. 4,997,856, also incorporated by reference herein, discloses melt spun, compacted dispersible systems containing a medicament, saccharide and an oleaginous substance such as a food oil.

In keeping with foregoing, improvements are continuously being sought using high shear and/or heat processing to enhance the delivery of medicaments. In the case of anti-ulcer medicaments such as sucralfate, investigation is being conducted to improve the protective and therapeutic action of the medicament on ulcerated areas of mucous membranes.

It is an object of the present invention to provide an improved method of treatment using medicaments spun in a matrix carrier.

It is a further object of the present invention to provide improved methods and compositions for preventing and treating ulcerated mucosa.

Other and further objects will become apparent to the artisan in view of the present disclosure, and the scope of the present application is not to be limited by the objects set forth above.

SUMMARY OF THE INVENTION

The present invention includes anti-ulcer compositions formed by having a medicament dispersed in a soluble matrix. The soluble matrix is formed by subjecting the feedstock to physical and/or chemical changes associated with flash flow processing, such as by melt-spinning the medicament with a mixture of a carrier material and a hydrogel. The anti-ulcer compositions can either be placed directly on the ulcer-bearing tissue/mucosa or may be dispersed in a liquid before contacting the affected tissue.

The medicament included in the composition of the present invention is preferably sucralfate. Alternatively, H_2-blocking agents such as cimetidine and the like or omeprazole may also be included.

The carrier materials included in the mixture are a saccharide-based and preferably materials such as maltodextrin, maltooligosaccharides or polydextrose. The hydrogel is selected from materials such as xanthan gum, guar gum and carrageenan. In a preferred embodiment, the melt spinning mixture also includes an oleaginous substance such as a vegetable oil. A method of preparing such anti-ulcer compositions is also disclosed.

The composition of the present invention can also include an analgesic and non-steroidal anti-inflammatory (NSAI) agent. The non-steroidal anti-inflammatory agent may be selected from the various classes of such compounds, e.g., salicylates, acetic acids, propionic acids, fenamates, oxicams, and oxidoles. A processing aid, such as glycerin, can be used in manufacture of the composition.

The composition of the present invention can also include steroids or other gastric irritating drugs. The steroids may be Andrenocorticoids such as Betamethasone, Cortisone,

Dexamethasone, Hydrocortisone, Methylprednisolone, Paramethasone, Prednisolone, Prednisone, Triamcinolone or Corticotropins and the like. Examples of steroids include, but are not limited to, medicaments set forth by trade name as follows: Aristocort - Lederle; Hydrocortone - Merck Sharp & Dohme; Kenalog (in Orabase) - Squibb; Cortone - Merck Sharp & Dohme; Decadron - Merck Sharp & Dohme; and Medrol - Upjohn.

In yet another embodiment an antacid can be included in the composition. The antacid can be incorporated in the feedstock before being processed under flash-flow condition, or, alternatively, it can be separately processed under flash-flow condition and combined in a delivery system. For example, the antacid can be processed separately to form flakes which can then be combined with flakes bearing anti-ulcer medicament and optionally analgesic, by tabletting the flakes together in a single tablet.

The present invention also includes a method of treating ulcer-bearing tissue. The method includes contacting the affected tissue with an anti-ulcer medicament dispersed in a soluble matrix as set forth above. Preferably, the medicament-containing matrix has been dispersed in a liquid such as water before contacting the ulcer-bearing tissue.

As a result of the present invention, anti-ulcer compositions are provided which present therapeutic agents in a rapidly soluble form. In addition, since the therapeutic agents are melt spun with a hydrogel in addition to a soluble carrier, the composition demonstrates mucosal adherence properties and enhanced mouthfeel due to the thickening effect of the hydrogel. These added features provide an enhanced therapeutic effect as well by rapidly placing the anti-ulcer medicament in contact with the affected tissue and affixing it there for a period of time. The hydrogel also acts to assist in suspending the medicament during melt spinning within the spun matrix.

Moreover, when the active agents set forth above are prepared in accordance with the present invention, the product has markedly enhanced tabletting capability. This product is ideal for preparing tabletted delivery systems such as pills, etc.

Yet another advantage is that the compositions of the present invention provide good coating action for internal tissue surfaces of the body by virtue of its substantially uniform adherence to mucosal tissue.

For a better understanding of the present invention, reference is made to the following description, and its scope will be pointed out in the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The anti-ulcer compositions of the present invention are formed by melt spinning medicaments with a mixture of a carrier material and hydrogel so that the medicament is suspended in a soluble matrix.

When a non-steroidal anti-inflammatory agent is included, sucralfate and the NSAI agents are admixed prior to processing. In a preferred embodiment, the carrier material is also mixed with the active ingredients prior to processing. A processing aid can be used to provide bulk for thorough mixing. Glycerin is useful as a processing aid.

The active ingredients are subjected to flash-flow processing. Flash-flow processing can be accomplished several ways. Flash heat and flash shear are two such processes which can be used. In the flash heat process, the feedstock material is heated sufficiently to create an internal flow condition which permits part of the feedstock to move at a subparticle level with respect to the rest of the mass and exit openings provided in the perimeter of a spinning head. The centrifugal

force created in the spinning head flings the flowing feedstock material outwardly from the head so that it reforms with a changed structure. The force required to separate and discharge flowable feedstock is centrifugal force which results from the spinning head. The flash heat process is one process for producing the product of this invention.

In the flash shear process, a shearform matrix is formed by raising the temperature of the feedstock material which includes a nonsolublized-carrier to a point where the carrier such as a saccharide-based material undergoes internal flow upon application of a fluid shear force. The feedstock is advanced and ejected while in internal flow condition, and subjected to disruptive fluid shear forces to form multiple parts or masses which have morphology different from that of the original feedstock.

The multiple masses are cooled substantially immediately after contact with the fluid shear force and are permitted to continue in a free-flow condition until solidified.

In the flash heat process, a spinning process is used herein, wherein the medicament is combined with a carrier and is spun with "cotton candy" fabricating type equipment. The floss spinning machine used herein can be any cotton candy type machine, such as the Econofloss Model 3017 manufactured by Gold Metal Products Company of Cincinnati, Ohio. It will be appreciated by those skilled in the art from the present description that any apparatus or physical process which provides similar forces and temperature gradient conditions can also be used. For simplicity in disclosing and describing this invention, the term "melt-spinning" will be understood to mean a process which includes a combination of temperature, shear, flow, flow rate, mechanical forces and thermal gradients of the type utilized in a cotton candy type machine.

In melt-spinning, the stock material, historically sucrose, is melted and forced through spinerettes. Conventional equipment includes a rotating spinning head surrounded by a bowl into which the fibers are spun. Typically, the temperature of the grid in the spinning machine required for spinning sucrose is from about 180°F to about 266°F at operating speeds of about 3800 RPM. Other saccharides such as maltodextrins and polydextrose, however, can be spun at temperatures as much as 30 to 40% lower and thus permit many heat-sensitive materials to safely undergo melt spinning. It has also been discovered that the extremely short amount of time the medicaments, saccharides and hydrogels are exposed to the melt spinning temperature and shear allows the inventive matrix to be formed without harm.

The flash shear process can be carried out in an apparatus which has means for increasing the temperature of a non-solubilized feedstock and means for simultaneously advancing it for ejection. A multiple heating zone twin screw extruder can be used for increasing the temperature and advancing feedstock. The second element of the apparatus is a means for ejecting the feedstock in a condition for shearing it to provide the product. The means for ejecting is in fluid communication with the means for increasing the temperature and is arranged at the point to receive the feedstock while it is in the internal flow conditions. The means for ejecting the feedstock is preferably a nozzle which provides high pressure ejection of the feedstock material. For a description of various apparati which can be used to produce the inventive delivery systems, see copending U.S. Serial No. (Docket 447-65), filed October 23, 1992 entitled "Process for Making Shearform Matrix", which is herein incorporated by reference.

Various anti-ulcer agents, such as H_2-blocking agents may be included in the anti-ulcer composition of the present invention. A non-limiting list of such agents include cimetadine, ranitadine, nizatidine and famotidine.

Alternatively, anti-ulcer agents such as omeprazole may be selected. In a preferred embodiment, however, the anti-ulcer agent is sucralfate. Mixtures of the above-identified medicaments are also contemplated.

The anti-ulcer agent will be present in amounts up to 50% by weight and preferably from 0.1 to about 20% by weight of the matrix. Most preferably, however, the medicament is present in amounts of from about 0.5 to about 15% by weight of the matrix. The amount of medicament in the matrix is that amount sufficient to achieve the desired therapeutic result. The optimum dosing of the anti-ulcer medicaments is left with the skill of the artisan.

The anti-ulcer medicament is melt spun with a mixture of a carrier material and hydrogel. The carrier material is preferably a saccharide-based material. A non-limiting list of suitable saccharides include sucrose, maltose, fructose, glucose and lactose. Alternatively, carrier materials can be selected from maltodextrins, polydextrose, corn syrup solids, maltooligosaccharides and mixtures thereof.

The hydrogels included in the melt-spinning mixture are selected from materials such as xanthan gum, guar gum, carrageenan gum, gum tragacanth, similar materials, and mixtures thereof. The hydrogel will be present in an amount of from about 0.2% to about 4% by weight of the matrix, with amounts of from about 0.8 to about 2.5% being preferred.

Hydrogels, which may also be referred to as water-soluble polymers, hydrocolloids or hydrophilic polymers, demonstrate the property of being able to adhere to mucous membranes. Materials such as pectins, gelatin, celluloses and polycarbophil are also of use. By including such mucous-adhering materials in the matrix, the anti-ulcer medicament can be maintained in contact with the affected area, that is, ulcer-bearing tissue. For example, upon contact with ulcer-

bearing mucosal tissue, the saccharide portion of the matrix quickly dissolves, leaving the medicament and hydrogel adhering to the affected area. Even when the matrix is dispersed in a liquid before administration, adherence of the medicament to mucosal areas is observable. Thus, the therapeutic properties of the medicament can be directed and affixed to the particular area needed.

In a further embodiment of the present invention, the mixture of the carrier material and hydrogel can also include an oleaginous substance which functions to assure that as the matrix is formed during melt spinning, the active ingredient is substantially evenly distributed in the carrier. In this regard, oleaginous substances such as polyvinylpyrrolidone (PVP) or vegetable oils such as corn oil, sunflower oil, olive oil and mixtures thereof may be present in amounts of from about 2 to about 20% by weight of the matrix, with amounts of from about 5 to about 15% being preferred.

The medicament, hydrogel, and carrier material may be combined prior to or during melt spinning. For example, the mixture containing the carrier and hydrogel are first combined into a uniform mixture before adding the medicament and any optionally present materials such as flavors, sweeteners or oleaginous materials.

In one embodiment, the composition can also include a non-steroidal anti-inflammatory (NSAI) agent selected from the various classes of such compounds. Such classes include, for example, salicylates such as acetylsalicylic acid and diflunisal; acetic acids such as indomethacin, sulindac, tolmetin, diclofenac, and etodolac; propionic acids such as flurbiprofen, indoprofen, naproxen, and ketoprofen; fenamates such as meclofenamate; oxicams such as piroxicam; and oxindoles such as tenidap.

When the composition incudes an NSAI agent, the actives are preferably mixed prior to flash-flow processing. The actives can be mixed with a processing aid which can be glycerin, for example.

The anti-ulcer composition may also optionally include a flavorant. Flavorants include flavors, sweeteners and combinations thereof. The flavors may be natural, artificial or mixtures thereof while the sweeteners may be natural, artificial or high intensity sweeteners or mixtures thereof. Such flavorant materials can be melt spun with the medicament and carrier/hydrogel mixture so that the flavorant is also dispersed within the spun matrix. The amount of flavorant included in the matrix will be a matter of preference for the artisan. It is anticipated that the flavorant will be present in amounts of from about 0.01 to about 3% by weight of the matrix. In addition, the anti-ulcer compositions prepared in accordance with the present invention may also include materials such as colorants, anti-oxidants, preservatives, and the like.

Depending upon the saccharide selected for inclusion in the matrix, the melt-spun medicament product will be in the form of floss, flakes, spicules and the like. In any event, the scope of the present invention is not confined to the physical form of the product, so long as the anti-ulcer medicament is sufficiently dispersed throughout.

In an alternative embodiment, antacid can also be included. Antacids are any alkaline substance which can be taken internally to neutralize stomach acidity. Substances which can be used as antacid include aluminum hydroxide, calcium carbonate, magnesia and alumina oral suspensions, magnesium oxide, magnesium trisilicate, magaldrate, simethicone, and sodium bicarbonate. Other substances can be used and the scope of the invention is not limited to those substances set forth above.

