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(54) Title: NOVEL METHOD FOR PREPARATION OF AMMONIUM SALTS OF ESOMEPRAZOLE

(57) Abstract: The present invention relates to a process for the preparation of quartenary ammoniumsalts of esomeprazole. Further, the present invention also relates to the use quartenary ammoniumsalts of esomeprazole for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them as well as the quartenary ammoniumsalts of esomeprazole, as such.

Novel method for preparation of ammonium salts of esomeprazole

Field of the invention

The present invention relates to a process for synthesis of salts of (*S*)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole (esomeprazole), in a pure and isolated form.

Background of the invention and prior art

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 0 005 129.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulphur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the *R*- and *S*-enantiomer of omeprazole, herein referred to as *R*-omeprazole and *S*-omeprazole, the latter have the generic name esomeprazole. The absolute configuration of the enantiomers of omeprazole has been determined by an X-ray study of an N-alkylated derivate of the *R*-enantiomer.

Omeprazole and esomeprazole are proton pump inhibitors, and are useful as antiulcer agents. In a more general sense, omeprazole and esomeprazole may be used for prevention and treatment of gastric acid related diseases in mammals and especially in man.
Specific alkaline salts of omeprazole are disclosed in EP 0 124 495. Herein, quaternary ammonium salts and guanidine salts of omeprazole are disclosed. Document WO 97/41114 discloses processes for preparing magnesium salt of benzimidazoles, including magnesium salt of omeprazole.

Certain salts of the single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988, for instance, quaternary ammonium salts of esomeprazole are mentioned.

The described salts of esomeprazole have improved pharmacokinetic and metabolic properties, which will give an improved therapeutic profile such as a lower degree of interindividual variation. WO 96/02535 and WO 98/54171 disclose preferred processes for preparing esomeprazole and salts thereof.

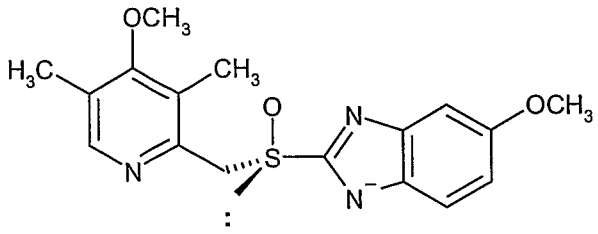
In the formulation of drug compositions, it is important for the active pharmaceutical ingredient to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations (e.g. oral dosage forms such as tablets) comprising the active pharmaceutical ingredient.

Further, in the manufacture of oral pharmaceutical compositions, it is important that a reliable, reproducible and constant plasma concentration profile of the active pharmaceutical ingredient is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active pharmaceutical ingredient are important properties for a pharmaceutical active compound. The active pharmaceutical ingredient, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the physico-chemical characteristics of the active pharmaceutical ingredient, e.g. its chemical composition, density, hygroscopicity and solubility.

Description of the invention

The present invention refers to a process for preparing a quartenary ammonium salt of esomeprazole of formula I



$N^+R^1R^2R^3R^4$

wherein I

R_1, R_2, R_3 and R_4 are individually selected from

(A) C_1-C_{14} alkyl group, which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O-, C_3-C_{12} cycloalkyl (which cycloalkyl is optionally substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, oxo, $R_{23a}OC(O)$- , $(R_{23b})(R_{23c})NC(O)$-, $R_{23d}C(O)N(R_{23e})$-, $R_{23f}C(O)O$-, $R_{23g}OC(O)$-NH-, $(R_{23h})(R_{23j})NC(O)O$-), aryl or Het^1 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, -CH_2OH, halogen, oxo, nitro, C_1-C_7 alkoxy, $R_{24a}OC(O)$- , $(R_{24b})(R_{24c})NC(O)$-, $R_{24d}C(O)N(R_{24e})$-, $R_{24f}C(O)O$-, $R_{24g}OC(O)$-NH-, $(R_{24h})(R_{24j})NC(O)O$-, aryl, Het^3 or $R_{25}C(O)$- (which aryl and Het^3 are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy, nitro); R_6 -O-$(CH_2)_m$ -O-, $R_{7a}OC(O)$-, $(R_{7b})(R_{7c})NC(O)$-, $R_{7d}C(O)N(R_{7e})$-, $R_{7f}C(O)O$- , $R_{7g}C(O)S$-, $R_{7h}OC(O)N(R_{7j})$-, $(R_{7k})(R_{7l})NC(O)O$-, $R_{7m}OC(O)O$-, R_8-SO_2-NH-, phtalimido, succinimido, $R_9C(O)$-, R_{10}-$(CH_2)_n$- C(O)- or $(R_{11a})(R_{11b})(R_{11c})$C-C(O)O- ;

(B) aryl or Het^2 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{12a}OC(O)$- , $(R_{12b})(R_{12c})NC(O)$-, $R_{12d}C(O)N(R_{12e})$-, $R_{12f}C(O)O$- , $R_{12g}OC(O)NR_{12h}$-, $(R_{12j})(R_{12k})NC(O)O$-, aryl, benzoyl or Het^4), $R_{13}C(O)$- or $(R_{14a})(R_{14b})N$-);

or R_1 and R_2 together may represent a cyclic structure containing 5-14 members, optionally substituted by one or more groups selected from hydroxy, oxo, C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from hydroxy, halogen, aryl or Het^7), $R_{15}O$-, $R_{16a}OC(O)$-, $(R_{16b})(R_{16c})NC(O)$-, $R_{16d}C(O)N(R_{16e})$-, $R_{16f}C(O)O$-, $R_{16g}OC(O)NR_{16h}$-, $(R_{16j})(R_{16k})NC(O)O$-, $R_{17}C(O)$-, aryl or Het^5 (which aryl or Het^5 are optionally substituted by one or more of C_1-C_7 alkyl, hydroxy, oxo, C_1-C_7 alkoxy, halogen, $R_{26a}OC(O)$- , $(R_{26b})(R_{26c})NC(O)$-, $R_{26d}C(O)N(R_{26e})$-, $R_{26f}C(O)O$-, $R_{26g}OC(O)NH$-, $(R_{26h})(R_{26j})NC(O)O$- , phenyl or benzoyl (which phenyl or benzoyl are optionally substituted by one or two halogens or C_1-C_5 alkyl C(O)O-)), phtalimido, succinimido or $(R_{18a})(R_{18b})(R_{18c})C$-C(O)O-;

or R_1, R_2 and R_3 together may represent a cyclic structure containing 5-16 members, optionally substituted by one or more groups selected from hydroxy, oxo, C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from hydroxy, halogen, oxo, aryl or Het^8), $R_{19}O$-, $R_{20}C(O)$-, aryl or Het^6 (which aryl or Het^6 are optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, oxo, $R_{27a}OC(O)$- , $(R_{27b})(R_{27c})NC(O)$-, $R_{27d}C(O)N(R_{27e})$-, $R_{27f}C(O)O$- , $R_{27g}OC(O)$-NH-, $(R_{27h})(R_{27j})NC(O)O$-, phenyl or benzoyl), $R_{21a}OC(O)$- , $(R_{21b})(R_{21c})NC(O)$-, $R_{21d}C(O)N(R_{21e})$-, $R_{21f}C(O)O$- , $R_{21g}OC(O)$-NR_{21h}-, $(R_{21j})(R_{21k})NC(O)O$-, phtalimido, succinimido or $(R_{22a})(R_{22b})(R_{22c})$ C-C(O)O-;

wherein

R_5 is selected from C_1-C_6 alkyl, aryl, Het^9 (which groups are optionally substituted by one or more groups selected from hydroxy, halogen, C_1-C_6 alkoxy);

R_6 is selected from aryl or Het^{10} (both groups optionally substituted by one or more groups selected from C_1-C_8 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{28a}OC(O)$-,

(R_{28b})(R_{28c})NC(O)-, R_{28d}C(O)N(R_{28e})-, R_{28f}C(O)O- , R_{28g}OC(O)-NH-, (R_{28h})(R_{28j})NC(O)O- , aryl, benzoyl or Het^{11});

R_{7a} to R_{7m} are independently selected, at each occurrence, from hydrogen, C_1-C_7 alkyl, aryl or Het^{12} (which C_1-C_7 alkyl, aryl and Het^{12} are optionally substituted by one or more groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, R_{29a}OC(O)- , (R_{29b})(R_{29c})NC(O)-, R_{29d}C(O)N(R_{29e})-, R_{29f}C(O)O- , R_{29g}OC(O)-NH-, (R_{29h})(R_{29j})NC(O)O-, aryl, benzoyl or Het^{13});

R_8 is selected from C_1-C_6 alkyl, aryl or Het^{14} (which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl);

