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(54) Title: COMBINATION OF A REFLUX INHIBITOR AND AN IMIDAZOPYRIDINE FOR THE TREATMENT OF GERD

(57) Abstract: The present invention relates to a medicament comprising, separately or together, (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine. A further aspect of the invention relates to methods of treatment of gastro-esophageal reflux disease, regurgitation, asthma, failure to thrive and lung disease.



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COMBINATION OF A REFLUX INHIBITOR AND AN IMIDAZOPYRIDINE FOR THE TREATMENT OF GERD

Field of the invention

5 The present invention provides a combination comprising, separately or together, (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine. A further aspect of the invention relates to methods of treatment of gastro-esophageal reflux disease, regurgitation, asthma, failure to thrive and lung disease.

Background of the invention

10 The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical
15 barrier is temporarily lost at such times, an event hereinafter referred to as "reflux".

Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter. However, more detailed studies (e.g. *Holloway & Dent (1990)*
20 *Gastroenterol. Clin. N. Amer.* 19, pp. 517-535) have shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESR), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD.

Outline of the invention

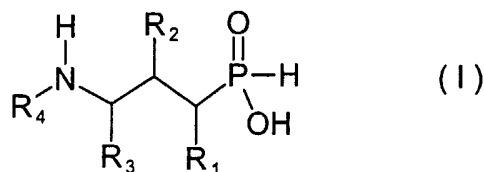
25 The present invention provides a combination comprising, separately or together, (i) at
30 least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V below.

The present invention relates to a combination of a reflux inhibitor and an imidazopyridine. Further, the invention relates to the use of a combination of a reflux inhibitor and an imidazopyridine for the preparation of a medicament for the treatment of gastro-esophageal reflux disease, regurgitation, asthma, failure to thrive and lung disease.

Reflux inhibitor

The wording "reflux inhibitor" is defined as an agent preventing reflux of gastric contents. GABA_B-receptor agonists are examples of reflux inhibitors useful in accordance with the present invention. GABA_B-receptor agonists have been shown to inhibit TLESR, which is disclosed in inter alia WO 98/11885 A1.

Examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula I



wherein

R₁ represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R₂ represents hydroxy, mercapto, halogen, or an oxo group;

R₃ represents hydrogen or lower alkyl (optionally substituted by hydroxy, mercapto, lower alkoxy, lower thioalkoxy or aryl);

R₄ represents hydrogen, lower alkyl (optionally substituted by aryl), or aryl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof. Examples of such compounds are (3-amino-2-fluoropropyl)phosphinic acid, (2*R*)-(3-amino-2-fluoropropyl)phosphinic acid, (2*S*)-(3-amino-2-fluoropropyl)phosphinic acid, (3-amino-2-fluoro-1-methylpropyl)phosphinic acid, (3-amino-2-oxopropyl)phosphinic acid, (*S*)-(3-

amino-2-hydroxypropyl)phosphinic acid,), (*R*)-(3-amino-2-hydroxypropyl)phosphinic acid and (3-amino-1-fluoro-2-hydroxypropyl)phosphinic acid.

In the definition of formula I above, it is to be understood that when R₂ is an oxo group the
5 bond between R₂ and the carbon is a double bond.

In the definition of formula I above, it is to be understood by "lower" radicals and compounds, for example, those having up to and including 7, especially up to and including 4, carbon atoms. Also the general terms have the following meanings:

10

Lower alkyl is, for example, C₁-C₄ alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C₅-C₇ alkyl group such as a pentyl, hexyl or heptyl group.

15 Lower alkoxy is, for example, C₁-C₄ alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C₅-C₇ alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

20 Lower thioalkoxy is, for example, C₁-C₄ thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C₅-C₇ thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

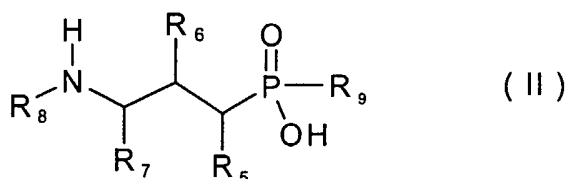
25 Halogen is, for example, halogen of an atomic number up to and including 35, such as fluorine or chlorine, less preferred, bromine.

The compounds according to formula I of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as
30 well as pharmaceutically acceptable salts formed with bases. Suitable acids for the

formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as ammonium salts, such as those with ammonia or organic amines.