The embodiment which includes antacids can be prepared with the antacid combined in the feedstock with the anti-ulcer medicament and/or analgesic before flash-flow processing. However, in yet another alterative, antacid can be flash-flow processed separately and then combined in a delivery system such as a tablet, capsule, powder, etc. For example, when the flash-flow product is a flake, separate anti-ulcer flakes and antacid flakes can be mixed and then tabletted. The resulting tablet carries both actives intimately bound together in a delivery system, yet physically separated to reduce chemical interaction. The practitioner will realize yet other methods for providing the antacid with the anti-ulcer medicament and, optionally, analgesic compounds using the flash-flow process, and it is intended to include these other methods which are within the scope of the present invention.

If desired, the resultant medicament-containing spun matrix can be compacted to less than 15% of the as-spun volume. An example of such compacting methods is set forth in commonly-assigned U.S. Patent No. 4,997,856, the disclosure of which is incorporated herein. In addition, the spun matrix may also be reduced in particle size such as by milling to provide medicament containing either "particles" or "particulate".

A further aspect of the present invention is a method of treating ulcer-bearing tissue. The method includes contacting ulcer-bearing tissue with an anti-ulcer medicament dispersed in a soluble matrix formed by melt-spinning the medicament with a mixture of a carrier material and a hydrogel, such as that set forth above as the anti-ulcer composition.

The medicament containing matrix may be placed in contact with the ulcer-bearing tissue in the as-spun form, as a compacted wafer or after being dispersed in a liquid. In the situations where the matrix is affixed directly to ulcer-bearing tissue, the presence of the hydrogel in the matrix allows the medicament to be affixed at the site of treatment.

Alternatively, an effective amount of anti-ulcer composition can be dispersed water and, after dissolving, can be taken orally for treatment of mouth or other gastrointestinal mucous-bearing tissue ulcers. The dosages can be varied depending upon the requirements of the patient and the severity of the condition being treated. The actual optimum dosage is within the skill of the artisan.

The compositions of the present invention may also be used as antacid substitutes for palliative relief of dyspepsia, reflux, gastritis and the like. In short, it is anticipated that the medicament-containing spun matrix can be used for any therapeutic indication for which the medicament included in the matrix is suited. Moreover, when the compositions of the present invention include NSAI agents, the unique combination is also preventative in nature.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention. Unless indicated otherwise, the Econofloss machine referred to above was used to form the flash-flow product.

EXAMPLE 1

ANTI-ULCER COMPOSITION

INGREDIENTS	WT. (GRAMS)
Sucralfate (Powder)	25.0
Xanthan Gum	2.0
Corn Oil	12.5
Peppermint Oil	0.5
Maltodextrin 35R (Corn Syrup Solid)	209.5

In this example, a sucralfate-containing anti-ulcer composition was prepared. Initially, the carrier material was prepared by mixing the xanthan gum and maltodextrin until a substantially homogeneous mixture was obtained. Thereafter, the sucralfate, corn oil and peppermint oil flavorant were added while mixing was continued. The resultant mixture was then spun at a low setting. A white spicule-like flake was obtained.

A one tablespoon quantity of the resulting matrix was added to a glass of tap water at room temperature. After quickly dissolving, a colloidal suspension was formed which had a viscosity thicker than tap water.

The resultant mixture was ingested by a host having distress from an ulcerated stomach. The inventive composition provided dramatic relief of stomach ulcer pain instantaneously. It appears that the unique combination of ingredients subjected to the high shear and heat processing had a remarkable effect on the speed and the extent of the treatment.

In the case of treatment of mouth ulcers, one tablespoon of the resulting matrix is added to two tablespoons of tap water to obtain a viscous solution which has excellent coating properties. The viscous solution provides excellent immediate and sustained relief when used for oral cavity ulcers.

EXAMPLE 2

ANTI-ULCER COMPOSITION

INGREDIENTS	WT. (GRAMS)
Sucralfate (Powder)	25.0
Xanthan Gum	1.68
Glycerin	11.25
Maltodextrin 35R (Corn Syrup Solid)	212.07

In this example, a sucralfate-containing anti-ulcer composition was prepared. Initially, the carrier material was prepared by mixing the xanthan gum, sucralfate and glycerin until a substantillay homogeneous mixture was obtained. Thereafter, the Maltodextrin was added while mixing was continued. The resulting mixture was then spun at a low setting. A white spicule-like flake was obtained.

Three tablespoons of the spun matrix was mixed with six tablespoons of water to make a viscous liquid mixture. The viscous mixture was used as a mouth rinse by a host having severe mouth ulcerations. About one day after using the viscous rinse, the host observed substantially reduced irritaiton of the ulcerated areas, especially when eating food.

EXAMPLE 3

ANTI-ULCER COMPOSITION

INGREDIENTS	WT. (GRAMS)
Cimetidine (Powder)	5.0
Xanthan Gum	2.0
Corn Oil	12.5
Peppermint Oil	0.5
Maltodextrin 35R (Corn Syrup Solid)	209.5

In this example, the process set forth in Example 1 is repeated except that the anti-ulcer agent cimetidine is used. A tablespoon quantity of the resultant spun matrix is added to a glass of water and quickly dissolves forming a somewhat viscous colloidal suspension.

The suspension is ingested by a host suffering gastric distress. The medication quickly relieves the stomach pain associated with gastritis and dyspepsia. The viscous suspension is also effective in relieving the discomfort associated with gastrointestinal reflux, since the viscous liquid adheres to the upper portion of the gastric mucosa as well as stomach contents.

EXAMPLE 4

ANTI-ULCER COMPOSITION

INGREDIENTS	WT. (GRAMS)
Sucralfate (Powder)	25
Xanthan Gum	2
Olive Oil	12.5
Spearmint Oil	0.5
Maltodextrin 35R (Corn Syrup Solid)	209.5

In this example, the medicament-containing matrix is prepared as in the Example 1, except that after the matrix is formed, it is compacted to about 15% of its as-spun volume in the form of wafers.

The wafers were then placed on ulcer-bearing oral cavity tissue of an affected host without being dissolved in water. Once placed on the ulcer-bearing tissue, the saccharide portion of the matrix quickly dissolves and the hydrogel portion of the composition, xanthan gum, along with the medicament remain affixed to the oral cavity ulcer-bearing tissue to provide instantaneous relief from the discomfort associated with the ulcerated tissue in the oral cavity.

EXAMPLE 5

In this example, the anti-ulcer medicament sucralfate was mixed with the NSAI agent acetylsalicylic acid. Glycerin was used as a processing aid and the active ingredients mixed by mortar and pestle. Corn syrup solids (D.E. = 36.5), Maltrin-365, was added and mixed well. Xanthan gum was also added to form the feedstock. The ingredients were mixed in the amounts set forth in the Table below.

NSAI PLUS SUCRALFATE/HYDROGEL

Active wt %	CSS DE=36.5 wt %	Aid wt %	Hydrogel wt %
Sucralfate 10%	Maltrin-365 74%	Glycerin 5%	Xanthan Gum 1%
Acetylsalicylic acid 10%			

The feedstock was processed by subjecting the feedstock to flash-flow conditions in a Tornado spinning machine which had been modified to control two parameters: temperature of the heating element, and speed (RPM) of the rotating head. The diameter of the head was 5.5 inches. The feedstock was processed at 3600 RPM and at 135°C.

The resulting product was in the form of flakes which contained a substantially uniform dispersion of the active ingredients. Furthermore, the product had a consistent color and texture, which made it easily adaptable for inclusion in a delivery system such as a tablet.

The above example can also be prepared with ibuprofen as a NSAI agent. The results are a flake which can be easily used in the formation of a delivery means such as a tabletted pill or capsule.

EXAMPLES 6 & 7

Corn Syrup Solids (D.E.=36.5) were melt spun in combination with three drugs to produce a flake-like matrix useful in the present invention. Two examples of this composition feature the drug sucralfate as the common active ingredient. In addition to sucralfate, in Example 6 aspirin has been incorporated; and in Example 7, ibuprofen has been incorporated.

Each composition was formed by first mixing the drugs with a processing aid (glycerin) by mortar and pestle. The excipient, corn syrup solid (Maltrin-365), was slowly added and mixed well. The entire admixture was then processed in a Cuisinart until homogeneous.

Both example mixtures were melt-spun with a modified Tornado spinning machine to allow for control of two parameters: temperature of the heating ribbon, and speed (RPM) of the rotating head. The diameter of the head was 5.5 inches.

The Table below indicates the relative weight percents of the melt-spun components as well as the temperature and rotational speed of the spinning head.

NSAI PLUS SUCRALFATE

Example	Drug wt %	CSS DE=36.5 wt %	Aid wt %	RPM	TempC
6	Sucralfate 10% Aspirin 10%	Maltrin-365 75%	Glycerin 5%	3,600	135
7	Sucralfate 10% Ibuprofen 10%	Maltrin-365 75%	Glycerin 5%	3,600	135

Flakes were analyzed for the presence of drugs with a Mattson Galaxy 5020 FTIR against a nitrogen purge background. Samples were compared to the FTIR spectra of the individual ingredients.

2 grams of each flake example were ground in a SPEX Wig L Bug ball mill. 5 mg resulting powder was added to 400 mg crystalline KBr and ground again in SPEX mill. This material was split in two equal portions to provide duplicate samples for analysis. Pellets were formed in a SPECAC press by exerting 10 tons of pressure for 1 minute.

IR spectrographs of the melt-spun material confirm the presence of sucralfate in both examples. Spectrographs also confirm that Aspirin was present in the processed sample of Example 6, while Ibuprofen was present in the processed sample of Example 7.

Thus, the product resulting from both example 6 and 7 provide both preventative and therapeutic effect at the site of delivery.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize the changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to claim all such changes and modifications as fall within the true scope of the invention.

WHAT IS CLAIMED IS:

1. An anti-ulcer composition comprising an anti-ulcer medicament dispersed in a soluble matrix formed by subjecting to flash-flow conditions said medicament with a mixture of a carrier material and a hydrogel.

2. The composition of Claim 1, wherein said anti-ulcer medicament is sucralfate.

3. The composition of Claim 1, wherein said anti-ulcer medicament is selected from the group consisting of cimetadine, ranitadine, nizatidine, famotidine, omeprazole and mixtures thereof.

4. The composition of Claim 1, wherein said medicament is present in an amount of from about 0.1 to about 50% by weight of said matrix.

5. The composition of Claim 4, wherein said medicament is present in an amount of from about 0.1 to about 20% by weight of said matrix.

6. The composition of Claim 5, wherein said carrier material is a saccharide.

7. The composition of Claim 6, wherein said carrier material is selected from the group consisting of

maltodextrins, corn syrup solids, polydextrose, maltooligosaccharides and mixtures thereof.

8. The composition of Claim 7, wherein said hydrogel is selected from the group consisting of xanthan gum, guar gum, carrageenan gum, gum tragacanth, sodium alginate, gum karaya, locust bean gum, gum acasia and mixtures thereof.

9. The composition of Claim 8, wherein said hydrogel is present in an amount of from about 0.2 to about 4% by weight of said matrix.

10. The composition of Claim 9, wherein said hydrogel is present in an amount of from about 0.8 to about 2.5% by weight of said matrix.

11. The composition of Claim 1, wherein said mixture further comprises an oleaginous substance.

12. The composition of Claim 11, wherein said oleaginous substance is selected from the group consisting of corn oil, sunflower oil, olive oil, vegetable oils and mixtures thereof.

13. The composition of Claim 12, wherein said oleaginous substance is present in an amount of from about 2 to about 20% by weight of said matrix.

14. The composition of Claim 13, wherein said oleaginous substance is present in an amount of from about 5 to about 15% by weight of said matrix.

15. The composition of Claim 1 which further comprises a gastric-irritating bio-affecting agent.

16. The composition of Claim 15, wherein said bio-affecting agent is a non-steroidal anti-inflammatory (NSAI) agent.

17. The composition of Claim 16 wherein said NSAI is selected from the groups consisting of salicylate NSAI agents, acetic acid NSAI agents, oxicam NSAI agents, oxidole NSAI agents and mixtures thereof.

18. The composition of Claim 15 wherein said bio-affecting agent is a steriod.

19. The composition of Claim 18 wherein said steroid is selected from the group consisting of andrenocorticoids and corticotropins.

20. The composition of Claim 1 wherein an antacid is included in said matrix by subjecting said antacid to flash-flow along with said medicament and said mixture.

21. The composition of Claim 20 which further comprises a non-steroidal anti-inflammatory (NSAI) agent subjected to flash-flow with said antacid and said medicament and said mixture.

22. A method of treating ulcer-bearing tissue, comprising contacting ulcer-bearing tissue with an anti-ulcer medicament dispersed in a soluble matrix formed by subjecting to flash-flow conditions said medicament with a mixture of a carrier material and a hydrogel.