R_9 is selected from linear or branched C_1 – C_{12} alkyl (optionally substituted by R_{30}OC(O)-), C_3-C_{12} cycloalkyl (which cycloalkyl group is optionally further substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, R_{31a}OC(O)-, (R_{31b})(R_{31c})NC(O)-, R_{31d}C(O)NR_{31e}-, R_{31f}C(O)O-, R_{31g}C(O)N(R_{31h})-, (R_{31j})(R_{31k})NC(O)O-), aryl, benzoyl or Het^{15}), aryl or Het^{16} (which aryl and Het^{16} are optionally substituted by one to three of the groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, ethylenedioxy, halogen, R_{32a}OC(O)-, (R_{32b})(R_{32c})NC(O)-, R_{32d}C(O)NR_{32e}-, R_{32f}C(O)O-, R_{32g}OC(O)NH-, (R_{32h})(R_{32j})NC(O)O-) , aryl, benzoyl or Het^{17});

R_{10} is selected from aryl and Het^{18} (which groups are optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, -COOH, ethylenedioxy);

R_{11a} is selected from hydroxy or –CH_2OH;

R_{11b} is phenyl (optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, R_{33a}OC(O)- , (R_{33b})(R_{33c})NC(O)-, R_{33d}C(O)N(R_{33e})-, R_{33f}C(O)O- , R_{33g}OC(O)-NH-, (R_{33h})(R_{33j})NC(O)O-;

R_{11c} is selected from hydrogen, C_5-C_6 cycloalkyl or phenyl (which groups are optionally substituted by one to three groups selected from C_1-C_3alkyl, hydroxy, C_1-C_3alkoxy, halogen, $R_{34a}OC(O)$- , $(R_{34b})(R_{34c})NC(O)$-, $R_{34d}C(O)N(R_{34e})$-, $R_{34f}C(O)O$- , $R_{34g}OC(O)NH$-, $(R_{34h})(R_{34j})NC(O)O$-);

R_{12a} to R_{12k} are independently selected, at each occurrence, from hydrogen, C_1-C_7alkyl, aryl, Het^{19} (which groups are optionally substituted by one or more groups selected from C_1-C_6alkyl, hydroxy, C_1-C_3alkoxy, halogen, $R_{35a}OC(O)$- , $(R_{35b})(R_{35c})NC(O)$-, $R_{35d}C(O)N(R_{35e})$-, $R_{35f}C(O)O$- , $R_{35g}OC(O)$-NH-, $(R_{35h})(R_{35j})NC(O)O$-, aryl, benzoyl or Het^{20});

R_{13} is selected from hydrogen or C_1-C_6 alkyl;

R_{14a} to R_{14b} are independently selected, at each occurrence, from hydrogen or C_1-C_6 alkyl;

R_{15} is selected from C_1-C_6 alkyl, aryl or Het^{21} (which groups are optionally substituted by one or more groups selected from hydroxy, halogen or C_1-C_6 alkoxy);

R_{16a} to R_{16k} are independently selected from, at each occurrence, hydrogen, C_1-C_7 alkyl, aryl or Het^{22} (which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{36a}OC(O)$- , $(R_{36b})(R_{36c})NC(O)$-, $R_{36d}C(O)N(R_{36e})$-, $R_{36f}C(O)O$- , $R_{36g}OC(O)$-NH-, $(R_{36h})(R_{36j})NC(O)O$-, aryl, benzoyl or Het^{23});

R_{17} is selected from hydrogen or C_1-C_6 alkyl;

R_{18a} is selected from hydroxy or $-CH_2OH$;

R_{18b} is phenyl (optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{37a}OC(O)$-, $(R_{37b})(R_{37c})NC(O)$-, $R_{37d}C(O)N(R_{37e})$-, $R_{37f}C(O)O$- , $R_{37g}OC(O)$-NH-, $(R_{37h})(R_{37j})NC(O)O$-);

R_{18c} is selected from hydrogen, C_5-C_6 cycloalkyl or phenyl (which groups are optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{38a}OC(O)$- , $(R_{38b})(R_{38c})NC(O)$-, $R_{38d}C(O)N(R_{38e})$-, $R_{38f}C(O)O$- , $R_{38g}OC(O)$-NH-, $(R_{38h})(R_{38j})NC(O)O$-;

R_{19} is selected from C_1-C_6 alkyl, aryl or Het^{24} (which groups are optionally substituted by one or more groups selected from hydroxy, halogen, C_1-C_6 alkoxy);

R_{20} is selected from hydrogen and C_1-C_6 alkyl;

R_{21a} to R_{21k} are independently selected, at each occurence, from hydrogen, C_1-C_7 alkyl, aryl or Het^{25} (which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{39a}OC(O)$- , $(R_{39b})(R_{39c})NC(O)$-, $R_{39d}C(O)N(R_{39e})$-, $R_{39f}C(O)O$- , $R_{39g}OC(O)$-NH-, $(R_{39h})(R_{39j})NC(O)O$-, aryl, benzoyl or Het^{26});

R_{22a} is selected from hydroxy or $-CH_2OH$;

R_{22b} is phenyl (optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{40a}OC(O)$- , $(R_{40b})(R_{40c})NC(O)$-, $R_{40d}C(O)N(R_{40e})$-, $R_{40f}C(O)O$- , $R_{40g}OC(O)NH$-, $(R_{40h})(R_{40j})NC(O)O$-);

R_{22c} is selected from hydrogen, C_5-C_6 cycloalkyl or phenyl (which optionally is substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{41a}OC(O)$- , $(R_{41b})(R_{41c})NC(O)$-, $R_{41d}C(O)N(R_{41e})$-, $R_{41f}C(O)O$-, $R_{41g}OC(O)NH$-, $(R_{41h})(R_{41j})NC(O)O$-);

R_{23a} to R_{23j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{24a} to R_{24j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{25} is selected from C_1-C_4alkyl, aryl or Het^{27} (which aryl and Het^{27} are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy, nitro);

R_{26a} to R_{26j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{27a} to R_{27j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{28a} to R_{28j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{29a} to R_{29j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{30} is selected from hydrogen or C_1-C_6 alkyl;

R_{31a} to R_{31k} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{32a} to R_{32c} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{33a} to R_{33j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{34a} to R_{34j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{35a} to R_{35j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{36a} to R_{36j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{37a} to R_{37j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{38a} to R_{38j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{39a} to R_{39j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{40a} to R_{40j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

$R_{41a}$to R_{41j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

m is an integer selected from 1 to 5;

n is an integer selected from 1 to 3.

The compound of formula I as defined by formula I is hereby defined as the compound of the invention.

The process for preparing the quaternary ammoniumsalts esomeprazole of formula I comprises the following steps:

(i): mixing esomeprazole and $N^+(R_1)(R_2)(R_3)(R_4)\ X^-$;

wherein R_1, R_2, R_3 and R_4 are as defined above; X^- is selected from Cl^-, Br^-, I^-, carboxylates, sulphonates, HSO_4^- and OH^-;
in an aqueous solvent system substantially saturated with potassium carbonate;

(ii): adding a water immiscible chlorinated hydrocarbon solvent;

(iii): isolating the organic phase;

(iv): recovering of the compound of formula I.

In one embodiment of the invention the reaction of the esomeprazole and the $N^+(R_1)(R_2)(R_3)(R_4)\ X^-$ as defined above is performed in an aqueous solvent solvent substantially saturated with potassium carbonate (K_2CO_3).

By "substantially saturated" it is meant a solution comprising equal or more than 40 % by weight potassium carbonate in an aqueous solvent, for example more than 45, 50 or 55 % by weight.

In one embodiment of the invention, the aqueous solvent system in step (i) is saturated with potassium carbonate, i.e. comprises about 56 % by weight potassium carbonate.

In one embodiment of the invention the esomeprazole and the quartenary ammoniumsalt of formula $N^+(R_1)(R_2)(R_3)(R_4)\ X^-$ are in step (i) added in equimolar amounts.

The aqueous solvent system may be selected from water or water soluble solvents, such as alcohols, ethers, amides, nitriles soluble in water; or mixtures thereof. Examples of water soluble solvents are methanol, ethanol, dioxane, tetrahydrofuran, acetonitril and DMF.

In one embodiment the aqueous solvent system is water.

The water immiscible solvent forming the organic phase are selected from solvents such as chlorinated solvents suitable for phase transfer. The solvent must also be stable in the presence of base, i.e. for the present invention the solvent should not degrade more than to some extent in the presence of the potassium carbonate. Examples of chlorinated solvents are dichloromethane, trichloromethane and 1,2-dichloroethane.