When one or more stereocentre is present in the molecule, the compounds according to formula I can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The compounds can also be in the form of solvates, e.g. hydrates.

Still further examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula II



wherein

R₅ represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R₆ represents hydroxy, mercapto, halogen, or an oxo group;

R₇ represents hydrogen or lower alkyl (optionally substituted by hydroxy, mercapto, lower alkoxy, aryl or lower thioalkoxy);

R₈ represents hydrogen, lower alkyl (optionally substituted by aryl) or aryl;

R₉ represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof.

Examples of such compounds are (3-amino-2-fluoropropyl)(methyl)phosphinic acid, (2*R*)-(3-amino-2-fluoropropyl)(methyl)phosphinic acid, (2*S*)-(3-amino-2-fluoropropyl)(methyl)phosphinic acid, (3-Amino-2-fluoro-1-methylpropyl)(methyl)phosphinic acid or pharmaceutically acceptable salts, solvates or the stereoisomers thereof.

In the definition of formula II above, it is to be understood that when R₆ is an oxo group the bond between R₆ and the carbon is a double bond.

Furthermore, in the definition of formula II above, it is to be understood by "lower" radicals and compounds, for example, those having up to and including 7, especially up to and including 4, carbon atoms. Also the general terms have the following meanings:

Lower alkyl is, for example, C₁-C₄ alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C₅-C₇ alkyl group such as a pentyl, hexyl or heptyl group.

Lower alkoxy is, for example, C₁-C₄ alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C₅-C₇ alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

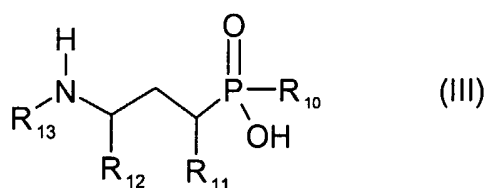
Lower thioalkoxy is, for example, C₁-C₄ thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C₅-C₇ thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

Halogen is, for example, halogen of an atomic number up to and including 35, such as fluorine, chlorine or bromine.

The compounds according to formula II of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts as well as ammonium salts, such as those with ammonia or organic amines.

When one or more stereocentre is present in the molecule, the compounds according to formula II can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The present compounds can also be in the form of solvates, e.g. hydrates.

Still further examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula III



wherein

R_{10} represents hydrogen, methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

R_{11} represents hydrogen, hydroxy, C_1 - C_7 alkyl, C_1 - C_7 alkoxy or halogen;

R_{12} represents hydrogen, C_1 - C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1 - C_7 alkoxy, C_1 - C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R₁₃ represents hydrogen, C₁-C₇ alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof.

- 5 Examples of compounds according to formula III are (3-amino-1-fluoropropyl)phosphinic acid, 3-[(4-chlorobenzyl)amino]propyl(methyl)phosphinic acid and 3-[1-({3-[hydroxy(oxido)phosphino]propyl}amino)ethyl]benzoic acid.

In the definition of formula III above, C₁-C₇ alkyl can be straight, branched or cyclic alkyl
10 and is, for example, C₁-C₄ alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C₅-C₇ alkyl group such as a pentyl, hexyl or heptyl group.

C₁-C₇ alkoxy is, for example, C₁-C₄ alkoxy, such as methoxy, ethoxy, n-propoxy or n-
15 butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C₅-C₇ alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

C₁-C₇ thioalkoxy is, for example, C₁-C₄ thioalkoxy, such as thiomethoxy, thioethoxy, n-
thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or
20 tertiary thiobutoxy, but may also be a C₅-C₇ thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

Halogen as used in Formula III is anyone of chlorine, fluorine, bromine or iodine.

25 The herein used term aryl means aromatic rings with 6-14 carbon atoms including both single rings and polycyclic compounds, such as benzyl or naphthyl, optionally substituted by one or more substituents such as C₁-C₇ alkyl, C₁-C₇ alkoxy, C₁-C₇ thioalkoxy, halogen, hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

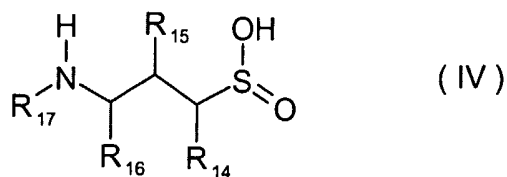
The term heteroaryl as used herein means aromatic rings with 5-14 carbon atoms, including both single rings and polycyclic compounds, in which one or several of the ring atoms is either oxygen, nitrogen or sulphur. The heteroaryl is optionally substituted by one or more substituents such as C₁-C₇ alkyl, C₁-C₇ alkoxy, C₁-C₇ thioalkoxy, halogen,
5 hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

The compounds according to formula III of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as
10 well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as
15 ammonium salts, such as those with ammonia or organic amines. The salts may be prepared by conventional methods.