23. The method of Claim 22, wherein said anti-ulcer medicament is sucralfate.

24. The method of Claim 22, wherein said anti-ulcer medicament is selected from the group consisting of cimetadine, ranitadine, nizatidine, famotidine, omeprazole and mixtures thereof.

25. The method of Claim 22, wherein said medicament is present in an amount of from about 0.5 to about 50% by weight of said matrix.

26. The method of Claim 25, wherein said medicament is present in an amount of from about 0.5 to about 20% by weight of said matrix.

27. The method of Claim 26, wherein said carrier material is a saccharide.

28. The method of Claim 27, wherein said carrier material is selected from the group consisting of maltodextrins, corn syrup solids, polydextrose, maltooligosaccharides and mixtures thereof.

29. The method of Claim 28, wherein said hydrogel is selected from the group consisting of xanthan gum, guar gum, carrageenan gum, gum tragacanth, sodium alginate, gum kayara, locust bean gum, gum acasia and mixtures thereof.

30. The method of Claim 29, wherein said hydrogel is present in an amount of from about 0.2 to about 4% by weight of said matrix.

31. The method of Claim 30, wherein said hydrogel is present in an amount of from about 0.8 to about 2.5% by weight of said matrix.

32. The method of Claim 31, wherein said mixture further comprises an oleaginous substance.

33. The method of Claim 32, wherein said oleaginous substance is selected from the group consisting of corn oil, sunflower oil, olive oil, vegetable oils and mixtures thereof.

34. The method of Claim 33, wherein said oleaginous substance is present in an amount of from about 2 to about 20% by weight of said matrix.

35. The method of Claim 34, wherein said oleaginous substance is present in an amount of from about 5 to about 15% by weight of said matrix.

36. The method of Claim 22 further comprising dispersing said matrix in a liquid before contacting said ulcer-bearing tissue.

37. A method of preparing an anti-ulcer composition having an anti-ulcer medicament dispersed in a soluble matrix comprising:

subjecting a feedstock comprising said medicament and a carrier material to flash-flow transformation.

38. The method of Claim 37 wherein said feedstock further comprises a hydrogel.

39. The method of Claim 37 wherein said feedstock further comprises a non-steroidal anti-inflammatory (NSAI) agent.

40. The method of claim 39 wherein said NSAI agent is selected from the groups consisting of salicylate NSAI agents, acetic acid NSAI agents, propionic acid NSAI agents, fenamate

NSAI agents, oxicam NSAI agents, oxidole NSAI agents and mixtures thereof.

41. The method of Claim 39 wherein said feedstock comprises an admixture of said NSAI agent and said medicament and a processing aid.

42. The method of claim 41 wherein said processing aid is glycerin.

43. The method of Claim 22 which further comprises including an antacid in said soluble matrix by subjecting said antacid to flash-flow conditions with said medicament and said mixture.

44. The method of Claim 43 which further comprises a non-steroidal anti-inflammatory (NSAI) agent.

45. A method of treatment with a non-steroidal anti-inflammatory (NSAI) agent comprising contacting a patient with an NSAI agent and an anti-ulcer medicament dispersed in a soluble matrix formed by subjecting a feedstock comprising carrier material, and said anti-ulcer medicament to flash-flow conditions.

46. The method of Claim 45 wherein said feedstock further comprises a hydrogel.

47. The method of Claim 45 wherein said anti-ulcer medicament is sucralfate.

48. The method of Claim 45 wherein said anti-ulcer medicament is selected from the group consisting of cimetadine, ranitadine, nizatidine, famotidine, omeprazole and mixtures thereof.

49. The method of claim 45 wherein said medicament is present in an amount from about 0.1 to about 50% by weight of said mixture.

50. The method of Claim 49 wherein said medicament is present in an about from about 0.5 to about 20% by weight of said mixture.

51. The method of Claim 50 wherein said carrier materials selected from the group consisting of maltodextrins, corn syrup solids, polydextrose, maltooligosaccarides and mixtures thereof.

52. The method of Claim 47 wherein said hydrogel is selected from the group consisting of xanthane gum, quar gum, carrageenan, gum tragaceanth, sodium algenate, gum cyaara, locust bean gum, gum acasiia and mixtures thereof.

53. The method of Claim 52 wherein said hydrogel is present in an amount from about 0.2 to about 4% by weight of said matrix.

54. The method of Claim 53 wherein said hydrogel is present in an amount from about 0.8 to about 2.5% by weight of said matrix.

55. The method of Claim 54 wherein said mixture further comprises an oleaginous substance.

56. The method of Claim 55 wherein said oleaginous substance is selected from the group consisting of corn oil, sunflower oil, olive oil, vegetable oils and mixtures thereof.

57. The method of claim 56 wherein said oleaginous substance is present in an amount of from about 2 to about 20% by weight of said matrix.

58. The method of claim 57 wherein said oleaginous substance is present in an amount of from about 5 to about 15% by weight of said matrix.

59. The method of claim 45 further comprising dispersing said matrix in a liquid before contacting with said patient.

60. The method of claim 45 wherein said feedstock further comprises a processing aid.

61. The method of Claim 45 wherein said feedstock further comprises an antacid.

62. An anti-ulcer medication comprising:

a) an anti-ulcer medicament dispersed in a first matrix formed by subjecting to flash-flow condition a first feedstock comprising said medicament and a mixture of a carrier material and hydrogel;

b) an antacid agent dispersed in a second matrix formed by subjecting flash-flow conditions a second feedstock comprising said antacid and a carrier material.

63. The medication of Claim 62 wherein said first feedstock further comprises a non-steroidal anti-inflammatory (NSAI) agent.

64. The medication of Claim 62 wherein said second feedstock further comprises a non-steroidal anti-inflammatory (NSAI) agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/10978

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/10, 9/14, 9/02, 9/22
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/434, 435, 484, 489, 465, 78.38, 426, 485, 488, 499, 500; 514/925-928, 960

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 3,762,846 (CHIVERS) 02 OCTOBER 1973 See column 3, lines 39-51.	1-11,15-32 36-55,59-64
X	US, A, 4,885,281 (HANSTEIN) 05 DECEMBER 1989 See column 2, lines 25-29; column 3, lines 41-46.	1-11,15-32 36-55,59-62
X	US, A, 4,855,326 (FUISZ) 08 AUGUST 1989 Abstract; column 9, Table V; column 11, line 41; column 4, lines 40-44.	1-11,15-32, 36-55,59-62

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

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(54) Title: THERAPEUTIC COMBINATIONS USEFUL IN THE TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

(57) Abstract

The invention concerns combinations of proton pump inhibitors and CCK-B/gastrin antagonists in pharmaceutical compositions that are useful in the treatment of peptic disorders such as ulcers and gastroesophageal reflux disease and in the treatment of Zollinger-Ellison Syndrome.

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THERAPEUTIC COMBINATIONS USEFUL IN THE TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

BACKGROUND OF THE INVENTION

Although gastrin exerts many pharmacological effects throughout the gastrointestinal (GI) tract, it appears that its main physiological functions are stimulation of acid secretion in the stomach, and stimulation of mucosal growth in the stomach, small intestine, and colon.

The secretory activity of the gastrin-producing G-cell of the gastric antrum depends on the intragastric pH, on the presence or absence of food in the stomach lumen, and on the activity of several epigastric endocrine, paracrine, or neuronal systems. Thus, abolition of acid secretion, as in the achlorhydria of pernicious anemia, is accompanied by a marked hypergastrinemia where gastrin levels may reach those seen in patients with gastrinoma, or with Zollinger Ellison syndrome (Yalow, R. S. and Berson, S. A., Radioimmunoassay of gastrin, Gastroenterology 58:1-14 (1970); McGuigan, J. E. and Trudeau, W. L., Serum gastrin concentrations in pernicious anemia, New Engl J Med 282:358-61 (1970); Creutzfeld, W., Arnold, R., Creutzfeld, C., Feurle, G., and Ketterer, H., Gastrin and G-cells in the antral mucosa of patients with pernicious anemia, acromegaly and hyperthyroidism and in a Zollinger-Ellison tumor of the pancreas, Eur J Clin Invest 1:461-79 (1971); Ganguli, P. C., Cullen, D. R., and Irvine, W. J., Radioimmunoassay of plasma gastrin in pernicious anaemia, achlorhydria without pernicious

anaemia, hypochlorhydria, and in controls, Lancet i:155-58 (1971)).

Hyperfunction of the G-cell in achlorhydria of pernicious anemia or after vagotomy is associated with increases in G-cell number in the antral mucosa, but the hyperplasia of the G-cell is a consequence of achlorhydria itself, and is independent of the degree of hypergastrinemia. However, in other gastric mucosal cells such as the acid-secreting parietal cell, or the histamine-forming enterochromaffin-like cell (ECL-cell), where gastrin has a trophic function, the hyperplasia of achlorhydria will be dependent on hypergastrinemia (Becker, H. D., Arnold, R., Börger, H. W., Creutzfeld, C., Schafmayer, A., and Creutzfeld, W., Influence of truncal vagotomy on serum and antral gastrin and G-cells, Gastroenterology 72:811 (1977); Delince, P., Williams, G., and de Graef, J., Antral gastrin cell proliferation after vagotomy in rats, Digestion 18:27-34 (1978); Arnold, R., von Hülst, M., Neuhof, C., Schwarting, H., Becker, H. D., and Creutzfeld, W., Antral gastrin-producing G-cells and somatostatin-producing D-cells in different states of acid secretion, Gut 23:285-91 (1982); Larsson, H., Carlsson, E., Håkabnson, R., Mattsson, M., Nilsson, G., Seensalu, R., Wallmark, B., and Sundler, F., Time course of development and reversal of gastric endocrine cell hyperplasia after inhibition of acid secretion. Studies with omeprazole and ranitidine in intact and adrenalectomized rats. Gastroenterology 95:1477-86 (1988); Håkanson, R., Oscarson, J., and Sundler, F., Gastrin and the trophic control of gastric mucosa, Scand J Gastroenterol 21(suppl. 118):18-30 (1986)).

The most powerful pharmacological agents for blocking acid secretion, clinically or experimentally, are the H_2-antagonists and the benzimidazole proton-pump inhibitors. The action of the former class of agent is by antagonism of the receptors for the histamine that has a dominant role in producing secretion of H^+-ions by the parietal cell; the latter group inhibit acid secretion by a direct action at sulphydryl groups of the H^+/K^+-ATPase of the parietal cell membrane. Treatment with either class of compound will produce achlorhydria, and a resulting hypergastrinemia; this in turn will affect the growth of GI mucosal cells. This effect has been most thoroughly investigated with omeprazole, or related compounds, in the rat stomach, but it is reported that treatment with the H_2-antagonist ranitidine is equally effective in producing hyperplasia of ECL-cells, and that toxicological studies in rats with omeprazole, or H_2-antagonists have revealed that chronic treatments were associated with increased incidence of carcinoid tumors. (Creutzfeld, W., Stöckman, F., Conlon, J. M., Fölsch, U. R., Bonatz, G., and Wulfrath, M., Effect of short and long-term feeding of omeprazole on rat gastric endocrine cells, Digestion 35(suppl. 1):84-97 (1986); Allen, J. M., Bishop, A. E., Daley, M. J., Larsson, H., Carlsson, E., Polack, J. M., and Bloom, S. R., Effect of inhibition of acid secretion on the regulatory peptides in the rat stomach, Gastroenterology 90:970-077 (1986); Larsson, H., Carlsson, E., Mattsson, H., Lundell, L., Sundler, F., Sundell, G., Wallmark, B., Watanabe, T., and Håkonson, R., Plasma gastrin and gastric enterochromaffin-like cell activation and proliferation. Studies with omeprazole and ranitidine in intact and adrenalectomized rats, Gastroenterology

90:391-399 (1986); Koop, H., Willemer, S., Steinbach, F., Eiselle, R., Tuch, K., and Arnold, R., Influence of chronic drug-induced achlorhydria by substituted benzimidazoles on the endocrine stomach in rats, Gastroenterology 92:406-13 (1987); Ryberg, B., Bishop, A. E., Bloom, S. R., Carlsson, E., Håkonson, R., Larsson, H., Mattsson, H., Polack, J. M., and Sundler, F., Omeprazole and ranitidine, antisecretagogues with different modes of action, are equally effective in causing hyperplasia of enterochromaffin-like cells in the rat stomach, Regul Pept 25:235-246 (1989); Betton, G.s R., Dormer, C. S., Wells, J., Pert, P., Price, C. A., and Buckley, P., Gastric ECL-cell hyperplasia and carcinoids in rodents following chronic administration of H_2-antagonists SKF 93479 and oxmetidine and omeprazole, Toxicol Pathol 16:288-98 (1988)).