In one embodiment the compound of the invention is a quartenary alkyl ammoniumsalt of esomeprazole of formula I wherein R_1 is selected from

(A) C_1-C_{14} alkyl group, which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O-, C_3-C_{12} cycloalkyl (which cycloalkyl is optionally substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, oxo, $R_{23a}OC(O)$- , $(R_{23b})(R_{23c})NC(O)$-, $R_{23d}C(O)N(R_{23e})$-, $R_{23f}C(O)O$-, $R_{23g}OC(O)$-NH- or $(R_{23h})(R_{23j})NC(O)O$-), aryl or Het^1 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, -CH_2OH, halogen, oxo, nitro, C_1-C_7 alkoxy, $R_{24a}OC(O)$- , $(R_{24b})(R_{24c})NC(O)$-, $R_{24d}C(O)N(R_{24e})$-, $R_{24f}C(O)O$-, $R_{24g}OC(O)$-NH-, $(R_{24h})(R_{24j})NC(O)O$-, aryl, Het^3 or $R_{25}C(O)$- (which aryl and Het^3 are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy, nitro); R_6 -O-$(CH_2)_m$ -O-, $R_{7a}OC(O)$-, $(R_{7b})(R_{7c})NC(O)$-, $R_{7d}C(O)N(R_{7e})$-, $R_{7f}C(O)O$- , $R_{7g}C(O)S$-, $R_{7h}OC(O)N(R_{7j})$-, $(R_{7k})(R_{7l})NC(O)O$-, $R_{7m}OC(O)O$-, R_8-SO_2-NH-, phtalimido, succinimido, $R_9C(O)$-, R_{10}-$(CH_2)_n$- C(O)- or $(R_{11a})(R_{11b})(R_{11c})$C-C(O)O-;

(B) aryl or Het^2 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{12a}OC(O)$- , $(R_{12b})(R_{12c})NC(O)$-, $R_{12d}C(O)N(R_{12e})$-, $R_{12f}C(O)O$- , $R_{12g}OC(O)NR_{12h}$-, $(R_{12j})(R_{12k})NC(O)O$-, aryl, benzoyl or Het^4), $R_{13}C(O)$- or $(R_{14a})(R_{14b})N$-);

R_2, R_3 and R_4 are individually selected from linear or branched C_1-C_{14}alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, phenyl and R_5O-) or aryl.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1, R_2 and R_3 are individually selected from

(A) C_1-C_{14} alkyl group, which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O-, C_3-C_{12} cycloalkyl (which cycloalkyl is optionally substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, oxo, $R_{23a}OC(O)$- , $(R_{23b})(R_{23c})NC(O)$-, $R_{23d}C(O)N(R_{23e})$-, $R_{23f}C(O)O$-, $R_{23g}OC(O)$-NH-, $(R_{23h})(R_{23j})NC(O)O$-), aryl or Het^1 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, -CH_2OH, halogen, oxo, nitro, C_1-C_7 alkoxy, $R_{24a}OC(O)$- , $(R_{24b})(R_{24c})NC(O)$-, $R_{24d}C(O)N(R_{24e})$-, $R_{24f}C(O)O$-, $R_{24g}OC(O)$-NH-, $(R_{24h})(R_{24j})NC(O)O$-, aryl, Het^3 or $R_{25}C(O)$- (which aryl and Het^3 are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy, nitro); R_6 -O-$(CH_2)_m$ -O-, $R_{7a}OC(O)$-, $(R_{7b})(R_{7c})NC(O)$-, $R_{7d}C(O)N(R_{7e})$-, $R_{7f}C(O)O$- , $R_{7g}C(O)S$-, $R_{7h}OC(O)N(R_{7j})$-, $(R_{7k})(R_{7l})NC(O)O$-, $R_{7m}OC(O)O$-, R_8-SO_2-NH-, phtalimido, succinimido, $R_9C(O)$-, R_{10}-$(CH_2)_n$- C(O)- or $(R_{11a})(R_{11b})(R_{11c})$C-C(O)O- ;

(B) aryl or Het^2 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{12a}OC(O)$- , $(R_{12b})(R_{12c})NC(O)$-, $R_{12d}C(O)N(R_{12e})$-, $R_{12f}C(O)O$- , $R_{12g}OC(O)NR_{12h}$-, $(R_{12j})(R_{12k})NC(O)O$-, aryl, benzoyl or Het^4), $R_{13}C(O)$- or $(R_{14a})(R_{14b})N$-); and R_4 is selected from linear or branched C_1-C_6alkyl group.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1, R_2 and R_3 are defined as above and R_4 is methyl.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 and R_2 are individually selected from

(A) C_1-C_{14} alkyl group, which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O-, C_3-C_{12} cycloalkyl (which cycloalkyl is optionally substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, oxo, $R_{23a}OC(O)$- , $(R_{23b})(R_{23c})NC(O)$-, $R_{23d}C(O)N(R_{23e})$-, $R_{23f}C(O)O$-, $R_{23g}OC(O)$-NH-, $(R_{23h})(R_{23j})NC(O)O$-), aryl or Het^1 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, -CH_2OH, halogen, oxo, nitro, C_1-C_7 alkoxy, $R_{24a}OC(O)$- , $(R_{24b})(R_{24c})NC(O)$-, $R_{24d}C(O)N(R_{24e})$-, $R_{24f}C(O)O$-, $R_{24g}OC(O)$-NH-, $(R_{24h})(R_{24j})NC(O)O$-, aryl, Het^3 or $R_{25}C(O)$- (which aryl and Het^3 are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy, nitro); R_6 -O-$(CH_2)_m$ -O-, $R_{7a}OC(O)$-, $(R_{7b})(R_{7c})NC(O)$-, $R_{7d}C(O)N(R_{7e})$-, $R_{7f}C(O)O$- , $R_{7g}C(O)S$-, $R_{7h}OC(O)N(R_{7j})$-, $(R_{7k})(R_{7l})NC(O)O$-, $R_{7m}OC(O)O$-, R_8-SO_2-NH-, phtalimido, succinimido, $R_9C(O)$-, R_{10}-$(CH_2)_n$- C(O)- or $(R_{11a})(R_{11b})(R_{11c})$C-C(O)O- ;

(B) aryl or Het^2 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{12a}OC(O)$- , $(R_{12b})(R_{12c})NC(O)$-, $R_{12d}C(O)N(R_{12e})$-, $R_{12f}C(O)O$- , $R_{12g}OC(O)NR_{12h}$-, $(R_{12j})(R_{12k})NC(O)O$-, aryl, benzoyl or Het^4), $R_{13}C(O)$- or $(R_{14a})(R_{14b})N$-); and R_3 and R_4 are individually selected from, at each occurrence, linear or branched C_1-C_6alkyl group.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 and R_2 are defined as above; and R_3 and R_4 are methyl.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 is as defined above, R_2, R_3 and R_4 are individually selected from, at each occurrence, linear or branched C_1-C_6alkyl group.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 is as defined above, R_2 and R_3 are individually selected from, at each occurrence, linear or branched C_1-C_6alkyl group; and R_4 is methyl.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 is as defined above, R_2 is selected from linear or branched C_1-C_6alkyl group; and R_3 and R_4 are methyl.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 is as defined above, R_2, R_3 and R_4 are methyl.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 is as defined above, R_2, R_3 and R_4 are individually selected from C_1-C_4-alkyl groups.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 and R_2 together may represent a cyclic structure containing 5 to10 members, optionally substituted by on or more groups selected linear or branched C_1-C_5 alkyl group, amino, hydroxy, halogen or R_5O-; R_3 and R_4 are selected from linear or branched C_1-C_4 alkyl group.

In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 is selected from linear or branched C_1-C_8 alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O- or aryl). R_2, R_3 and R_4 are individually selected from linear or branched C_1-C_4alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen or R_5O-) or aryl.

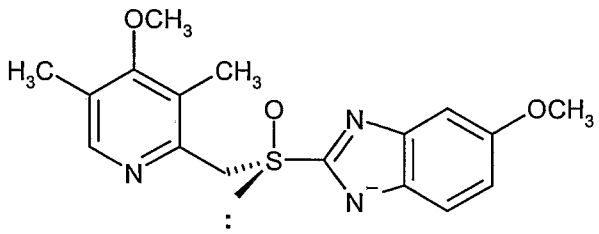
In one embodiment of the invention the compound of the invention is according to formula I wherein R_1 is selected from linear or branched C_1-C_8 alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O- or phenyl). R_2, R_3 and R_4 are individually selected from linear or branched C_1-C_4alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen or R_5O-) or phenyl.

In one embodiment R_1 is selected from linear or branched C_1-C_8 alkyl group, which alkyl group is optionally substituted by one or more groups selected from phenyl, amino, hydroxy, halogen or R_5O-. R_2, R_3 and R_4 are selected from linear or branched C_1-C_4 alkyl group, for example, methyl, ethyl, n-propyl or isopropyl.

In one embodiment R_1 and R_2 together may represent a cyclic structure containing 5 to10 members, optionally substituted by on or more groups selected linear or branched C_1-C_5 alkyl group, amino, hydroxy, halogen or R_5O-. R_3 and R_4 are selected from linear or branched C_1-C_4 alkyl group, for example, methyl, ethyl, n-propyl or isopropyl.