When one or more stereocentre is present in the molecule, the compounds according to formula III can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers
20 and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The compounds can also be in the form of solvates, e.g. hydrates.

Still further examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula IV

25



wherein

R₁₄ represents hydrogen, hydroxy, C₁-C₇ alkyl, C₁-C₇ alkoxy or halogen;

R₁₅ represents hydrogen, hydroxy, mercapto, halogen, or an oxo group;

R₁₆ represents hydrogen or C₁-C₇ alkyl (optionally substituted by hydroxy, mercapto, C₁-
5 C₇ alkoxy, C₁-C₇ thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R₁₇ represents hydrogen, C₁-C₇ alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof.

10

Examples of compounds according to formula IV are (3-amino-2-fluoropropyl)sulphinic acid, (2*S*)-(3-amino-2-fluoropropyl)sulphinic acid, (2*R*)-(3-amino-2-fluoropropyl)sulphinic acid, (2*S*)-(3-amino-2-hydroxypropyl)sulphinic acid, (2*R*)-(3-amino-2-hydroxypropyl)sulphinic acid and (3-amino-2-oxopropyl)sulphinic acid.

15

In the definition of formula IV above, it is to be understood that when R₁₅ is an oxo group the bond between R₁₅ and the carbon is a double bond.

20

In the definition of formula IV above, C₁-C₇ alkyl can be straight, branched or cyclic alkyl and is, for example, C₁-C₄ alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C₅-C₇ alkyl group such as a pentyl, hexyl or heptyl group.

25

C₁-C₇ alkoxy is, for example, C₁-C₄ alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C₅-C₇ alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

C₁-C₇ thioalkoxy is, for example, C₁-C₄ thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C₅-C₇ thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

5

Halogen as used in Formula IV is anyone of chlorine, fluorine, bromine or iodine.

The herein used term aryl means aromatic rings with 6-14 carbon atoms including both single rings and polycyclic compounds, such as benzyl or naphthyl, optionally substituted by one or more substituents such as membered rings optionally substituted by one or more substituents such as C₁-C₇ alkyl, C₁-C₇ alkoxy, halogen, C₁-C₇ thioalkoxy, hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

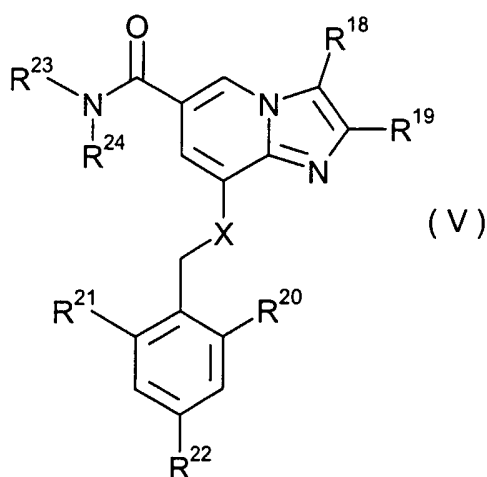
The term heteroaryl as used herein means aromatic rings with 5-14 carbon atoms, including both single rings and polycyclic compounds, in which one or several of the ring atoms is either oxygen, nitrogen or sulphur. The heteroaryl is optionally substituted by one or more substituents such as C₁-C₇ alkyl, C₁-C₇ alkoxy, C₁-C₇ thioalkoxy, halogen, hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

The compounds according to formula IV of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as ammonium salts, such as those with ammonia or organic amines. The salts may be prepared by conventional methods.

When one or more stereocentre is present in the molecule, the compounds according to formula IV can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The compounds can also be in the form of solvates, e.g. hydrates.