It is clear that with long-term therapy utilizing powerful blockers of acid secretion where hypergastrinemia is apparent, there may be consequences for either the growth, or turnover rate of GI mucosal cells, with the hypersecretion of gastrin a causal factor. It is also clear that if any of the effects of the hypergastrinemia of iatrogenic achlorhydria may be of serious clinical consequences, and they are to be avoided, there will be a clinical role for any agent that is a selective blocker of the release of gastrin, or a selective blocker of the action of gastrin at its receptor.

Although antagonists of gastrin-releasing peptide ("bombesin antagonists") are known, no agent has been available that will produce a powerful and selective block of the release of gastrin.

SUMMARY OF THE INVENTION

The instant invention concerns pharmaceutical compositions containing a CCK-B/gastrin antagonist or a long-acting and potent H_2 antagonist and an ATP'ase proton pump inhibitor with or without a pharmaceutically acceptable carrier.

CCK_B antagonists (gastrin antagonists) include but are not limited to:

L-365-091 which is 1-((3-((((4-chlorophenyl)-amino)carbonyl)amino)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)acetyl)-pyrrolidine; and

(S)-5-[(10,11-dihydrodibenzo[a,d]cyclohepten-5-yl)amino]4-[(1H-indol-2-yl)carbonyl]amino]-5-oxo-pentanoic acid.

Other compounds useful in the compositions and methods of the instant invention are:

L-365,260 which is (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-N'-(3-methylphenyl)urea,

Butanoic acid, 4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]carbonyl]amino]propyl]amino]-1-phenylethyl]-amino]-4-oxo-, [1S-[1α,2ß[S*(S*)],4ß]]-,

[R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)-carbonyl]amino]propyl]amino]-3-phenylpropyl]amino]-4-oxo-2-butenoic acid,

[R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)carbonyl]-amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid,

[R-[R*,R*-(E)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)-

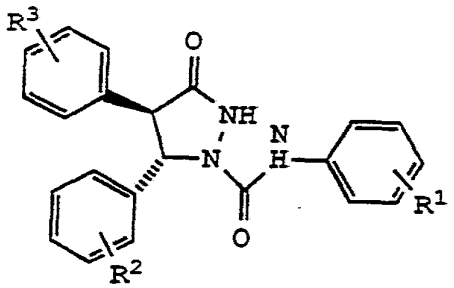
carbonyl]amino]propyl]amino]-1-phenylethyl]amino]-4-oxo-2-butenoic acid,

LY-262,690 which is *trans*-1-Pyrazolidinecarboxamide, 5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(trifluoromethyl)phenyl]-,

LY-262,691 which is *trans*-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(bromo)phenyl]-1-pyrazolidinecarboxamide, and

trans-1-pyrazolidinecarboxamide-N-(4-bromophenyl)-5-(2-chlorophenyl)-3-oxo-4-phenyl-.

Other compounds useful in the instant invention are pyrazolidinones of formula



or a pharmaceutically acceptable salt thereof wherein

R^1 is 2,3-dichloro,
3,4-$(CH_2)_4$,
4-CF_3, or
4-Br;

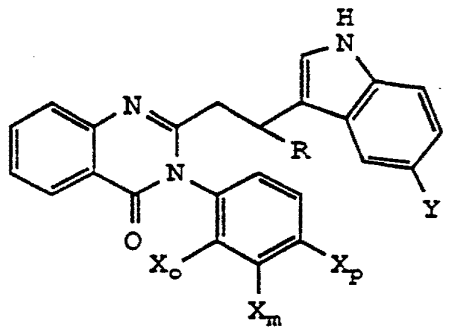
R^2 is hydrogen,
2-chloro,
2,3-dichloro, or
CN; and

R^3 is hydrogen -trans or -cis.

These are disclosed in Drugs of the Future 16(7):631-740 (1991). The compounds are made as described in Synthetic Examples 1 and 2 below.

Other compounds useful in the compositions and methods of treatment of the instant invention and

quinazolinones disclosed in J. Med. Chem. 34:1505-1508 (1991) of formula



or a pharmaceutically acceptable salt thereof wherein

X_0 is hydrogen, fluorine, chlorine, methoxy, or trifluoromethyl;

X_n is hydrogen, fluorine, chlorine, bromine, methyl ethyl isopropyl, methoxy, trifluoromethyl, propoxy, isopropoxy, cyclopentyloxyl, MeS, or NMe_2;

X_p is hydrogen, methoxy, ethoxy, isopropoxy, isopropyl, MeS, or NMe_2; or X_m and X_p together are $-OCH_2O-$;

Y is hydrogen, methyl, methoxy, fluorine, chlorine, or bromine; and

R is hydrogen or methyl.

Although several synthetic routes are available for preparing the above series, the compounds are also made as described in Synthetic Example 3 below.

Proton pump inhibitors include but are not limited to: omeprazole, BY308, SK&F 95601 which is 2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole; and SK&F 96067 which is 3-butyryl-4-(2-methylphenylamino)-8-methoxyquinoline.

The instant invention also includes a method of treating peptic disorders such as gastroesophageal reflux disease and ulcers.

The instant invention also includes a method of treating Zollinger-Ellison Syndrome.

The compositions of the instant invention contain from 0.1 mg/kg to 10 mg/kg of a CCK-B antagonist and from 10 mg to 360 mg of an ATP'ase proton pump inhibitor.

Especially preferred is a composition of [R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid and omeprazole.

BRIEF DESCRIPTION OF DRAWINGS

Figure I shows serum gastrin levels in venous blood from rats.

Figure II shows enterochromaffin-like cell (ECL) proliferation in the corpus of rat gastric mucosa.

DETAILED DESCRIPTION

Irreversible proton pump inhibitors such as omeprazole, BY308, and others are extremely effective in gastroesophageal reflux disease (GERD), as indeed are the longer acting and potent H_2 antagonists, as well as in all other peptic disorders caused or aggravated by gastric acid. A long-acting H_2 antagonist means dosing usually is once per day; that is once in 24 hours, usually nocturnally. Unfortunately, the compounds cause carcinoid tumors in animals because of the elevated levels of gastrin. This problem means that the duration of treatment

with, for example, omeprazole in GERD is restricted. Omeprazole is indicated for short-term treatment (4-8 weeks). [Physicians' Desk Reference (1991)].

Reversible inhibitors of the gastric (H^+ and K^+)-ATP'ase, such as SK&F 96067 are also included in the instant invention.

Gerd is a chronic problem and the relief to sufferers provided by existing treatments renders them dependent on permanent therapy.

Proton pump inhibitors are also useful in the treatment of ulcers but the same problems pertain to the use of the drugs for ulcer treatment.

Proton pump inhibitors are also useful in the long-term treatment of Zollinger-Ellison syndrome.

The pharmaceutical compositions of the instant invention that contain combinations of an ATP'ase proton pump inhibitor and a CCK-B antagonist are useful for all of the above problems.

At high doses of omeprazole, for example, which totally suppress gastric acid secretion and raise gastrin blood levels very significantly, a CCK-B antagonist blocks the cellular hypertrophy of gastric mucosal cells.

Gastrin antagonists coadministered with proton pump inhibitors offer great therapeutic advantage over H_2 antagonists. Gastrin has been implicated as a growth factor in many areas of the gastrointestinal and respiratory tracts.

Studies have shown that achlorhydria causes a marked hypergastrinemia due to hypertrophy, hyperplasia, and hyperfunction of the gastrin-cell (G-cell) mass in the gastric mucosa. This increased gastrin secretion, in turn, has been suggested to be the underlying cause of a proliferation of the number, size, and activity of the enterochromaffin-like (ECL)

cells in the gastric or duodenal mucosa in achlorhydric animals. Thus, it appears that gastric carcinoid tumors formed from ECL cell hyperplasia in omeprazole-treated rats are related to the achlorhydria and secondary hypergastrinemia produced by the drug. If this is the case then treatment with gastrin antagonists should inhibit this omeprazole-induced phenomenon.

Other gastrin-dependent tumors include a human small cell carcinoma of the lung, which was recently reported to contain CCK-B/gastrin receptors, and a mouse carcinoid tumor of the colon.

CCK-B/gastrin antagonist compounds of the instant invention are able to block acid secretion in the rat in response to stimulation by pentagastrin (Hayward, N. J., Harding, M., Lloyd, S. A. C., McKnight, A. T., Hughes, J., and Woodruff, G. N., The effect of CCK_B gastrin antagonists on stimulated gastric acid secretion in the anesthetized rat, Br J Pharmacol, 104: 973-977 (1991).

Some of the compounds that are CCK-B antagonists and useful in the instant invention are fully described in European Application Publication Number 0405537 (United States Serial Number 07/545,222, filed June 28, 1990), United States Serial Numbers 07/726,656, 07/726655, 07/726,654, 07/726,653, 07/726,652, and 07/726,651, all filed on July 12, 1991 by Horwell, et al. All of the above United States applications are hereby incorporated by reference.

Other compounds which are CCK-B/gastrin antagonists and useful in the instant invention are fully described in United States Patent 4,820,834, which is hereby incorporated by reference.

Proton pump inhibitors such as BY 308, 5-trifluoromethyl-2-[4-methoxy-3-methyl-2-pyridyl-methyl]-thio-[1H]-benzimidazole, which are described and claimed in United States Patent 4,472,409, are useful in the instant invention. The patent is hereby incorporated by reference.

Proton pump inhibitors such as omeprazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, which are described and claimed in United States Patent 4,255,431, are useful in the instant invention. The patent is hereby incorporated by reference.

Other useful proton pump inhibitors include but are not limited to:

[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]-methyl]sulfenamide;

(Z)-5-methyl-2-[2-(1-naphthyl)ethenyl]-4-piperidinopyridine HCl;

2-(4-cyclohexyloxy-5-methylpyridin-2-yl)-3-(1-naphthyl)-1-propanol;

methyl 2-cyano-3-(ethylthio)-3-(methylthio)-2-propenoate;

2-((4-methoxy-2-pyridyl)methylsulphinyl)-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole sodium;

5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole, sodium;

2-[[[4-(2,2,3,3,4,4,4-heptafluorobutoxy)-2-pyridyl]methyl]sulfinyl]-1H-thieno[3,4-d]imidazole;

2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole;

2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole;

2-methyl-8-(phenylmethoxy)-imidazo(1,2-A)-pyridine-3-acetonitrile;

(2-((2-dimethylaminobenzyl)sulfinyl)-benzimidazole);

4-(N-allyl-N-methylamino)-1-ethyl-8-((5-fluoro-6-methoxy-2-benzimidazolyl)sulfinylmethyl)-1-ethyl-1,2,3,4-tetrahydroquinolone;

2-[[(2-dimethylaminophenyl)methyl]sulfinyl]-4,7-dimethoxy-1H-benzimidazole;

2-[(2-(2-pyridyl)phenyl)sulfinyl)-1H-benzimidazole;

(2-[(2-amino-4-methylbenzyl)sulfinyl]-5-methoxybenzo[d]imidazole;

(4-(2-methylpyrrol-3-yl)-2-guanidisothiazole);

4-(4-(3-(imidazole)propoxy)phenyl)-2-phenylthiazole;

(E)-2-(2-(4-(3-(dipropylamino)butoxy)phenyl)-ethenyl)benzoxazole;

(E)-2-(2-(4-(3-(dipropylamino)propoxy)phenyl)-ethenyl)-benzothiazole;

Benzeneamine, 2-[[(5-methoxy-1H-benzimidazol-2-yl)sulfinyl]methyl]-4-methyl-;

Pumilacidin A;

2,3-dihydro-2-methoxycarbonylamino-1,2-benzisothiazol-3-one;

2-(2-ethylaminophenylmethylsulfinyl)-5,6-dimethoxybenzimidazole;

2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine-3-acetonitrile;

3-amino-2-methyl-8-phenylmethoxyimidazo[1,2-a]-pyrazine HCl;

2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]-sulfinyl]-5-methoxy-(1H)-benzimidazole;

[3-butyryl-4-(2-methylphenylamino)-8-methoxy-quinoline];

2-indanyl 2-(2-pyridyl)-2-thiocarbamoylacetate HCl;

2,3-dihydro-2-(2-pyridinyl)-thiazolo(3,2-a)-benzimidazole;

3-cyanomethyl-2-methyl-8-(3-methyl-2-butenyloxy)-(1,2-a)imidazopyridine;

Zinc L-carnosine.

Figure I concerns serum gastrin levels. It shows levels of gastrin-like immunoreactivity in venous blood from rats, before and after 1, 4, 7, or 14 days of treatment with vehicles (veh/veh: isotonic saline 3 subcutaneous injections at 8-hour intervals, methocel orally at 8:00 a.m.) Compound 1 which is [R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)-carbonyl]amino]propyl]amino]-3-phenylpropyl]amino]-4-oxo-2-butenoic acid, 18 mg/kg thrice daily (veh/1189), BY 308 40 mg/kg orally in methocel (308/veh) or BY 308 and Compound 1.