In one embodiment R_1, R_2, R_3 and R_4 are as defined above, provided that R_1, R_2, R_3 and R_4 are not simultaneously C_1 alkyl group (methyl).

In one embodiment of the invention the compound of the invention is quaternary alkyl ammoniumsalt of *S*-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole (esomeprazole) of formula I



$N^+R^1R^2R^3R^4$ I

wherein

R_1, R_2, R_3 and R_4 are as defined in any place in this application, obtainable by the process described above.

Unless otherwise specified, alkyl groups and alkoxy groups as defined herein may be linear or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms be branched, and/or cyclic.

As used herein, the term "C_1-C_{14} alkyl group" is an alkyl group having 1 to 14 carbon atoms. Examples of said group includes, but is not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and dekanyl and when the alkyl is branched, iso-propyl, iso-butyl, sec-butyl, *tert*-butyl, sec-pentyl, iso-pentyl and neo-pentyl.

The term "C_3-C_{12} cycloalkyl" is a cyclic alkyl group having 3 to 12 carbon atoms. The cyclic group may be a mono, di or polycyclic-group, and it may optionally be substituted with 1, 2, or 3 methyl groups. Examples of said cyclic alkyl group includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl.

Unless otherwise specified, the alkyl and alkoxy groups may also be substituted by one or more fluoro atoms. Examples of said substituted alkyl or alkoxy groups are trifluoromethyl, trifluoromethoxy and trifluoroethyl.

Alkylene groups as defined herein are divalent and may be linear or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms, be branched. Unless

otherwise specified, alkylene groups may also be substituted by one or more halogen atoms, and especially fluoro atoms.

The term "aryl", when used herein, includes C_6-C_{10} aryl groups such as phenyl, naphtyl, and the like. Unless otherwise specified, the aryl group may be substituted by one or more substituents including –OH, cyano, nitro, C_1-C_7 alkoxy, C_1-C_7 alkyl, halogen for example fluoro. Examples are phenyl substituted by one, two or three halogens such as fluoro.

Unless otherwise specified the term "benzoyl" also includes benzoyl groups which may be substituted by one or more halogen, for example fluoro.

Het groups (Het^1 to Het^{27}) that may be mentioned include those ring systems having a total number of atoms in the ring system or between five and twelwe atoms and containing 1 to 5 heteroatoms (selected from N, O and S). Het groups may be fully saturated, wholly aromatic, partly aromatic and/or bi- or polycyclic in character. Heterocyclic groups that may be mentioned include benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzimidazolyl, benzomorpholinyl, benzoxazinonyl, benzothiophenyl, chromanyl, cinnolinyl, dioxanyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, indolyl, isoquinolinyl, isoxazolyl, morpholinyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimindinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thienyl, thiochromanyl, triazolyl, xanthanyl and the like. Substituents on Het groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het groups may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system. Het groups may also be in the N- or S-oxidised form. Unless otherwise specified, the Het group may be substituted by one or more substituents including –OH, cyano, nitro, C_1-C_7 alkoxy, C_1-C_7 alkyl, halogen for example fluoro.

The term "halogen", when used herein, includes fluoro, chloro, bromo and iodo.

The phrase "R_1 and R_2 together may represent a cyclic structure containing 5-14 members" means that a mono-, bi-, tri- or polycyclic structure containing 5-14 atoms, of which optionally 1 to 5 are heteroatoms selected from N, O and S is formed. The cyclic structure may contain one or more double bond, and which cyclic structure may have one or more condensed aryl or Het. The cyclic structure may be further substituted. Examples of compounds included are pyrrolidine, piperidine, azepane, piperidone, piperazine, morpholine, tetrahydropyridine, imidazole, imidazoline, isoindoline, tetrahydroisoquinoline, carbazole, 6,7-dihydro-5*H*-dibenzo[c,e]azepine, 8-aza-bicyclo[3,2,1]octane, desmethyltropine, 3-oxa-9-aza-tricyclo[3.3.1.0*2,4*]nonane and desmethylscopine.

The phrase "R_1, R_2 and R_3 together may represent a cyclic structure containing 5-16 members" means that R_1, R_2 and R_3 together form a tri-, tetra- or polycyclic structure containing 5 to 16 atoms, of which optionally 1 to 5 are heteroatoms selected from N, O and S. The cyclic structure may contain one or more double bond, and which cyclic structure may have a condensed aryl or Het and which cyclic structure may optionally be further substituted by one or more groups. Examples of structures included are hexamethylenetetramine and quinuclidine.

The $N^+(R_1)(R_2)(R_3)(R_4)\,X^-$ added in step (i) is defined to be salts of Cl^-, Br^-, I^-, carboxylates, sulphonates, HSO_4^- and OH^-. Examples of carboxylates are aliphatic carboxylic acids, for example C_1-C_6 alkyl carboxylic acid, such as acetic acid and propionic acid; of sulphonates are alkylsulphonates, for example C_1-C_6 alkyl sulphonates such as methane-, ethane- or propanesulphonic acid.

In one embodiment of the invention, the compound of the invention provided by the process above is

tetra-n-butyl ammoniumsalt of esomeprazole;

cholin salt of esomeprazole;

benzyltrimethylammonium salt of esomeprazole;

(1*S*)-N, N, N, trimethyl-1-phenylethylammonium salt of esomeprazole;

(1*R*, 2*S*)-N,N-dimethylephedrinium salt of esomeprazole;

(1*S*, 2*R*)-N,N-dimethylephedrinium salt of esomeprazole;
(1*R*, 2*S*)-N-benzyl-N-methylephedrinium salt of esomeprazole;
(1*S*, 2*R*)-N-benzyl-N-methylephedrinium salt of esomeprazole or
cis-2,6-dimethyl-N,N-dimethylpiperidinium salt of esomeprazole.

Due to tautomerism the chemical name (*S*)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole ammonium salt does not necessarily mean that the methoxy group of the two benzimidazole moieties is in the 5-position but may as well be in the 6-position, or there may be mixtures of the two.

The compounds of the invention may be prepared in the form of solvates, hydrates, and anhydrates.

The esomeprazole mixed in step (i) of the process of the invention is the neutral form esomeprazole, or the sodium salt or potassium salt of esomeprazole.

The process of the present invention is advantageous because of its simplicity. The process of the present of invention is defined by increased ease of handling including improved phase separation in step (iii) and an inherent drying off effect. During a phase transfer, most often a small amount of water remains in the organic phase. However, the presence of potassium carbonate in the present process reduces or even eliminates the remaining parts of aqueous solvent system in the organic phase, and thus also the need for a following drying step. It further gives products of high purity.

The compounds of the present invention are effective as gastric acid secretion inhibitors, and are thus useful as antiulcer agents. In a more general sense, they can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. They may also be used in patients in intensive

care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid, to prevent and treat stress ulceration and asthma, and for improvement of sleep. Further, the compounds of the invention may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and related diseases. The compounds of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the quartenary ammoniumsalt of esomeprazole. For example, peroral or parenteral formulations, including i.v., and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions, solutions and the like.

It is further provided a pharmaceutical composition comprising the compounds of the present invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other active pharmaceutical ingredients. Compositions comprising other therapeutic ingredients are of interest in the treatment of the conditions listed above. The invention also provides the use of the compounds of the invention in the manufacture of a medicament for use in said conditions as well as a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a pharmaceutically effective amount of the compounds of the invention.

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of galenic pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of the therapeutic dose will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are

somewhat lower than average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long-term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

In general, a suitable oral dosage form of the compound of the invention may cover a dose range from 5 mg to 300 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 10 mg to 80 mg.

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 0 247 983, the disclosures of which are hereby as a whole included by reference.

Combination preparations comprising the compounds of the invention and other active ingredients may also be used. Examples of such active ingredients include, but are not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

The compounds of the invention may be further processed before formulation into a suitable pharmaceutical formulation.

For the avoidance of doubt, "treatment" includes the therapeutic treatment, as well as the prophylaxis, of a condition.

Examples

The examples below will further illustrate the preparation of the compound of the invention. These examples are not intended to limit the scope if the invention as defined hereinabove or as claimed below.

The quaternary ammoniumsalt of formula $N^{+}(R_1)(R_2)(R_3)(R_4)Cl^{-}$ as defined above may be commercially available or otherwise synthesized according to the methods described below in Example A to Example F.

Example A

Preparation of (1*S*)-N,N,N- trimethyl-1-phenethylammonium chloride

(1S)-N,N-dimethyl-1-phenetylamine (0.61g, (4 mmol)) was dissolved in acetone (20ml) and methyl iodide (2g (14 mmol)) was added. The flask was sealed and the mixture was left over night at ambient temperature before it was diluted with diethyl ether (50 ml). The crystalline salt was filtered off and washed with diethyl ether. The quarternary ammonium iodide was dissolved in water (deionised) and the solution was filtered through an anion exchanger (50ml Amberlite IRA-400; 20-50 mesh; Cl^-- form) and eluted with deionized water. The eluate was concentrated to ca 20 ml at reduced pressure and freeze drying gave 600 mg (3 mmol) of crystalline (1S)-N,N,N- trimethyl-1-phenetylammonium chloride.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.59 (m, 1H), 7.43 (m, 3H), 5.33 (q, 2H), 3.34 (s, 9H), 1.81 (δ, 3H).