Imidazopyridines

The imidazopyridine is a compound of formula V:



or a pharmaceutically acceptable salt thereof, wherein

R^{18} is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

R^{19} is

- (a) CH_3
- (b) CH_2CH_3

R^{20} is

- (a) H
- (b) C_1 - C_6 alkyl,
- (c) hydroxylated C_1 - C_6 alkyl
- (d) halogen

R²¹ is

- (a) H,
- (b) C₁-C₆ alkyl,
- (c) hydroxylated C₁-C₆ alkyl, or
- (d) halogen;

R²² is

- (a) H, or
- (b) halogen;

R²³ and R²⁴ are the same or different, selected from any one of

- (a) H,
- (b) C₁-C₆ alkyl;
- (c) hydroxylated C₁-C₆ alkyl
- (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

X is

- (a) NH, or
- (b) O;

In the definition of formula V above, the term "C₁-C₆ alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C₁-C₆ alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

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

As the drug substance used in accordance with the present invention are both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the present invention as the active drug substance, as well as derivatives of the compounds of the formula V that have the biological function of the compounds of the formula V, such as prodrugs.

It will also be appreciated by those skilled in the art, although derivatives of compounds of formula V may not possess pharmacological activity as such, they may be administered orally and thereafter metabolised in the body to form compounds that are

5 pharmacologically active. Such derivatives may therefore be described as "prodrugs".

Prodrugs of compounds of formula V are also within the scope of the invention.

Depending on the process conditions the end products of the formula V are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

10

In one aspect of the invention, the active drug substance is a compound of the formula V wherein R¹ is CH₃ or CH₂OH; R² is CH₃ or CH₂CH₃; R³ is CH₃ or CH₂CH₃; R⁴ is CH₃ or CH₂CH₃; R⁵ is H, Br, Cl, or F.

15 In a further aspect of the present invention, the active drug substance of the formula V is a compound selected from any one of

- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-propyl-imidazo[1,2-a]pyridine-6-carboxamide;
- 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide;
- 20 • 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 25 • 8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide;
- 8-(2-ethyl-6-methylbenzylamino)-N,N,2,3-tetramethylimidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2,6-dimethylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide,
- 30 N-[2-(dimethylamino)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide;

- 2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate;
- 2,3-dimethyl-8-(2-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2,6-dimethyl-4-fluoro-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate;
- 2,3-dimethyl-8-(2-methyl-6-isopropylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate;
- 2,3-dimethyl-8-(2,6-diethyl-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2-ethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3 dimethyl-8-(2-ethyl-6-methyl-benzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide;
- N-(2,3-dihydroxypropyl)-2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-[1,2-a]pyridine-6-carboxamide;
- 2,3 dimethyl-8-(2-ethyl-6-methyl-benzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2-methyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2-bromo-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2-(2-hydroxyethyl)-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 8-(2-ethyl-6-methylbenzylamino)-N,N-bis(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide;
- 8-(2-ethyl-6-methylbenzylamino)-N-(2-hydroxyethyl)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide; and
- 2,3-dimethyl-8-(2-ethyl-6-methylbenzyloxy)-imidazo[1,2-a]pyridine-6-carboxamide; or a pharmaceutically acceptable salt thereof.

In still a further aspect of the present invention, the imidazopyridine of formula V is a compound selected from any one of

- 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide;
- 5 • 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 10 • 2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2,6-dimethyl-4-fluoro-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 2,3-dimethyl-8-(2,6-diethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide;
- 15 • 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide; and
- 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide; or a pharmaceutically acceptable salt thereof.

20 Compounds of the formula V above and their preparation, are described in the patent application PCT/SE99/00663 (WO 99/55706), which is hereby incorporated in full as reference.

Combination of a reflux inhibitor and an imidazopyridine of formula V

25 The present invention provides a combination comprising, separately or together, (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V.

A “combination” according to the invention may be present as a “fix combination” or as a “kit of parts combination”.

A "fix combination" is defined as a combination wherein the (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are present in one unit. One example of a "fix combination" is a pharmaceutical composition wherein the (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are present in admixture, such as in a formulation. Another example of a "fix combination" is a pharmaceutical combination wherein the (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are present in one unit without being in admixture.

A "kit of parts combination" is defined as a combination wherein the (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are present in more than one unit. One example of a "kit of parts combination" is a combination wherein the (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are present separately. The components of the "kit of parts combination" may be administered simultaneously, sequentially or separately, i.e. separately or together.