Days of treatment are along the X-axis and serum gastrin (pg/md) on the Y-axis.

 is veh/veh;  is veh/compound 1;
 is 308/veh; and  308/compound 1.

Figure II concerns ECL-cell proliferation in the corpus. It shows the uptake of ^{3}H-thymidine into enterochromaffin-like cells (ECL-cell) of rat gastric mucosa after 14 days of treatments (as Figure 1); and labelled ECL-cells as a percentage of total ECL-cell count in the field ("labelling index").

 is Methocel/NaCl;  is Methocel/compound 1;
 is BY308/NaCl; and is BY308/compound 1.

Female Sprague-Dawley rats were used with free access to lab diet and water. Groups of 10 animals were treated three times daily with 18 mg/kg of compound 1 for 14 days as follows:

S.C. saline (x3) + oral Methocel (8 am)
S.C. saline (x3) + BY 308 40 mg/kg in methocel (8 am)
S.C. Compound 1 in saline + oral methocel
S.C. Compound 1 in saline + BY 308 40 mg/kg

Two animals were used from the Compound 1 groups, for preparation with gastric fistulae, to confirm that the acid secretory response to pentagastrin remained blocked after long-term treatment with the gastrin antagonist.

Blood was drawn from the retro-orbital venous plexus before treatment on Days 0, 1, 4, 7, and 14 for assay of serum gastrin and CCK levels.

Three days before sacrifice ^{3}H-thymidine was infused into a tail vein (1 µCi/g body weight as a bolus injection, followed by continuous infusion for 8 hours of 0.25 µCi/g/h), for subsequent measurement of ECL-cel labeling index by autoradiography.

Optimal tissue preservation was achieved by perfusion fixation in Bouin's fixative for 8 minutes, and by fixation for 24 hours of excised tissue blocks in Bouin's solution, with embedding in paraffin wax. For estimation of cell density, 5 µm sections were cut; 2 µm for autoradiography (Eissele, R., Rosskopf, B., Koop, H., Adler, G., and Arnold, R., Proliferation of endocrine cells in rat stomach caused by drug-induced achlorhydria, Gastroenterology, in press (1991)).

Antral G-cells were visualized after removal of the paraffin wax by immunostaining for gastrin using

the avidin-biotin-peroxidase complex technique (Hsu, S. M., Raine, L., and Fanger, H., Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques; a comparison between ABC and unlabeled antibody (PAP) procedures, J Histochem Cytochem 29:577-780 (1981)).

ECL-cell density was evaluated in sections of oxyntic mucosa by the silver impregnation method or by immunostaining for chromogranin for autoradiographic studies (Grimelius, L., A silver nitrate stain for A_2 cells of human pancreatic islets, Acta Soc Med Ups 73:271-294 (1968)).

Gastrin levels in unfixed sections of antrum and somatostatin in the fundus were measured by radioimmunoassay. Unfixed samples of pancreas were taken to assay for enzyme and DNA levels by standard methods.

Treatment with the proton-pump inhibitor BY 308 (Koop, H., Schubert, B., Schwarting, H., Schikierka, D., Eissele, R., Willemer, S., and Arnold, R., Increased visualization of antral gastrin-producing G-cells after acute stimulation of gastrin release in the rat, Eur J Clin Invest 17:111-16 (1987)) produced the expected rise in serum gastrin levels, irrespective of the presence or absence of co-treatment with Compound 1. The compound had no effect by itself on gastrin levels (Figure 1). Levels of gastrin in antral sections were also increased in the groups treated with BY 308, but somatostatin in the fundus was not affected by any treatment.

Antral mucosal G-cells were increased from 56/mm (saline + methocel), or 60\mm (([R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo-[3.3.1.$1^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl]amino]-3-

phenylpropyl]amino]-4-oxo-2-butenoic acid, + methocel) to 75/mm and 88/mm in the corresponding groups given BY 308. The increases by BY 308 were statistically significant at the 2% level. That is, the increase in G-cell number is attributable to the achlorhydria, and is obtained in either group treated with BY 308.

In keeping with previous data from this group that ECL-cell density is not much affected until exposure to BY 308 extends beyond the third week of treatment, in the present 2-week study ECL-cell number was not significantly affected by any treatment (density around 200/mm). As in the earlier study by this group, however, the ^{3}H-thymidine labeling index, as an indicator of cell turnover, was increased from between 0.3% and 0.5% of cells in vehicle-treated controls to between 3% and 4% in the group treated for 14 days with the proton-pump inhibitor. This increase was abolished in the group also given Compound 1 for the 14-day period; by itself the compound had no effect on ECL-cell labeling index (Figure 2).

The above experiments show that in the female rat in achlorhydria with chronic treatment with the proton pump inhibitor BY 308, the resultant hypergastrinemia is unaffected by cotreatment with a dose of Compound 1 high enough to guarantee complete blockade of the gastrin receptor on the parietal cell. The 14-day treatment with the high dose of Compound I did not affect gastrin levels.

The 14-day treatment with BY 308 showed there was a substantial increase in the incorporation of thymidine into the ECL-cells of the fundic mucosa, indicating an increased rate of cell division. The increased thymidine labeling index was completely blocked by Compound 1, indicating that the effect is

truly a consequence of the hypergastrinemia of achlorhydria.

These results show CCK_B/gastrin antagonists are expected to have clinical utility in the periphery, in the management of gastrin-dependent hyperplasias.

The compositions or combinations of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides pharmaceutical compositions comprising a compound which is a CCK-B/gastrin antagonist (or a long-acting and potent H_2 antagonist) or a pharmaceutically acceptable salt thereof and a proton pump inhibitor or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, if desired.

The composition can be given orally formulated as liquids, for example, syrups, suspensions or emulsions, tablets, capsules, and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound of pharmaceutically acceptable salt in a suitable liquid carrier(s), for example, ethanol, glycerine, nonaqueous solvent, for example, polyethylene glycol, oils, or water with a suspending agent, preservative, flavoring or coloring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a

dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example, aqueous gums, celluloses, silicates, or oils, and the dispersion or suspension, then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example, polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil, or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins, or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compositions of the invention will normally be administered to a subject for the treatment of peptic disorders and other conditions caused or exacerbated by gastric acidity. The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose

of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example, for a week or more.

The dosing regimen will be within the skill or a skilled physician.

In addition, the composition of the present invention can be coadministered with further active ingredients such as antacids (for example, magnesium carbonate or hydroxide and aluminum hydroxide), nonsteroidal antiinflammatory drugs (for example, indomethacin, aspirin, or naproxen), steroids, or nitrite scavengers (for example, ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example, pirenzepine, prostanoids, for example, 16,16-dimethyl PGE_2, or histamine H_2-antagonists (for example, cimetidine, ranitidine, famotidine, and nazatidine).

EXAMPLE 1

Tablet		
(1) Compound 1	30 mg	
(2) Corn starch	20 mg	
(3) Lactose	85.2 mg	
(4) Micro crystalline cellulose	60 mg	
(5) Light anhydrous silicic acid	1.8 mg	
(6) Magnesium stearate	3.0 mg	
(7) Magnesium hydroxide	30 mg	
(8) L-Cysteine	20 mg	
	250 mg	(One Tablet)

EXAMPLE 2

Capsule	
(1) Compound 1	30 mg
(2) Corn starch	40 mg
(3) Lactose	74 mg
(4) Hydroxypropylcellulose	6 mg
(5) Magnesium carbonate	50 mg
(6) Water	(0.1 mL)
	200 mg

EXAMPLE 3

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

Omeprazole	2.0 g
Saccharin	0.6 g
Sugar	30.0 g
Glycerin	5.0 g
Flavoring agent	0.1 g
Ethanol 96%	10.0 mL

Distilled water (sufficient to obtain a final volume of 100 mL), sugar, saccharin, and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavoring agents dissolved in ethanol were added. Water was added to the mixture to obtain a final volume of 100 mL.

The above given active sustance may be replaced with other pharmaceutically acceptable acid addition salts.

SYNTHETIC EXAMPLE 1

Trans-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(bromophenyl]-1-pyrazolidinecarboxamide

Step 1. Preparation of αphenyl-2-chlorocinnamic acid

Method used: Org. Syn. Coll. IV:777 (1963).

Phenylacetic acid (54.46 g, 0.4 M) was dissolved in acetic anhydride (80 mL). O-chlorobenzaldehyde (56.23 g, 0.4 M) was added slowly, with stirring. This was followed by the slow addition of triethylamine (40 mL). The reaction mixture was stirred at reflux for 5 hours. The reaction mixture was steam distilled until the distillate was no longer cloudy. The distillate was discarded. The aqueous residue was cooled. The solution was decanted from the gummy solid. This solid was dissolved in a 10% K_2CO_3 solution. The basic solution was charcoaled then filtered through a pooled Super cell. The filtrate was made acidic (pH 1) with 10% HCl, cooled, and the solid filtered. The product was recrystallized from 50% ethanol/H_2O to yield 52.14 g of white solid, mp 158-161°C.

Step 2. Preparation of αphenyl-2-chlorocinnamic acid methyl ester

αPhenyl-2-chlorocinnamic acid (26.29 g (0.102 M) was dissolved in methanol (300 cc). Anhydrous HCl was bubbled through the reaction mixture with stirring for 15 minutes. The reaction mixture was refluxed for 2 hours, then HCl was bubbled through the reaction mixture for another 15 minutes. The reaction was stirred at reflux overnight. The methanol was removed in vacuo and the residue taken up in ether. The ether solution was washed with H_2O, saturated $NaHCO_3$ solution, and brine. It was then dried over $MgSO_4$. The ether solution was concentrated in vacuo to yield

an oil that quickly solidified to yield 27.13 g of product, mp 67-69°C.

Step 3. Preparation of 4-(O'-chlorophenyl)-5-phenyl-3-pyrazolidine

The ester from Step 2 (27.05 g, 0.0993 M) was dissolved in ethanol (75 cc). Eighty-five percent hydrazine hydrate (5.76 g, 0.0993 M) was added. The reaction mixture was stirred at reflux for 24 hours, then cooled. H_2O was added slowly with stirring. The product oiled out. The ethanol water was decanted from the oil. The oil was taken up in ether. The ether solution was washed with cold water, then dried over $MgSO_4$. The ether solution was concentrated in vacuo. A small amount of ether was added to the residue. The white solid was filtered and dried in vacuo to yield 9.56 g of product, mp 123-124°C.

Step 4. Preparation of trans-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(bromophenyl]-1-pyrazolidine-carboxamide

The pyrazolidone obtained in Step 3 (2.73 g, 0.01 M) was dissolved in THF (100 mL). p-Bromophenyl isocyanate (1.98 g, 0.01 M) was added. The reaction mixture was stirred overnight at room temperature. The clear solution was concentrated in vacuo to yield 4.73 g of a white solid. The solid was boiled in isopropyl ether. The insoluble solid was filtered from the warm ether and dried to yield 3.71 g of the product, mp 189-190°C.

Analysis for $C_{22}H_{17}BrClN_3O_2$ (MW 470.762):

Calcd.: C, 56.13; H, 3.64; N, 8.91.

Found: C, 56.43; H, 3.87; N, 8.71.

IR NMR and MS consistent for the desired product.

SYNTHETIC EXAMPLE 2

Trans-5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(trifluoromethyl)phenyl]-1-pyrazolidinecarboxamide

Substituting ααα-trifluoro-p-tolyl isocyanate (1.87 g, 0.01 M) for p-bromophenyl isocyanate in Step 4, one obtains 3.6 g of the product, mp 193-194°C.

Analysis for $C_{23}H_{17}ClF_3N_3O_2$ (MW 459.859):

Calcd.: C, 60.07; H, 3.73; N, 9.14.

Found: C, 60.16; H, 3.81; N, 9.09.

IR, NMR and MS consistent for the desired product.

SYNTHETIC EXAMPLE 3

3-nitrophenol (50.0 g, 360 mmol), isopropyl iodide (76.19 g, 450 mmol), and K_2CO_3 (60 g) were combined and heated at reflux under N_2 overnight in acetone (400 mL). After solvent removal in vacuo, the residue was partitioned between EtOAc and H_2O. The separated organic layer was washed with 1 N NaOH, brine, dried over Na_2SO_4, and concentrated in vacuo to provide 56 g (86%) of 3-isopropoxynitrobenzene as a clear yellow oil.