Example B

Preparation of (1*R*, 2*S*)-N,N-dimethylephedrinium chloride

(1*R*,2*S*)-N-methylephedrin (0.72g, (4 mmol)) was dissolved in acetone (20ml) and methyl iodide (2g (14 mmol)) was added. The flask was sealed and the mixture was left over night at ambient temperature before it was diluted with diethyl ether (50 ml). The crystalline salt was filtered off and washed with diethyl ether. The quarternary ammonium iodide was dissolved in water (deionised) and the solution was filtered through an anion exchanger (50ml Amberlite IRA-400; 20-50 mesh; Cl^-- form) and eluted with deionized water. The eluate was concentrated to ca 20 ml at reduced pressure and freeze drying gave 685 mg (3 mmol) of crystalline (1R,2S)-N,N- dimethylephedrinium chloride.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.27 (m, 2H), 7.22 (m, 2H), 5.42 (s, 1H), 3.46 (m, 1H), 3.19 (m, 1H), 3.16 (s, 9H), 1.08 (m, 3H).

Example C

Preparation of (1*S*, 2*R*)-N,N-dimethylephedrinium chloride

(1*S*, 2*R*)-N-methylephedrin (0.72g, (4 mmol)) was dissolved in acetone (20ml) and methyl iodide (2g (14 mmol)) was added. The flask was sealed and the mixture was left over night at ambient temperature before it was diluted with diethyl ether (50 ml). The crystalline salt was filtered off and washed with diethyl ether. The quarternary ammonium iodide was dissolved in water (deionised) and the solution was filtered through an anion exchanger (50ml Amberlite IRA-400; 20-50 mesh; Cl^--form) and eluted with deionized water. The eluate was concentrated to ca 20 ml at reduced pressure and freeze drying gave 850 mg (3.7 mmol) of crystalline (1S,2R)-N,N- dimethylephedrinium chloride.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.27 (m, 2H), 7.22 (m, 2H), 5.42 (s, 1H), 3.46 (m, 1H), 3.19 (m, 1H), 3.16 (s, 9H), 1.08 (m, 3H).

Example D

Preparation of (1*R*, 2*S*)-N-benzyl-N-methylephedrinium bromide

(1*R*,2*S*)-N-methylephedrin (0.5 g, (2.79 mmol)) was dissolved in dimethoxyethane (5ml) and benzyl bromide (0.6 g (3.5 mmol)) was added. The flask was sealed and the mixture was left over night at ambient temperature before it was diluted with diethyl ether (10 ml). The crystalline salt was filtered off and washed with diethyl ether. Air drying at room temperature gave 0.74 g (2.11 mmol) of the title compound.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.60 (d, 2H), 7.40 (bm, 5H), 7.19 (m, 2H), 7.12 (m, 1H), 5.95 (d, 1H), 5.37 (d, 1H), 5.20 (d, 1H), 4.91 (d, 1H), 3.98 (q, 1H), 3.30 (s, 3H), 3.19 (s, 3H), 1.24 (d, 3H).

Example E

Preparation of (1*S*, 2*R*)-N-benzyl-N-methylephedrinium bromide

(1*S*,2*R*)-N-methylephedrin (0.5 g, (2.79 mmol)) was dissolved in dimethoxyethane (5ml) and benzyl bromide (0.6 g (3.5 mmol)) was added. The flask was sealed and the mixture was left over night at ambient temperature before it was diluted with diethyl ether (10 ml). The crystalline salt was filtered off and washed with diethyl ether. Air drying at room temperature gave 0.75 g (2.14 mmol) of the title compound.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.60 (d, 2H), 7.40 (bm, 5H), 7.19 (m, 2H), 7.12 (m, 1H), 5.95 (d, 1H), 5.37 (d, 1H), 5.20 (d, 1H), 4.91 (d, 1H), 3.98 (q, 1H), 3.30 (s, 3H), 3.19 (s, 3H), 1.24 (d, 3H).

Example F

Preparation of cis-2,6-dimethyl-N,N-dimethylpiperidinium iodide

Methyl iodide (2 g (14 mmol)) was added to a mixture of cis-2,6-dimethylpiperidine (0.46 g (4 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol)) and water (1 ml) in dichloromethane (8 ml). The mixture was shaken carefully for 10 min whereupon the phases were separated. The organic phase was concentrated to drieness at reduced pressure and the crystalline residue was treated with acetone. Filtration and air drying gave 0.92 g (3.42 mmol) of the title compound.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 4.20 (m, 2H), 3.35 (s, 3H), 2.86 (s, 3H), 1.86 (m, 6H), 1.47 (d, 6H).

Example 1

Preparation of tetra-n-butylammoniumsalt of esomeprazole

Esomeprazole sodium salt (0.37 g (1 mmol)) was added to a mixture of tetra-n-butylammonium chloride (0.28 g (1 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken by hand (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.58 g (0.98 mmol) of tetra-n-butylammonium salt of esomeprazole (oil) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.21 (s, 1H), 7.54 (d, 1H), 7.18 (m, 1H), 6.74 (dm, 1H), 4.94 (d, 1H), 4.65 (D, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 2.97 (bm, 8H), 2.19 (s, 3H), 2.18 (s, 3H), 1.29 (bm, 16H), 0.93 (bt, 12H).

Example 2

Preparation of cholin salt of esomeprazole

Esomeprazole sodium salt (0.37 g (1 mmol)) was added to a mixture of cholin chloride (0.14 g (1 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol) and water (1 ml). Dichloromethane (8 ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.44 g (0.98 mmol) cholin salt of esomeprazole (amorphous foam) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.14 (s, 1H), 7.50 (d, 1H), 7.10 (m, 1H), 6.79 (dm, 1H), 4.83 (d, 1H), 4.57 (d, 1H), 3.84 (m, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 3.27 (m, 1H), 3.10 (m, 1H), 2.93 (s, 9H), 2.20 (s, 3H), 2.19 (s, 3H).

Example 3

Preparation of benzyltrimethylammonium salt of esomeprazole

Esomeprazole sodium salt (0.37 g (1 mmol)) was added to a mixture of benzyl trimethyl ammonium chloride (0.19 g (1 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.48 g (0.97 mmol) of benzyltrimethylammonium salt of esomeprazole (oil) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.12 (s, 1H), 7.52 (d, 1H), 7.38 (bm, 3H), 7.21 (bd, 2H), 7.14 (m, 1H), 6.74 (dm, 1H), 4.91 (d, 1H), 4.62 (d, 1H), 4.13 (s, 2H), 3.76 (s, 3H), 3.65 (s, 3H), 2.74 (s, 9H), 2.20 (s, 3H), 2.15 (s, 3H).

Example 4

Preparation of (1*S*)-N, N, N, trimethyl-1-phenylethylammonium salt of esomeprazole

Esomeprazole sodium salt (0.37 g (1 mmol)) was added to a mixture of (1S)-N, N, N, trimethyl-1-phenylethylammonium chloride (0.2 g (1 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol)) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.50 g (0.98 mmol) of (1S)-N, N, N, trimethyl-1-phenylethylammonium salt of esomeprazole (oil) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.15 (s, 1H), 7.54 (d, 1H), 7.35 (bm, 5H), 7.15 (m, 1H), 6.77 (dm, 1H), 4.92 (d, 1H), 4.66 (d, 1H), 3.78 (s, 3H), 4.57 (q, 1H) 3.65 (s, 3H), 2.84 (s, 9H), 2.20 (s, 3H), 2.17 (s, 3H), 1.54 (d, 3H).

Example 5

Preparation of (1*R*, 2*S*)-N,N-dimethylephedrinium salt of esomeprazole

Esomeprazole sodium salt (0.37 g (1 mmol)) was added to a mixture of (1*R*, 2*S*)-N,N-dimethylephedrinium chloride (0.23 g (1 mmol)), potassium carbonate (anhydrous) (1 g

(7.3 mmol)) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.505 g (0.98 mmol) of (1*R*, 2*S*)-N,N-dimethylephedrinium salt of esomeprazole (amorphous foam) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.06 (s, 1H), 7.38 (bm, 3H), 7.26 (bm, 2H), 7.19 (m, 1H), 6.88 (m, 1H), 6.68 (dm, 1H), 5.83 (s, 1H), 4.65 (d, 1H), 4.42 (d, 1H), 3.65 (s, 3H), 3.56 (s, 3H), 3.10 (q, 1H), 2.86 (s, 9H), 2.14 (s, 3H), 1.93 (s, 3H), 1.10 (d, 3H).