The molar ratio of the imidazopyridine of formula V to the reflux inhibitor used according to the invention is within the range of from 1:100 to 100:1, such as from 1:50 to 50:1 or from 1:20 to 20:1 or from 1:10 to 10:1. The two drugs may be administered separately in the same ratio.

A suitable daily dose of the imidazopyridine of formula V is in the range of 10 to 60 mg per day, such as 20 or 30 or 40 or 50 mg per day. A suitable daily dose of the reflux inhibitor is in the range of 1 µg to 100 mg per day and kg body weight, such as 10 µg to 20 mg per day and kg body weight.

Examples of reflux inhibitors useful in a "kit of parts" or in a "fix combination" as described above, are any reflux inhibitors of formula I, II, III or IV above, used in combination with any compound of formula V. Another aspect of the invention is the use of GABA (γ-aminobutyric acid) or baclofen as reflux inhibitor.

A further aspect of the present invention is a method for the treatment of GERD, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is administered to a

subject in need of such treatment. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Effective management of regurgitation would be an important way of preventing, as well
5 as curing lung disease due to aspiration of regurgitated gastric contents, and for managing failure to thrive due to excessive loss of ingested nutrient. Thus, a further aspect of the invention is the use of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a medicament for the treatment of regurgitation. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of
10 formula V are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the treatment of regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is
15 administered to a subject in need of such treatment. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of (i) at least one reflux
20 inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a medicament for the treatment or prevention of lung disease. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

25 Still a further aspect of the invention is a method for the treatment or prevention of lung disease, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is administered to a subject in need of such treatment. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered
30 simultaneously, sequentially or separately.

Another aspect of the invention is the use of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a medicament for the management of failure to thrive due. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered
5 simultaneously, sequentially or separately.

Still a further aspect of the invention is a method for the management of failure to thrive, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is
10 administered to a subject in need of such treatment. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a
15 medicament for the prevention of reflux. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

20 Another aspect of the present invention is a method for the prevention of reflux, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is administered to a subject in need of such prevention. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

25 Still a further aspect of the invention is the use of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a medicament for the inhibition of TLESRs. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or
30 separately.

A further aspect of the present invention is a method for the inhibition of TLESRs, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is administered to a subject in need of such inhibition. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a medicament for the treatment of esophagitis. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the prevention of esophagitis, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is administered to a subject in need of such treatment. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

20

Still a further aspect of the invention is the use of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a medicament for the treatment of asthma, such as reflux-related asthma or non reflux-related asthma. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the treatment of asthma, such as reflux-related asthma or non reflux-related asthma, whereby a pharmaceutically and pharmacologically effective amount of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is administered to a subject in need of such treatment. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V for the manufacture of a medicament for the treatment of laryngitis, such as chronic laryngitis. The (i) at least one
5 reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the treatment of laryngitis, such as chronic laryngitis, whereby a pharmaceutically and pharmacologically effective amount of
10 a combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V is administered to a subject in need of such treatment. The (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V are administered simultaneously, sequentially or separately.

15 For the purpose of this invention, the term "agonist" should be understood as including full agonists as well as partial agonists, whereby a "partial agonist" should be understood as a compound capable of partially, but not fully, activating a receptor.

The wording "TLESR", transient lower esophageal sphincter relaxations, is herein defined
20 in accordance with *Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*

The wording "reflux" is defined as fluid from the stomach being able to pass into the
25 esophagus, since the mechanical barrier is temporarily lost at such times.

The wording "GERD", gastro-esophageal reflux disease, is defined in accordance with *van Heerwarden, M.A., Smout A.J.P.M., 2000; Diagnosis of reflux disease. Baillière's Clin. Gastroenterol. 14, pp. 759-774.*

30

The term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Pharmaceutical formulations

For clinical use, the combination of (i) at least one reflux inhibitor; and (ii) at least one
5 imidazopyridine of formula V, is in accordance with the present invention suitably
formulated into pharmaceutical formulations for oral administration. Also rectal, parenteral
or any other route of administration may be contemplated to the skilled man in the art of
formulations. Thus, the combination of (i) at least one reflux inhibitor; and (ii) at least one
imidazopyridine of formula V, is formulated with at least one pharmaceutically and
10 pharmacologically acceptable carrier or adjuvant. The carrier may be in the form of a solid,
semi-solid or liquid diluent. The (i) at least one reflux inhibitor; and (ii) at least one
imidazopyridine of formula V are administered simultaneously, sequentially or separately.