A mixture of the above product (8.5 g, 50 mmol), PtO_2 (0.3 g), and EtOH (200 mL) was hydrogenated (40 psi H_2) at room temperature for 1.5 hours in a Paar shaker. The mixture was filtered through Celite and concentrated in vacuo to furnish 7.08 g of the desired aniline. This material was combined with isatoic anhydride (7.35 g, 45 mmol) and heated at 90°C for 2 hours. Upon cooling and addition of hexanes, the product crystallized to give 10.19 g (83%) of 2-amino-N-(3-isopropoxyphenyl)benzamide as a white solid. An analytical sample was obtained by recrystallization from 20% EtOAc/hexanes, mp 79-86°C; ^1H NMR ($CDCl_3$) δ 1.36 (6H, d, J=6.1 Hz), 4.59 (1H, h,

J=6.1 Hz), 5.2 (2H, bs), 6.6-6.8 (3H, m), 7.0-7.1 (1H, m), 7.2-7.4 (3H, m), 7.47 (1H, d, J=7.7 Hz), 7.80 (1H, bs); IR ($CHCl_3$) 1664, 1611, 1524, 1490 cm^{-1}; MS (FD) 270 (M^+). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

A solution of 3-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl]-5-bromoindole (4.12 g, 12 mmol) prepared according to the method of Farlow, et al (Farlow, D. S.; Flaugh, M. E.; Horvath, S. D.; Lavignino, E. R.; Pranc, P. Two Efficient Syntheses of Indole-3-Propionic Esters and Acids. Further Applications of Meldrum's Acid. Org. Prep. Proced. Int. 13:39-48 (1981), the above benzamide (3.48 g, 13 mmol) and pyridinium p-toluenesulfonate (1.64 g, 6.5 mmol) in 50 mL of pyridine was heated at reflux for 3.5 days. The reaction mixture was concentrated in vacuo, chromatographed (SiO_2, 30% EtOAc/hexanes), and crystallized to give 2.13 g (36%) of compound 22, mp 179-181°C; ^1H NMR ($CDCl_3$) δ 1.31 (3H, d, J=6.0 Hz), 1.34 (3H, d, J=6.1 Hz), 2.8 (2H, m), 3.2 (2H, m), 4.53 (1H, h, J=6.0 Hz), 6.7-7.6 (9H, m), 7.8 (2H, m), 8.2-8.4 (2H, m); IR (KBr) 1671 cm^{-1}; MS (FAB) 502, 504 ($M^+ + H$). Anal. ($C_{27}H_{24}N_3O_2Br$) C, H, N.

CLAIMS

1. A pharmaceutical composition containing a CCK-B/gastrin antagonist and an ATP'ase proton pump inhibitor with or without a pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to Claim 1 wherein the CCK-B antagonist is one or more selected from

[R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid,

[R-[R*,R*-(E)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl]amino]-1-phenylethyl]amino]-4-oxo-2-butenoic acid,

Butanoic acid, 4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[[(1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl)oxy]carbonyl]amino]propyl]-amino]-1-phenylethyl]amino]-4-oxo-, [1S-[1α,2ß[S*(S*)],4ß]]-, and

[R-[R*,S*-(E)]]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.$1^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl]amino]-3-phenyl-propyl]amino]-4-oxo-2-butenoic acid.

3. A pharmaceutical composition according to Claim 1 wherein the CCK-B antagonist is (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-N'-(3-methylphenyl)urea.

4. A pharmaceutical composition according to Claim 1 wherein the CCK-B antagonist is *trans*-1-

pyrazolidinecarboxamide, 5-(2-chlorophenyl)-3-oxo-4-phenyl-N-[4-(trifluoromethyl)phenyl]-.

5. A pharmaceutical composition according to Claim 1 wherein the ATP'ase proton pump inhibitor is one or more selected from: BY308, omeprazole, SK&F 95601 and SK&F 96067.

6. A pharmaceutical composition according to Claim 1 wherein the CCK-B antagonist is [R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-amino]propyl]amino-1-phenylethyl]amino]-4-oxo-butanoic acid and the proton pump inhibitor is omeprazole.

7. A method for treating peptic disorders in a patient suffering therefrom which comprises administering a composition according to Claim 1.

8. A method according to Claim 7 wherein the peptic disorder is gastroesophageal reflux.

9. A method according to Claim 7 wherein the peptic disorder is ulcer.

10. A method for treating Zollinger-Ellison Syndrome in a patient suffering therefrom which comprises administering a composition according to Claim 1.

11. A pharmaceutical composition according to Claim 1 containing from 0.1 mg/kg to 10 mg/kg of a CCK-B antagonist and from 10 mg to 360 mg of an ATP'ase proton pump inhibitor.

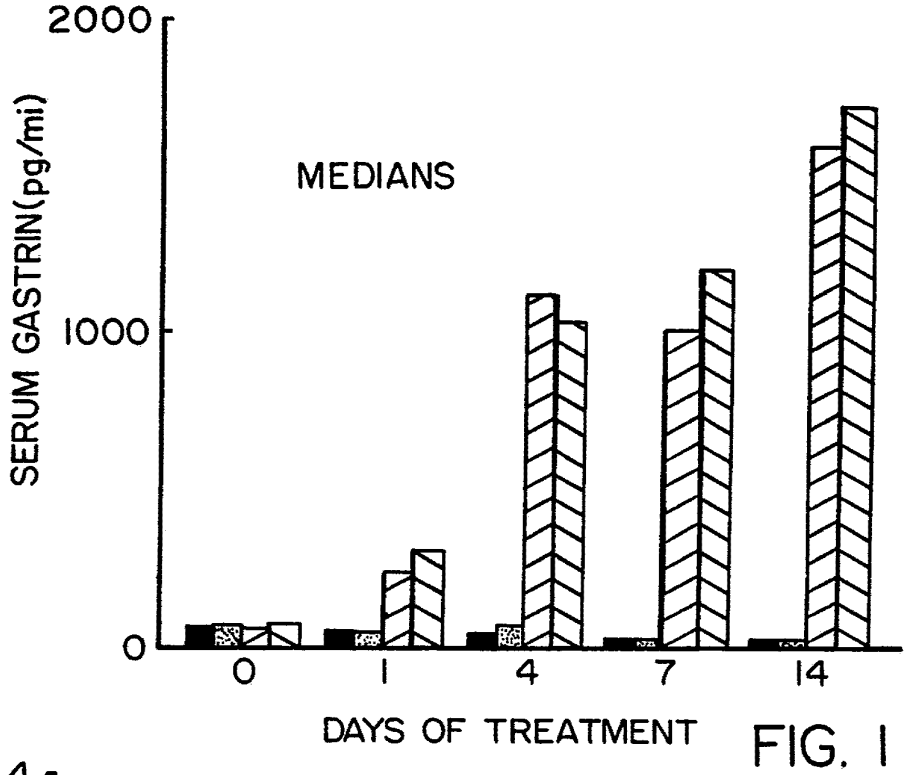

2000
1000
0
SERUM GASTRIN(pg/ml)
MEDIANS
0
1
4
7
14
DAYS OF TREATMENT

FIG. 1

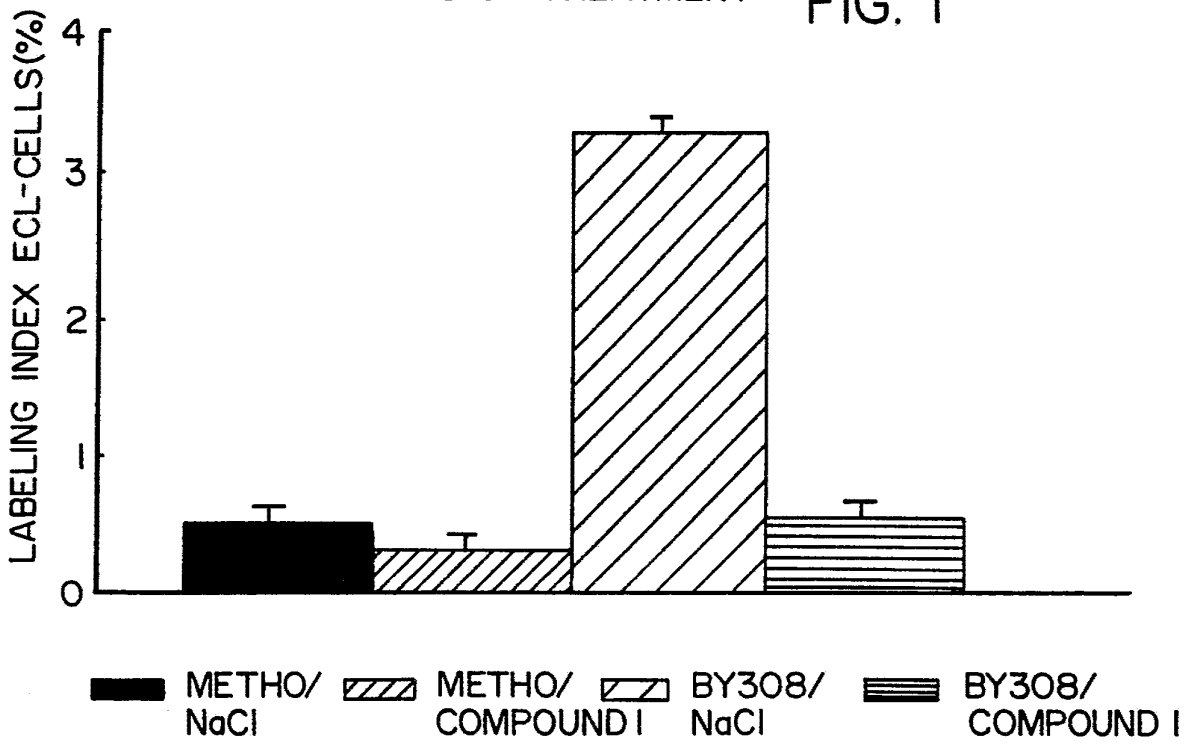

LABELING INDEX ECL-CELLS(%)
4
3
2
1
0
METHO/ NaCl
METHO/ COMPOUND I
BY308/ NaCl
BY308/ COMPOUND I

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/10692

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K45/06; A61K31/44; //(A61K31/44,31:405)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	FEBS LETT, VOL. 281, NO. 1-2, PAGE(S) 20-2, 1991, DIMALINE R ET AL. 'Histidine decarboxylase gene expression in rat fundus is regulated by gastrin.' see page 22, column 1, line 2 - line 13 ---	1,5
A	EP,A,0 272 876 (GLAXO GROUP LIMITED) 29 June 1988 see abstract ---	1-11
A	BRITISH JOURNAL OF PHARMACOLOGY vol. 104, no. 4, December 1991, page 973-977 HAYWARD ET AL. 'The effect of CCK-B gastrin antagonists on stimulated gastric acid secretion in the anaesthetized rat' see abstract -----	1-11

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18 MARCH 1993	30. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LEHERTE C.F.M.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/10692

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAMIS 7-10 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

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

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

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9210692
SA 68014

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 18/03/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0272876	29-06-88	AU-B- 618943	16-01-92
		AU-A- 8261587	23-06-88
		JP-A- 63246337	13-10-88

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International Bureau

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Filed on 29 September 1992 (29.09.92)

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(54) Title: IBUPROFEN-H_2 ANTAGONIST COMBINATIONS

(57) Abstract

This invention relates to pharmaceutical compositions for use in the treatment of pain and inflammation and in the relief of indigestion, sour stomach, heartburn and other gastrointestinal disorders in mammals, including humans, by administering compositions comprising (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and (ii) an amount effective in the relief of indigestion, sour stomach, heartburn, overindulgence and other gastrointestinal disorders of at least one of the H_2 antagonists.

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TITLE OF THE INVENTION
IBUPROFEN-H_2 ANTAGONIST COMBINATIONS

BACKGROUND OF THE INVENTION

The non-steroidal anti-inflammatory drugs (NSAID) have been utilized in the treatment of pain/inflammation and a number of other symptoms including stiffness that are associated with painful conditions affecting muscles, bones, and joints. NSAIDs have been prescribed to relieve back pain, arthritic pain, gout, menstrual pain, headaches, mild pain following surgery, and pain from soft tissue injuries such as sprains and strains. NSAIDs are within the broader class of non-narcotic analgesics which also includes acetyl salicyclic acid (aspirin) and acetaminophen. NSAIDs, except for acetaminophen, are generally considered to exert their effect by blocking the production of prostaglandins at the site of pain, irritation or injury so that the pain signal does not reach the brain.

Ibuprofen (2-(4-isobutylphenyl)propionic acid) is a well known and commonly employed NSAID. Amino acid salts of racemic ibuprofen including the lysine or arginine salt are also known pain relievers. See U.S. Pat. No. 4,279,926. Recently, it has been found that a faster onset of pain relief and an enhanced analgesic response can be obtained by utilizing the single enantiomer (S)-ibuprofen (also known as (+)-ibuprofen or dexibuprofen) rather than the racemic mixture of ibuprofen. See U.S. Patent 4,877,620.