Example 6

Preparation of (1*S*, 2*R*)-N,N-dimethylephedrinium salt of esomeprazole

Esomeprazole sodium salt (0.37 g (1 mmol)) was added to a mixture of (1*S*, 2*R*)-N,N-dimethylephedrinium chloride (0.23 g (1 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol)) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.53 g (0.98 mmol) of (1*S*, 2*R*)-N,N-dimethylephedrinium salt of esomeprazole (amorphous foam) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.09 (s, 1H), 7.35 (bm, 3H), 7.28 (bm, 2H), 7.22 (m, 1H), 6.79 (m, 1H), 6.66 (dm, 1H), 5.60 (s, 1H), 4.76 (d, 1H), 4.52 (d, 1H), 3.62 (s, 3H), 3.57 (s, 3H), 3.13 (q, 1H), 2.96 (s, 9H), 2.17 (s, 3H), 2.09 (s, 3H), 1.12 (d, 3H).

Example 7

Preparation of (1*R*, 2*S*)-N-benzyl-N-methylephedrinium salt of esomeprazole

Esomeprazole sodium salt (0.185 g (0.5 mmol)) was added to a mixture of (1*R*, 2*S*)-N-benzyl-N-methylephedrinium bromide (0.175 g (0.5 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol)) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4

and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.265 g (0.43 mmol) of (1*R*, 2*S*)-N-benzyl-N-methylephedrinium salt of esomeprazole (amorphous foam) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.00 (s, 1H), 7.49 (d, 1H), 7.44 (d, 2H), 7.39 (t, 1H), 7.27 (bm, 3H), 7.13 (d, 2H), 6.99 (d, 1H), 6.70 (dd, 1H), 6.2 (s, 1H), 4.64 (d, 1H), 4.52 (s, 2H), 4.49 (d, 1H), 3.71 (s, 3H), 3.57 (s, 3H), 3.49 (q, 1H), 2.92 (s, 3H), 2.92 (s, 3H), 2.12 (s, 3H), 1.97 (s, 3H), 1.34 (d, 3H).

Example 8

Preparation of (1*S*, 2*R*)-N-benzyl-N-methylephedrinium salt of esomeprazole

Esomeprazole sodium salt (0.185 g (0.5 mmol)) was added to a mixture of (1*S*, 2*R*)-N-benzyl-N-methylephedrinium bromide (0.175 g (0.5 mmol)), potassium carbonate (anhydrous) (1 g (7.3 mmol)) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.260 g (0.42 mmol) of (1*S*, 2*R*)-N-benzyl-N-methylephedrinium salt of esomeprazole (amorphous foam) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.01 (s, 1H), 7.40 (m, 3H), 7.37 (d, 1H), 7.27 (bm, 3H), 7.18 (d, 2H), 6.86 (d, 1H), 6.66 (dd, 1H), 5.83 (s, 1H), 4.79 (d, 1H), 4.54 (d, 1H), 4.51 (d, 1H), 4.39 (d, 1H), 3.62 (s, 6H), 3.45 (q, 1H), 2.95 (s, 3H), 2.92 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.29 (d, 3H).

Example 9

Preparation of cis-2,6-dimethyl-N,N-dimethylpiperidinium salt of esomeprazole

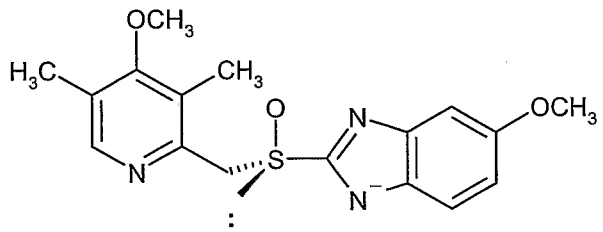
Esomeprazole sodium salt (0.368 g (1 mmol)) was added to a mixture of cis-2,6-dimethyl-N,N-dimethylpiperidinium iodide (0.270 g (0.5 mmol)), potassium carbonate (anhydrous)

(1 g (7.3 mmol)) and water (1 ml). Dichloromethane (8ml) was added and the mixture was shaken (1 min). After separation, the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to drieness at reduced pressure. 0.470 g (0.96 mmol) cis-2,6-dimethyl-N,N-dimethylpiperidinium salt of esomeprazole (amorphous foam) was obtained.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.90 (s, 1H), 7.43 (d, 1H), 7.04 (d, 1H), 6.66 (dd, 1H), 4.61 (d, 1H), 4.44 (d, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.41 (bm, 2H), 2.84 (s, 3H), 2.41 (s, 3H), 2.13 (s, 3H), 2.00 (s, 3H), 1.58 (m, 4H), 1.48 (m, 2H), 1.15 (dd, 6H).

CLAIMS

1. A process for preparation of a quaternary ammonium salt of (*S*)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole (esomeprazole),



$N^+R^1R^2R^3R^4$ I

wherein

R_1, R_2, R_3 and R_4 are individually selected from

(A) C_1-C_{14} alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O-, C_3-C_{12} cycloalkyl (which cycloalkyl is optionally substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, oxo, $R_{23a}OC(O)$- , $(R_{23b})(R_{23c})NC(O)$-, $R_{23d}C(O)N(R_{23e})$-, $R_{23f}C(O)O$-, $R_{23g}OC(O)$-NH-, $(R_{23h})(R_{23j})NC(O)O$-), aryl or Het^1 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl , hydroxy, -CH_2OH, halogen, oxo, nitro, C_1-C_7 alkoxy, $R_{24a}OC(O)$- , $(R_{24b})(R_{24c})NC(O)$-, $R_{24d}C(O)N(R_{24e})$-, $R_{24f}C(O)O$-, $R_{24g}OC(O)$-NH-, $(R_{24h})(R_{24j})NC(O)O$-, aryl, Het^3 or $R_{25}C(O)$- (which aryl and Het^3 are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy, nitro)); R_6 -O-$(CH_2)_m$ -O-, $R_{7a}OC(O)$-, $(R_{7b})(R_{7c})NC(O)$-, $R_{7d}C(O)N(R_{7e})$-, $R_{7f}C(O)O$- , $R_{7g}C(O)S$-, $R_{7h}OC(O)N(R_{7j})$-, $(R_{7k})(R_{7l})NC(O)O$-, $R_{7m}OC(O)O$-, R_8-SO_2-NH-, phtalimido, succinimido, $R_9C(O)$-, R_{10}-$(CH_2)_n$- C(O)- , $(R_{11a})(R_{11b})(R_{11c})$C-C(O)O-);

(B) aryl or Het^2 (both groups are optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{12a}OC(O)$- , $(R_{12b})(R_{12c})NC(O)$-, $R_{12d}C(O)N(R_{12e})$-, $R_{12f}C(O)O$- , $R_{12g}OC(O)NR_{12h}$-, $(R_{12j})(R_{12k})NC(O)O$-, aryl, benzoyl or Het^4), $R_{13}C(O)$-, $(R_{14a})(R_{14b})N$-);

or R_1 and R_2 together may represent a cyclic structure containing 5-14 members, optionally substituted by one or more groups selected from hydroxy, oxo, C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from hydroxy, halogen, aryl or Het^7), $R_{15}O$-, $R_{16a}OC(O)$-, $(R_{16b})(R_{16c})NC(O)$-, $R_{16d}C(O)N(R_{16e})$-, $R_{16f}C(O)O$- , $R_{16g}OC(O)NR_{16h}$-, $(R_{16j})(R_{16k})NC(O)O$-, $R_{17}C(O)$-, aryl or Het^5 (which aryl and Het^5 are optionally substituted by one or more of C_1-C_7 alkyl, hydroxy, oxo, C_1-C_7 alkoxy, halogen, $R_{26a}OC(O)$- , $(R_{26b})(R_{26c})NC(O)$-, $R_{26d}C(O)N(R_{26e})$-, $R_{26f}C(O)O$-, $R_{26g}OC(O)NH$-, $(R_{26h})(R_{26j})NC(O)O$-, phenyl or benzoyl (which phenyl or benzoyl are optionally substituted by one or two halogens, C_1-C_5 alkyl C(O)O-)), phtalimido, succinimido or $(R_{18a})(R_{18b})(R_{18c})C$-C(O)O-;

or R_1, R_2 and R_3 together may represent a cyclic structure containing 5-16 members, optionally substituted by one or more groups selected from hydroxy, oxo, C_1-C_7 alkyl (which alkyl group is optionally substituted by one or more groups selected from hydroxy, halogen, oxo, aryl or Het^8), $R_{19}O$-, $R_{20}C(O)$-, aryl and Het^6 (which aryl and Het^6 are optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, oxo, $R_{27a}OC(O)$- , $(R_{27b})(R_{27c})NC(O)$-, $R_{27d}C(O)N(R_{27e})$-, $R_{27f}C(O)O$- , $R_{27g}OC(O)$-NH-, $(R_{27h})(R_{27j})NC(O)O$-, phenyl or benzoyl), $R_{21a}OC(O)$- , $(R_{21b})(R_{21c})NC(O)$-, $R_{21d}C(O)N(R_{21e})$-, $R_{21f}C(O)O$- , $R_{21g}OC(O)$-NR_{21h}-, $(R_{21j})(R_{21k})NC(O)O$-, phtalimido, succinimido or $(R_{22a})(R_{22b})(R_{22c})$ C-C(O)O-;