In the preparation of oral pharmaceutical formulations in accordance with the invention,
15 the combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of
formula V, to be formulated is mixed with solid, powdered ingredients such as lactose,
saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or
another suitable ingredient, as well as with disintegrating agents and lubricating agents
such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene
20 glycol waxes. The mixture is then processed into granules or compressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the
combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of
formula V, with vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard
25 gelatine capsules may contain the combination of (i) at least one reflux inhibitor; and (ii) at
least one imidazopyridine of formula V, in combination with solid powdered ingredients
such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin,
cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (1) in the form of suppositories which contain the active substance(s) mixed with a neutral fat base; (2) in the form of a gelatine rectal capsule which contains the combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V, in a mixture with a vegetable oil, paraffin oil, or other suitable vehicle for gelatine rectal capsules; (3) in the form of a ready-made micro enema; or (4) 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 the combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V, and the remainder of the formulation 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 or other 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 combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V, in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of 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.

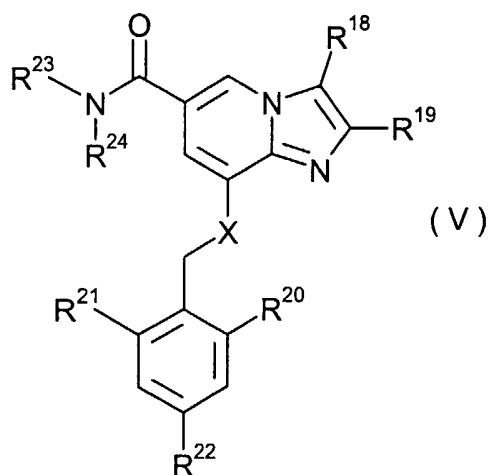
In one aspect of the present invention, the combination of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V, may be administered once or twice daily, depending on the severity of the patient's condition.

Biological studies

The effect of a reflux inhibitor, such as a GABA_B receptor agonist, and an imidazopyridine of formula V, on acid and bile reflux is studied in freely moving dogs. An esophagostomy is formed surgically, and after recovery, the dog is equipped with a vest. A pH electrode as well as a bile acid sensor (Bilitec) are positioned 3 cm above the lower esophageal
5 spincter, the location of which is determined manometrically. The data loggers are placed in pockets in the vest. Acid and bile reflux is measured in four conditions: 1) After placebo treatment; 2) After treatment with a reflux inhibitor; 3) After treatment with an imidazopyridine of formula V; and 4) After combination treatment with a reflux inhibitor
10 and an imidazopyridine of formula V.

Claims

1. A combination comprising, separately or together, (i) at least one reflux inhibitor;
and (ii) at least one imidazopyridine of formula V:



or a pharmaceutically acceptable salt thereof, wherein

R^{18} is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

R^{19} is

- (a) CH_3
- (b) CH_2CH_3

R^{20} is

- (a) H
- (b) C_1-C_6 alkyl,
- (c) hydroxylated C_1-C_6 alkyl
- (d) halogen

R^{21} is

- (a) H,
- (b) C_1 - C_6 alkyl,
- (c) hydroxylated C_1 - C_6 alkyl, or
- (d) halogen;

R^{22} is

- (a) H, or
- (b) halogen;

R^{23} and R^{24} are the same or different, selected from any one of

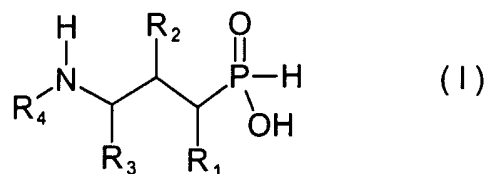
- (a) H,
- (b) C_1 - C_6 alkyl;
- (c) hydroxylated C_1 - C_6 alkyl
- (d) C_1 - C_6 alkoxy-substituted C_1 - C_6 alkyl

X is

- (a) NH, or
- (b) O;

2. A combination according to claim 1, said combination being a pharmaceutical composition, further comprising pharmaceutically and pharmacologically acceptable carriers and/or diluents.