H_2 antagonists are commonly prescribed to treat and prevent ulcers in the walls of the stomach, duodenum or esophagus. H_2 antagonists are also used to treat non-ulcerative conditions. Damage to the mucus lining surrounding these tissues enables destructive action of stomach acids which erodes the underlying tissue. Commonly known H_2 antagonists for the treatment of ulcers include cimetidine, ranitidine, nizatidine, roxatidine and famotidine.

Combinations of ibuprofen with H_2 antagonists have been disclosed. See EPO App. No. 426479A which discloses a pharmaceutical composition for treating the symptoms of

overindulgence (headache and acid indigestion) using H_2 antagonists including famotidine and an analgesic effective amount of a NSAID including ibuprofen wherein the term is defined to include administration of both the racemic mixture or the pure S enantiomer of ibuprofen. There is a need to employ a compound with faster acting and enhanced analgesic capability such as (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; in combination with an H_2 antagonist such as famotidine to treat and prevent the pain and discomfort associated with headaches, indigestion, sour stomach, heartburn or other gastrointestinal disorders. There is a need to employ a combination wherein an advantage is that the (S)-ibuprofen lysine salt is more stable than the free acid of ibuprofen and is extremely soluble in water to give substantially neutral (versus acidic) aqueous solutions. The ibuprofen/lysine salt is therefore more suitable for administration to patients than the free acid because of its enhanced solubility in water (and in plasma) and because of its neutrality. Because of these improved and advantageous physical properties, administration of the combination is more effective in the treatment of pain, inflammation, and overindulgence. In addition, an advantage of the (S)-ibuprofen-(S)-lysine in the combination claimed in the instant invention is that this salt is neutral and not acidic and, therefore, unlike the prior art disclosures of H_2 antagonist and ibuprofen, does not both acerbate and treat stomach conditions simultaneously.

The present invention provides both faster onset and enhanced relief of aches and pains associated with the body, head and stomach to provide broad and concurrent symptomatic relief. The combination with famotidine is especially advantageous since (S)-ibuprofen-lysine does not interfere with the metabolism of famotidine nor does famotidine interfere with the metabolism of alcohol.

DETAILED DESCRIPTION OF THE INVENTION

This invention claims pharmaceutical compositions for use in the treatment of pain and inflammation and the treatment of mild stomach and esophagus disorders including the treatment of heartburn. The composition comprises:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the H_2 antagonists.

This invention is also directed to a method of treating pain and inflammation and concurrently treating indigestion, sour stomach, heartburn, overindulgence and other gastrointestinal disorders in mammals, including humans, in need thereof, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the H_2 antagonists.

This invention is further directed to a method of eliciting an onset hastened and enhanced response for the treatment of pain and inflammation and the treatment of gastrointestinal or esophagus disorders in mammals, including humans, in need thereof, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the H_2 antagonists.

Substantially free of (R)-ibuprofen means that the ratio of (S)-ibuprofen to (R)-ibuprofen is at least 90:10.

Salts of (S)-ibuprofen include pharmaceutically acceptable salts such as alkali metals (sodium or potassium), alkaline earth metals (calcium), or salts with other metals such as magnesium, aluminum, iron, zinc, copper, nickel or cobalt.

Pharmaceutically acceptable salts of (S)-ibuprofen further include the amino acid salts, particularly the basic amino acids such as lysine or arginine. Specifically included within the composition of the instant invention is (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine.

The term mammals or mammalian organism includes but is not limited to man, dog, cat, horse and cow.

The term treatment encompasses the complete range of therapeutically positive effects associated with pharmaceutical medication including reduction of, alleviation of and relief from the symptoms or illness which affect the organism.

(S)-ibuprofen may be prepared following the procedures disclosed in U.S. Patent 4,877,620. Metal salts of ibuprofen may be obtained by contacting a hydroxide, or carbonate with ibuprofen. Amino acid salts of ibuprofen may be obtained by contacting an amino acid in solution with ibuprofen. U.S. Patent No. 4,994,604 describes a process for the formation and resolution of (S)-ibuprofen-(S)-lysine that employs preferential crystallization to separate a pair of diastereomeric salts, (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine. The basic procedure involves (a) contacting (R),(S)-ibuprofen and (S)-lysine in an aqueous-organic solvent mixture; (b) separating any suspended solid from the mixture; and (c) cooling the clear mixture until the mixture is supersaturated with respect to each of the (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine salts; (d) contacting the supersaturated mixture with a slurry of (S)-ibuprofen-(S)-lysine in an aqueous-organic solvent; and (e) separating the formed crystalline (S)-ibuprofen-(S)-lysine.

Specifically, the racemic ibuprofen starting material is mixed with an organic solvent that is miscible with water. The (S)-

lysine is mixed with water and the ibuprofen and lysine solutions are combined.

The mixture is agitated for a time period sufficient to crystallize all the salts, if any, in excess of the solubility limit. The suspended salts are separated to obtain a clear mother liquor which is generally saturated with respect to the diastereomeric salts (S)-ibuprofen-(S)-lysine and (R)-ibuprofen-(S)-lysine. Filtration may be employed to effect the separation. The liquor is then cooled to a temperature at which it is supersaturated with respect to each of the diastereomeric salts. It is preferred that the liquor be cooled to the point at which maximum supersaturation is obtained with respect to each salt without nucleation of either crystallizable species. Typically the temperature of the mother liquor must be lowered by about 5°C to reach maximum supersaturation without precipitation of either salt. However, the degree of cooling will depend on the particular solvent composition. The supersaturated liquor is then passed into a vessel containing a slurry of (S)-ibuprofen-(S)-lysine, hereafter referred to as the (S,S) salt, in the same solvent system employed above for the mixture of racemic ibuprofen and (S)-lysine. In the presence of the (S,S) salt crystals acting as a seed, the supersaturation of the (S,S)-salt in the feed liquor is released by the growth of further crystals of the (S,S)-salt. Conversely, there is little or no change in the (R)-ibuprofen-(S)-lysine supersaturation because the growth rate of the (R,S) crystals is essentially zero in the absence of any initial (R,S) salt seed. The (S,S) crystals are then separated by filtration or centrifugation and washed with aqueous-organic solvent to yield (S)-ibuprofen-(S)-lysine of purity approximating 98%.

The pharmaceutical compositions of the present invention are useful in the rapid and enhanced treatment of pain and inflammation and in the treatment of various mild gastrointestinal disorders including indigestion, sour stomach, overindulgence and heartburn. In particular, the (S)-ibuprofen-(S)-lysine combined with an H_2 antagonist such as famotidine is useful for the treatment of pain, inflammation, and the various gastrointestinal disorders such as indigestion, sour stomach, or

heartburn. The utilization of (S)-ibuprofen and in particular (S)-ibuprofen-(S)-lysine in an analgesic/H_2 antagonist combination offers significant advantages over the combination of racemic ibuprofen and an H_2 antagonist or (S)-ibuprofen and an H_2 antagonist.

(S)-ibuprofen and in particular the (S)-lysine salt of (S)-ibuprofen provides a faster onset of pain and inflammation relief and an enhanced degree of relief compared to racemic ibuprofen. These benefits contribute to overall enhanced and faster relief of symptoms associated with headaches and other aches and pains that often accompany gastrointestinal disorders and overindulgence when the (S)-ibuprofen-(S)-lysine is combined with an H_2 antagonist such as famotidine.

The absence or reduction of (R)-ibuprofen also provides significant benefits. The allergic contraindications sometimes associated with ibuprofen administration are absent or reduced in a (R)-ibuprofen-free or substantially-free composition. An additional advantage may be that less metabolic energy will be used to convert the inactive (R)-ibuprofen to the active (S)-ibuprofen. In addition, a reduced burden may be placed on the urogenital system since administration of the pure (S)-ibuprofen eliminates the need to excrete the (R)-ibuprofen or its metabolites. The absence of the (R)-enantiomer also reduces or eliminates the incorporation of this molecule into fatty tissue. The renal burden and renal toxicities sometimes associated with racemic ibuprofen therapy may be reduced or eliminated in a (S)-ibuprofen composition that is substantially free of the (R) enantiomer.

H_2 antagonists are well known in the treatment of ulcers and other gastrointestinal disorders and may be used in combination with (S)-ibuprofen-(S)-lysine. H_2 antagonists used for ulcer therapy fall into four major structural classes: imidazole derivatives; substituted furans; aminoalkylphenoxy derivatives and guanidinothiazole compounds. Famotidine (N'-(aminosulfonyl)-3-[[[2-[(diamino-methylene)amino]-4-thiazolyl]methyl]thio] propanimidamide), a member of the latter class, is a competitive inhibitor of histamine H_2-receptors and its primary pharmacological activity is the inhibition of

gastric acid secretion. Famotidine suppresses both the acid concentration and the volume of gastric acid secretion. Famotidine is well tolerated and has minimal side effects and thus advantageously may be used in the present invention in combination with (S)-ibuprofen-(S)-lysine. Famotidine is also the most potent and selective H_2 antagonist. The combination of famotidine and (S)-ibuprofen-(S)-lysine provides a combination which simultaneously and selectively provides relief from headaches, pain, inflammation, and discomfort and injury to the stomach, esophagus, or duodenum from excess production of gastric acid. Furthermore, famotidine may not interact with alcohol so that it may be administered prior to or during ingestion of meals or beverages which contain alcohol. The combination of (S)-ibuprofen-(S)-lysine with famotidine provides rapid and enhanced relief of pain while also providing long acting relief from and treatment of gastrointestinal disorders associated with gastric acid secretion.

The absence of inactive enantiomers, particularly (R)-ibuprofen provides for significant size and weight advantages in a combination dosage form, particularly a sustained release dosage form. Where a sustained release dosage of ibuprofen may have required 800 to 1000 mg, the employment of (S)-ibuprofen-(S)-lysine reduces the weight to 400 to 500 mg, and provides for a more practical size tablet for an ibuprofen/H_2 antagonist combination. In particular, the combination of famotidine which is a highly potent H_2 antagonist with (S)-ibuprofen-(S)-lysine reduces the size and weight of all pharmaceutical delivery forms or combination formulations and therefore improves patient compliance or tolerance. The tablet or capsule form of this combination is more readily swallowable by patients in need of treatment thereof.

An effective amount of (S)-ibuprofen, or a salt thereof, for use in a unit dose composition of this invention may range from 50-800 mg of (S)-ibuprofen equivalents. The preferred amount of (S)-ibuprofen is about 100 to 400 mg. The amount of a salt such as (S)-ibuprofen-(S)-lysine is determined based on the amount of (S)-ibuprofen contained therein.

The H_2 antagonist employed herein may be selected from any of the commercially available or known H_2 antagonists such as cimetidine, ranitidine, roxatidine, nizatidine or famotidine. Famotidine is advantageously used in the present invention in combination with (S)-ibuprofen-(S)-lysine. The amount of famotidine used in the present invention in humans may range from 2.5 mg/day to 40 mg/day. Advantageously, 2.5 to 20 mgs/day is administered in combination with 100 to 400 mg of (S)-ibuprofen-(S)-lysine. The combination claimed in the instant invention is advantageously administered orally. However, in patients with hypersecretory conditions, intractable ulcers, or in patients who are unable to take oral medication, the claimed combination may be administered intravenously in a suitable dosage within the limits described for oral treatment.

The present composition may be administered in the form of tablets, caplets, gelcaps, capsules, elixirs, syrups, or suspensions. For oral administration, the active ingredients may be admixed with a pharmaceutically acceptable diluent such as lactose, sucrose, cellulose, dicalcium phosphate, calcium sulfate, mannitol, and, in a liquid composition, ethyl alcohol. Acceptable emulsifying or suspending agents such as PVP, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, guar gum, agar, bentonite, carboxymethylcellulose sodium, polyethylene glycol and waxes, may also be admixed with the active components. Where necessary, lubricants such as magnesium stearic acid talc or magnesium stearate, and disintegrators or superdisintegrators such as starch, sodium starch glycolate or cross-linked PVP may also be included. Electrolytes such as dicalcium phosphate, sodium benzoate, sodium acetate and sodium chloride may also be used.

The active components may also be formulated in sustained release or effervescent formulations. These formulations depending upon whether they are sustained release or effervescent may be employed in oral, dermal, rectal or vaginal administrations. The sustained release formulations also include layered formulations which

provide for distinct release ratio and thus may be more effective in allowing for short and long term relief.

The following examples illustrate the compositions of the present invention which may be readily prepared and as such are not to be considered as limiting the invention set forth in the claims.