R_5 is selected from C_1-C_6 alkyl, aryl, Het^9 (which groups are optionally substituted by one or more groups selected from hydroxy, halogen, C_1-C_6 alkoxy);

R_6 is selected from aryl or Het^{10} (both groups optionally substituted by one or more groups selected from C_1-C_8 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{28a}OC(O)$-, $(R_{28b})(R_{28c})NC(O)$-, $R_{28d}C(O)N(R_{28e})$-, $R_{28f}C(O)O$-, $R_{28g}OC(O)$-NH-, $(R_{28h})(R_{28j})NC(O)O$-, aryl, benzoyl or Het^{11});

R_{7a} to R_{7m} are independently selected, at each occurrence, from hydrogen, C_1-C_7 alkyl, aryl or Het^{12} (which C_1-C_7 alkyl, aryl and Het^{12} are optionally substituted by one or more groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{29a}OC(O)$-, $(R_{29b})(R_{29c})NC(O)$-, $R_{29d}C(O)N(R_{29e})$-, $R_{29f}C(O)O$-, $R_{29g}OC(O)$-NH-, $(R_{29h})(R_{29j})NC(O)O$-, aryl, benzoyl or Het^{13});

R_8 is selected from C_1-C_6 alkyl, aryl or Het^{14} (which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl);

R_9 is selected from linear or branched C_1 – C_{12} alkyl (optionally substituted by $R_{30}OC(O)$-), C_3-C_{12} cycloalkyl (which cycloalkyl group is optionally further substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{31a}OC(O)$-, $(R_{31b})(R_{31c})NC(O)$-, $R_{31d}C(O)NR_{31e}$-, $R_{31f}C(O)O$-, $R_{31g}C(O)N(R_{31h})$-, $(R_{31j})(R_{31k})NC(O)O$-), aryl, benzoyl or Het^{15}), aryl or Het^{16} (which aryl and Het^{16} are optionally substituted by one to three of the groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, ethylenedioxy, halogen, $R_{32a}OC(O)$-, $(R_{32b})(R_{32c})NC(O)$-, $R_{32d}C(O)NR_{32e}$-, $R_{32f}C(O)O$-, $R_{32g}OC(O)NH$-, $(R_{32h})(R_{32j})NC(O)O$-), aryl, benzoyl or Het^{17});

R_{10} is selected from aryl and Het^{18} (which groups are optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, -COOH, ethylenedioxy);

R_{11a} is selected from hydroxy or $-CH_2OH$;

R_{11b} is phenyl (optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{33a}OC(O)$- , $(R_{33b})(R_{33c})NC(O)$-, $R_{33d}C(O)N(R_{33e})$-, $R_{33f}C(O)O$- , $R_{33g}OC(O)$-NH-, $(R_{33h})(R_{33j})NC(O)O$-);

R_{11c} is selected from hydrogen, C_5-C_6 cycloalkyl, phenyl (which groups are optionally substituted by one to three groups selected from C_1-C_3alkyl, hydroxy, C_1-C_3alkoxy, halogen, $R_{34a}OC(O)$- , $(R_{34b})(R_{34c})NC(O)$-, $R_{34d}C(O)N(R_{34e})$-, $R_{34f}C(O)O$- , $R_{34g}OC(O)NH$-, $(R_{34h})(R_{34j})NC(O)O$-);

R_{12a} to R_{12k} are independently selected, at each occurrence, from hydrogen, C_1-C_7alkyl, aryl, Het^{19} (which groups are optionally substituted by one or more groups selected from C_1-C_6alkyl, hydroxy, C_1-C_3alkoxy, halogen, $R_{35a}OC(O)$- , $(R_{35b})(R_{35c})NC(O)$-, $R_{35d}C(O)N(R_{35e})$-, $R_{35f}C(O)O$- , $R_{35g}OC(O)$-NH-, $(R_{35h})(R_{35j})NC(O)O$-, aryl, benzoyl or Het^{20});

R_{13} is selected from hydrogen or C_1-C_6 alkyl;

R_{14a} to R_{14b} are independently selected, at each occurrence, from hydrogen or C_1-C_6 alkyl;

R_{15} is selected from C_1-C_6 alkyl, aryl or Het^{21} (which groups are optionally substituted by one or more groups selected from hydroxy, halogen or C_1-C_6 alkoxy);

R_{16a} to R_{16k} are independently selected from, at each occurrence, hydrogen, C_1-C_7 alkyl, aryl or Het^{22} (which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{36a}OC(O)$- , $(R_{36b})(R_{36c})NC(O)$-, $R_{36d}C(O)N(R_{36e})$-, $R_{36f}C(O)O$- , $R_{36g}OC(O)$-NH-, $(R_{36h})(R_{36j})NC(O)O$-, aryl, benzoyl or Het^{23};

R_{17} is selected from hydrogen or C_1-C_6 alkyl;

R_{18a} is selected from hydroxy or $-CH_2OH$;

R_{18b} is phenyl (optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{37a}OC(O)$-, $(R_{37b})(R_{37c})NC(O)$-, $R_{37d}C(O)N(R_{37e})$-, $R_{37f}C(O)O$- , $R_{37g}OC(O)$-NH-, $(R_{37h})(R_{37j})NC(O)O$-);

R_{18c} is selected from hydrogen, C_5-C_6 cycloalkyl or phenyl (which optionally is substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{38a}OC(O)$- , $(R_{38b})(R_{38c})NC(O)$-, $R_{38d}C(O)N(R_{38e})$-, $R_{38f}C(O)O$- , $R_{38g}OC(O)$-NH-, $(R_{38h})(R_{38j})NC(O)O$-);

R_{19} is selected from C_1-C_6 alkyl, aryl or Het^{24} (which groups are optionally substituted by one or more groups selected from hydroxy, halogen or C_1-C_6 alkoxy);

R_{20} is selected from hydrogen and C_1-C_6 alkyl;

R_{21a} to R_{21k} are independently selected, at each occurence, from hydrogen, C_1-C_7 alkyl, aryl or Het^{25} (which groups are optionally substituted by one or more groups selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{39a}OC(O)$- , $(R_{39b})(R_{39c})NC(O)$-, $R_{39d}C(O)N(R_{39e})$-, $R_{39f}C(O)O$- , $R_{39g}OC(O)$-NH-, $(R_{39h})(R_{39j})NC(O)O$-, aryl, benzoyl or Het^{26});

R_{22a} is selected from hydroxy or $-CH_2OH$;

R_{22b} is phenyl (optionally substituted by one to three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{40a}OC(O)$- , $(R_{40b})(R_{40c})NC(O)$-, $R_{40d}C(O)N(R_{40e})$-, $R_{40f}C(O)O$- , $R_{40g}OC(O)NH$-, $(R_{40h})(R_{40j})NC(O)O$-);

R_{22c} is selected from hydrogen, C_5-C_6 cycloalkyl or phenyl (which optionally is substituted by one or three groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, $R_{41a}OC(O)$- , $(R_{41b})(R_{41c})NC(O)$-, $R_{41d}C(O)N(R_{41e})$-, $R_{41f}C(O)O$-, $R_{41g}OC(O)NH$-, $(R_{41h})(R_{41j})NC(O)O$-);

R_{23a} to R_{23j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{24a} to R_{24j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{25} is selected from C_1-C_4alkyl, aryl or Het^{27} (which aryl and Het^{27} are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy, nitro);

R_{26a} to R_{26j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{27a} to R_{27j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{28a} to R_{28j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{29a} to R_{29j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{30} is selected from hydrogen or C_1-C_6 alkyl;

R_{31a} to R_{31k} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{32a} to R_{32j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{33a} to R_{33j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{34a} to R_{34j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{35a} to R_{35j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{36a} to R_{36j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{37a} to R_{37j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{38a} to R_{38j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{39a} to R_{39j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

R_{40a} to R_{40j} are independently selected, at each occurrence, from hydrogen or C_1-C_6alkyl;

$R_{41a}$to R_{41j} are independently selected, at each occurrence, from hydrogen or C_1-C_6 alkyl;

m is an integer selected from 1 to 5;

n is an integer selected from 1 to 3.

which process comprises the following steps:

(i): mixing esomeprazole and $N^+(R_1)(R_2)(R_3)(R_4)X^-$;

wherein

R_1, R_2, R_3 and R_4 are as defined above;

X^- is selected from Cl^-, Br^-, I^-, C_1-C_6 alkyl carboxylates, C_1-C_6 alkyl sulphonates, HSO_4^- and OH^-;

in an aqueous solvent system comprising more than 40 % w/w potassium carbonate;

(ii): adding a water immiscible chlorinated hydrocarbon solvent;

(iii): isolating the organic phase;

(iv): recovering of the compound of formula I.