EXAMPLE 1

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	40 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 2

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	20 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 3

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	15 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 4

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	10 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 5

(S)-Ibuprofen lysine/famotidine Tablet

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	5 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg

EXAMPLE 6

(S)-Ibuprofen lysine/famotidine Sustained Release

(S)-ibuprofen-(S)-lysine	400 mg
famotidine	40 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg

EXAMPLE 7

(S)-Ibuprofen (S)-lysine/famotidine Sustained Release

(S)-ibuprofen-(S)-lysine	400 mg
famotidine	20 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg

EXAMPLE 8

(S)-Ibuprofen-(S)-lysine/famotidine Solution

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	10 mg
g.s. syrup	5 ml

EXAMPLE 9

(S)-Ibuprofen-(S)-lysine/famotidine Solution

(S)-ibuprofen-(S)-lysine	342 mg
famotidine	20 mg
g.s. syrup	5 ml

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the treatment of pain and inflammation and the treatment of gastrointestinal disorders such as indigestion, sour stomach, overindulgence and heartburn in a mammals, including humans comprising:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in the relief of gastrointestinal disorders and in inhibition of gastric acid secretion of an H_2 receptor antagonist.

2. The composition of Claim 1 wherein the ibuprofen is present as (S)-ibuprofen-(S)-lysine.

3. The composition of Claim 1 comprising at least 50 mg of (S)-ibuprofen-(S)-lysine.

4. The composition of Claim 1 wherein the H_2 antagonist is selected from: cimetidine, ranitidine, roxatidine, nizatidine or famotidine or a pharmaceutically acceptable salt thereof.

5. The composition of claim 4 wherein the H_2 antagonist is famotidine.

6. The composition of claim 5 comprising between 5 mg to 40 mgs of famotidine.

7. A method of treating pain and inflammation and treating gastrointestinal disorders such as indigestion, sour stomach, overindulgence and heartburn in a mammalian organism in need of such treatment, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in the treatment of gastrointestinal disorders or associated symptoms of at least one of the H_2 antagonists.

8. A method according to Claim 7 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

9. A method of eliciting an onset enhanced and hastened response for the treatment and prevention of pain and inflammation and the treatment of gastrointestinal disorders such as indigestion, sour stomach, symptoms associated with overindulgence and heartburn in a mammalian organism in need of such treatment, comprising administering to such organism:

(i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and

(ii) an amount effective in the treatment of gastrointestinal disorders or associated symptoms of at least one of the H_2 antagonists.

10. A method according to claim 9 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

11. A method of reducing the side effects associated with the administration of an ibuprofen/H_2 antagonist combination which comprises the administration of (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and at least one of the H_2 antagonists.

12. A method according to Claim 11 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

13. A method of reducing the size and weight of a pharmaceutically effective amount of an ibuprofen/H_2 antagonist combination dosage form which comprises combining (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and at least one of the H_2 antagonists.

14. A method according to Claim 13 wherein the composition administered to a mammalian organism in need thereof comprises:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;

(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

15. A method of treating gastrointestinal disorders, overindulgence and pain before or during ingestion of a meal accompanied by alcoholic beverages, comprising:
administration of a combination of (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine and (ii) famotidine wherein the famotidine does not interact with ethanol from the ingestion of the alcoholic beverage.

16. A method according to Claim 15 wherein the composition administered to a mammalian organism in need thereof comprises:
(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;
(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

17. A method of providing rapid relief of pain and inflammation with (i) an analgesically and anti-inflammatory effective amount of a salt of (S)-ibuprofen substantially free of (R)-ibuprofen wherein the salt is selected from (S)-ibuprofen-(S)-lysine and (S)-ibuprofen-(R)-lysine; and providing long lasting relief of gastrointestinal disorders associated with the secretion of gastric acid with a pharmaceutically effective amount of famotidine.

18. A method according to Claim 17 wherein the composition administered to a mammalian organism in need thereof comprises:
(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen-(S)-lysine;
(ii) an amount effective in the inhibition of gastric acid secretion of famotidine.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 49/00, 31/445, 31/425, 31/415, 31/34
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/10; 514/331 370, 400, 471

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,994,604 (Tung et al.) 19 February 1991, see Abstract and column 1, lines 10-25.	1-18
Y	US, A, 5,009,895 (Lui) 23 April 1991, see column 2, lines 20-27.	1-18
Y	GB, A, 2,105,193 (Marriott et al.) 23 March 1983, see page 1, lines 5-27.	1-18
Y	EP, A, 426,479 (Goldman et al.) 08 May 1991, see Abstract.	1-18

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

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(54) Title: OPTICALLY PURE SALTS OF PYRIDINYLMETHYL SULFINYL-IH-BENZIMIDAZOLE COMPOUNDS

(57) Abstract

The novel optically pure compounds Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

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Optically pure salts of pyridinylmethyl sulfinyl-IH-benzimidazole compounds.

Field of the invention

The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

Background of the invention

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application

this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralisation will create heat which will be difficult to handle in large scale production.

The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

There is no example known in the prior art of any isolated or characterized salt of optically pure omeprazole, i.e. single enantiomers of omeprazole neither of any isolated or characterized salt of any optically pure omeprazole analogue.

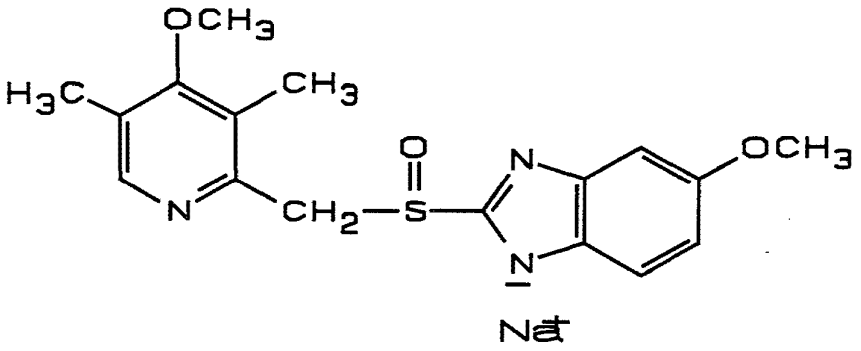
Detailed description of the invention

The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1-4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms.

Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

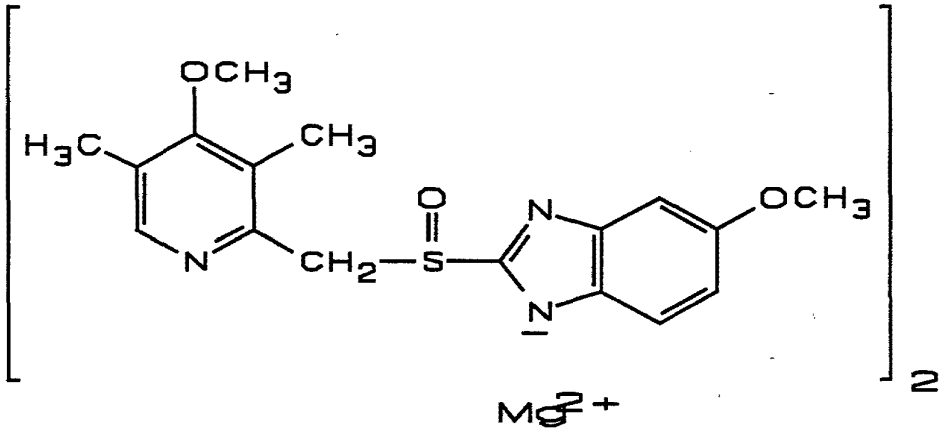


(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb



(IIa, IIb)

IIa (+)-enantiomer

IIb (-)-enantiomer

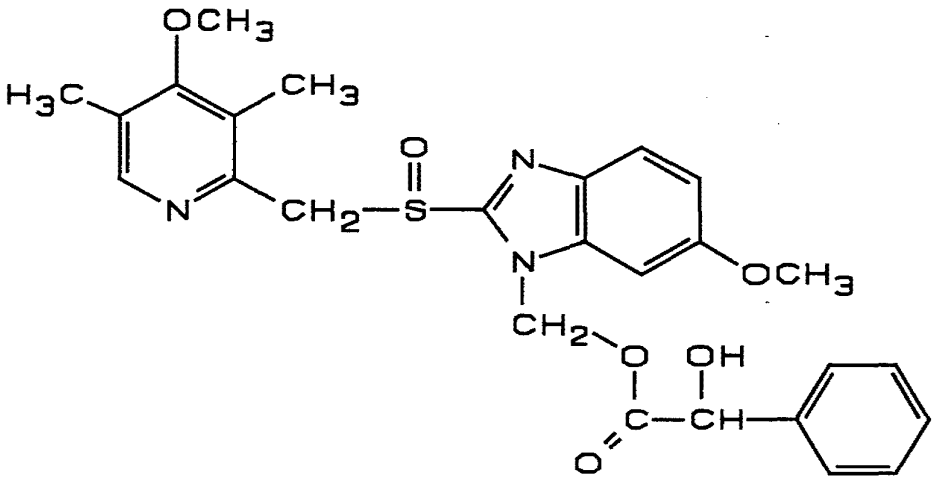
With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole, the salts defined by the present invention are easy to obtain. In addition, the salts, however not the neutral forms, are obtained as crystalline products. Because it is possible to purify optically impure salts of the enantiomers of omeprazole by crystallisation, they can be obtained in very high optical purity, namely ≥99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable towards racemization both in neutral pH and basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was expected to cause racemization under alkaline conditions. This high stability towards racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

The specific method of preparation of the single enantiomers of omeprazole is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomers of omeprazole in neutral from as well as the salts thereof.

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with accute upper gastrointestinal bleeding. They may also be used

in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

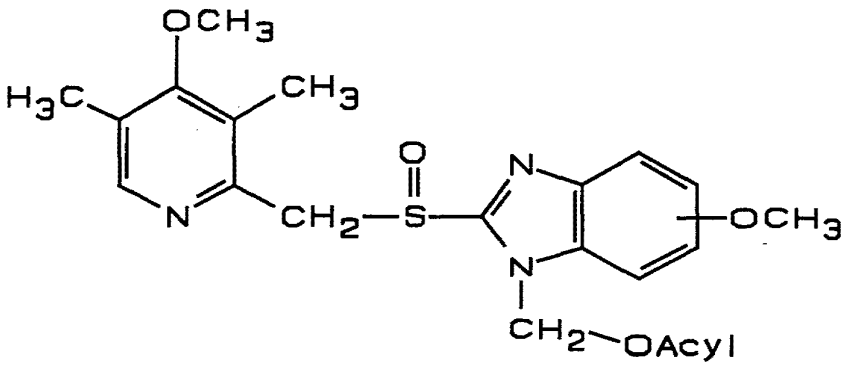
Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.



(III)

Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



(IV)

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

The diastereomeric esters can be separated either by chromatography or fractional crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

To obtain the optically pure Na^+ salts of the invention, i.e. the single enantiomers of omeprazole Na^+ salts, the resulting compound is treated with a base, such as

NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with $NaNH_2$. Also alkaline salts wherein the cation is Li^+ or K^+ may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

To obtain the optically pure Mg^{2+} salts of the invention, optically pure Na^+ salts are treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compound IIa and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+(R)_4$, where R is an alkyl with 1-4 C-atoms.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for

parenteral use and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These soultions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$= +42,8° (c=0.5%, water).

NMR data are given below.

Example 2. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247-249°C.

The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$= -44.1° (c=0.5%, water).

NMR data are given below.

Example 3. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off. A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$= +101.2° (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

Example 4. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2xH_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by

chromatography on an analytical chiral column. $[\alpha]_D^{20}$= +129.9° (c=1%, methanol).

Example 5. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2xH_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$= -128.2° (c=1%, methanol).

Table 1

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
2.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

Preparation of the synthetic intermediates according to the invention will be described in the following examples.

Example 6. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

NMR data are given below.

Example 7. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 6 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na_2SO_4 and

evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

NMR data are given below.

Example 8. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 6. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

Example 9. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 7. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a

pure state as a colourless syrup.

NMR data are given below.

Example 10. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$= -155° (c=0.5%, chloroform).

NMR data are given below

Example 11. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxid in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and

25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 µl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}$= +157° (c=0.5%, chloroform).

NMR data are given below

Table 2.

Ex.	Solvent	NMR data δ ppm
6.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
7.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
8.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d,

1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).

9. $CDCl_3$ 500 MHz — 2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).

10. $CDCl_3$ 300 MHz — 2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).

11. $CDCl_3$ — 2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.20 (s, 1H).

The best mode of carrying out the invention known at present is to use the sodium salts of the optically pure compounds of the invention, thus the compounds described in Example 1 and Example 2.

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 2	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g

Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 3 as Mg salt	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to Example 3, powder, was mixed with lactose and

granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcolhol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^{R}, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to Example 1	300 g

Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 2	4 g
Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Stability towards racemization at different pH:es

The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations in refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ($c=10^{-5}M$) was warmed for 26 hours at 37°C without any racemization at all being observed.