2. A process according to claim 1 wherein the aqueous solvent system in step (i) comprises more than 50 % by weight potassium carbonate.

3. A process according to claim 1 wherein the aqueous solvent system in step (i) is saturated with potassium carbonate.

4. A process according to claim 1 wherein the chlorinated water immiscible solvent is selected from 1,2 dichlormethane, trichlormethane and 1,2-dichloretane.

5. A process according to claim 1 wherein the chlorinated water immiscible solvent is dichlormethane.

6. A process according to claim 1 wherein esomeprazole in step (i) is the sodium salt or potassium salt of esomeprazole.

7. A process according to claim 1 wherein R_1 is selected from

(A) C_1-C_{14} alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O-, C_3-C_{12} cycloalkyl (which cycloalkyl is optionally substituted by one or more groups selected from C_1-C_3 alkyl, hydroxy, C_1-C_3 alkoxy, halogen, oxo, $R_{23a}OC(O)$- , $(R_{23b})(R_{23c})NC(O)$-, $R_{23d}C(O)N(R_{23e})$-, $R_{23f}C(O)O$-, $R_{23g}OC(O)$-NH-, $(R_{23h})(R_{23j})NC(O)O$-), aryl or Het^1 (both groups optionally substituted by one to three groups selected from C_1-C_7 alkyl , hydroxy, -CH_2OH, halogen, oxo, nitro, C_1-C_7 alkoxy, $R_{24a}OC(O)$- , $(R_{24b})(R_{24c})NC(O)$-, $R_{24d}C(O)N(R_{24e})$-, $R_{24f}C(O)O$-, $R_{24g}OC(O)$-NH-, $(R_{24h})(R_{24j})NC(O)O$-, aryl, Het^3 or $R_{25}C(O)$- (which aryl, Het^3 and R_{25} are optionally substituted by one or two halogens, C_1-C_4 alkyl, hydroxy C_1-C_4alkyl, C_1-C_4 alkoxy, hydroxy C_1-C_4 alkoxy or nitro), R_6-O-$(CH_2)_m$ -O-, $R_{7a}OC(O)$-, $(R_{7b})(R_{7c})NC(O)$-, $R_{7d}C(O)N(R_{7e})$-, $R_{7f}C(O)O$- , $R_{7g}C(O)S$-, $R_{7h}OC(O)N(R_{7j})$-, $(R_{7k})(R_{7l})NC(O)O$-, $R_{7m}OC(O)O$-, R_8-SO_2-NH-, phtalimido, succinimido, $R_9C(O)$-, R_{10}-$(CH_2)_n$-C(O)- , $(R_{11a})(R_{11b})(R_{11c})$C-C(O)O- ;

(B) aryl or Het^2 (both groups are optionally substituted by one to three groups selected from C_1-C_7 alkyl, hydroxy, C_1-C_7 alkoxy, halogen, $R_{12a}OC(O)$- , $(R_{12b})(R_{12c})NC(O)$-, $R_{12d}C(O)N(R_{12e})$-, $R_{12f}C(O)O$- , $R_{12g}OC(O)NR_{12h}$-, $(R_{12j})(R_{12k})NC(O)O$-, aryl, benzoyl or Het^4), $R_{13}C(O)$-, $(R_{14a})(R_{14b})N$-);

R_2, R_3 and R_4 are individually selected from, at each occurrence, linear or branched C_1-C_{14} alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, phenyl and R_5O-) or aryl.

8. A process according to any of claims 1 and 7 wherein R_4 is selected from linear or branched C_1-C_6 alkyl group.

9. A process according to claim 8 wherein R_4 is methyl.

10. A process according to any of claims 1 and 7 wherein R_3 and R_4 are individually selected from, at each occurrence, linear or branched C_1-C_6 alkyl group.

11. A process according to claim 10 wherein R_3 and R_4 are methyl.

12. A process according to any of claims 1 and 7 wherein R_2, R_3 and R_4 are individually selected from, at each occurrence, linear or branched C_1-C_6 alkyl group.

13. A process according to any of claims 1 and 7 wherein R_2 and R_3 are individually selected from, at each occurrence, linear or branched C_1-C_6 alkyl group; and R_4 is methyl.

14. A process according to any of claims 1 and 7 wherein R_2 is selected from linear or branched C_1-C_6 alkyl group; and R_3 and R_4 are methyl.

15. A process according to any of claims 1 and 7 wherein R_2, R_3 and R_4 are methyl.

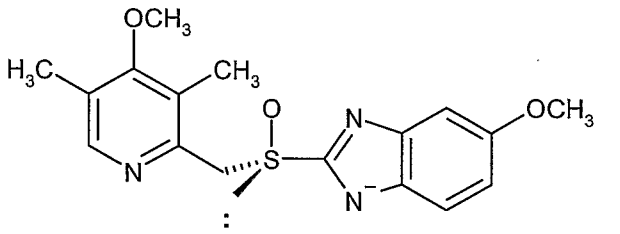
16. A process according to any of claims 1 and 7 wherein R_2, R_3 and R_4 are individually selected from C_1-C_4 alkyl groups.

17. A process according to claim 1 wherein R_1 is selected from linear or branched C_1-C_8 alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O- or aryl); R_2, R_3 and R_4 are individually selected from linear or branched C_1-C_4alkyl group (which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen or R_5O-) or aryl.

18. A process according to claim 1 wherein R_1 is selected from linear or branched C_1-C_8 alkyl group, which alkyl group is optionally substituted by one or more groups selected from amino, hydroxy, halogen, R_5O- or phenyl; R_2, R_3 and R_4 are independently, at each occurrence, selected from methyl, ethyl, n-propyl or isopropyl (which group is optionally substituted by one or more groups selected from amino, hydroxy, halogen or R_5O-) or phenyl.

19. A process according to claim 1 wherein R_1 and R_2 together may represent a cyclic structure containing 5 to10 members, optionally substituted by on or more groups selected linear or branched C_1-C_5 alkyl group, amino, hydroxy, halogen or R_5O-; R_3 and R_4 are selected from linear or branched C_1-C_4 alkyl group.

20. Quaternary alkyl ammoniumsalts of *S*-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole (esomeprazole) of formula I



$N^+R^1R^2R^3R^4$ I

wherein

R_1, R_2, R_3 and R_4 are as defined in any of claims 1 to 19 .

21. Quarternary ammoniumsalt according to claim 20, said salt being:
tetra-n-butyl ammoniumsalt of esomeprazole;
cholin salt of esomeprazole;
benzyltrimethylammonium salt of esomeprazole;
(1*S*)-N, N, N, trimethyl-1-phenylethylammonium salt of esomeprazole;
(1*R*, 2*S*)-N,N-dimethylephedrinium salt of esomeprazole;
(1*S*, 2*R*)-N,N-dimethylephedrinium salt of esomeprazole;
(1*R*, 2*S*)-N-benzyl-N-methylephedrinium salt of esomeprazole;
(1*S*, 2*R*)-N-benzyl-N-methylephedrinium salt of esomeprazole or
cis-2,6-dimethyl-N,N-dimethylpiperidinium salt of esomeprazole.

22. Use of the compound according to any of claims 20 and 21 for the manufacture of a medicament for administration to a mammal or man for the treatment of gastrointestinal disorders.

23. A pharmaceutical formulation comprising a quartenary ammoniumsalt of esomeprazole as defined in any of claims 20 and 21 in admixture with at least one pharmaceutically acceptable excipient.

24. A method of treatment which comprises administration of a therapeutically effective amount of a quartenary ammoniumsalt of esomeprazole as defined in any of claims 20 and 21, to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000548

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2137616 A (AKTIEBOLAGET HASSLE (SWEDEN)), 10 October 1984 (10.10.1984), see Example 7, page 3	20-23
A	WO 2005023796 A1 (ASTRAZENECA AB), 17 March 2005 (17.03.2005), see Example 2, page 13	1-24
A	WO 03074514 A1 (ASTRAZENECA AB), 12 Sept 2003 (12.09.2003), see Example 2, page 15	1-24
A	WO 2005023797 A1 (ASTRAZENECA AB), 17 March 2005 (17.03.2005), see Example 2, page 11	1-24

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent 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 when the document is taken alone
"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

Date of the actual completion of the international search	Date of mailing of the international search report
10 Sept 2007	13-09-2007
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000548

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 24
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 24 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 searched 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 and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000548

International patent classification (IPC)

C07D 401/12 (2006.01)
A61K 31/4439 (2006.01)
A61P 1/04 (2006.01)

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- e-tjänster/anförda dokument(service in Swedish).

Use the application number as username.
The password is **YJPZPHDHMT**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

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