3. A combination according to claim 1 or 2, wherein the reflux inhibitor is a compound according to formula I



wherein

R_1 represents hydrogen;

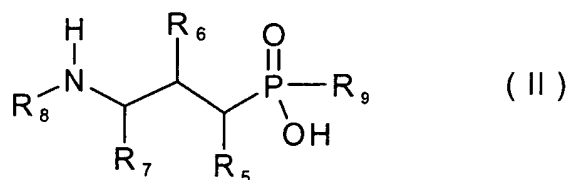
R_2 represents hydroxy, fluoro or an oxo group;

R_3 represents hydrogen;

5 R_4 represents hydrogen;
or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

4. A combination according to claim 1 or 2, wherein the reflux inhibitor is a compound according to formula II

10



wherein

R_5 represents hydrogen or lower alkyl;

15 R_6 represents a fluoro group;

R_7 represents hydrogen;

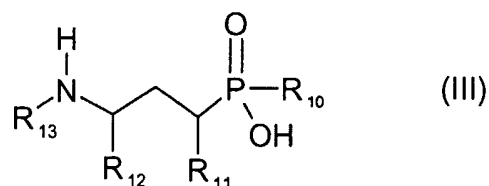
R_8 represents hydrogen;

20

R_9 represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl;
or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

5. A combination according to claim 1 or 2, wherein the reflux inhibitor is a
25 compound according to formula III

27



wherein

R₁₀ represents hydrogen, methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

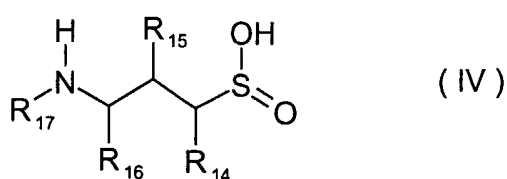
5 R₁₁ represents hydrogen, hydroxy, C₁-C₇ alkyl, C₁-C₇ alkoxy or halogen;

R₁₂ represents hydrogen, C₁-C₇ alkyl (optionally substituted by hydroxy, mercapto, C₁-C₇ alkoxy, C₁-C₇ thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

10 R₁₃ represents hydrogen, C₁-C₇ alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

6. A combination according to claim 1 or 2, wherein the reflux inhibitor is a
15 compound according to formula IV



wherein

R₁₄ represents hydrogen, hydroxy, C₁-C₇ alkyl, C₁-C₇ alkoxy or halogen;

20

R₁₅ represents hydrogen, hydroxy, mercapto, halogen, or an oxo group;

R₁₆ represents hydrogen or C₁-C₇ alkyl (optionally substituted by hydroxy, mercapto, C₁-C₇ alkoxy, C₁-C₇ thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

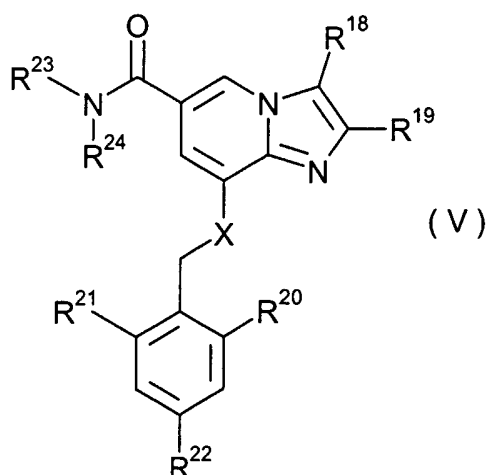
25

R_{17} represents hydrogen, C_1 - C_7 alkyl (optionally substituted by aryl or heteroaryl),
aryl or heteroaryl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

- 5 7. A combination according to any one of claims 1-6, wherein the combination is a
combined preparation for simultaneous, sequential or separate administration.
8. Use of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of
formula V:

10



15

20

or a pharmaceutically acceptable salt thereof, wherein

R^{18} is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

25

R^{19}
 R^{19} is

- (a) CH_3
- (b) CH_2CH_3

30

R^{20} is

- (a) H
- (b) C_1 - C_6 alkyl,

(c) hydroxylated C₁-C₆ alkyl

(d) halogen

R²¹ is

5

(a) H,

(b) C₁-C₆ alkyl,

(c) hydroxylated C₁-C₆ alkyl, or

(d) halogen;

10

R²² is

(a) H, or

(b) halogen;

R²³ and R²⁴ are the same or different, selected from any one of

15

(a) H,

(b) C₁-C₆ alkyl;

(c) hydroxylated C₁-C₆ alkyl

(d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

20

X is

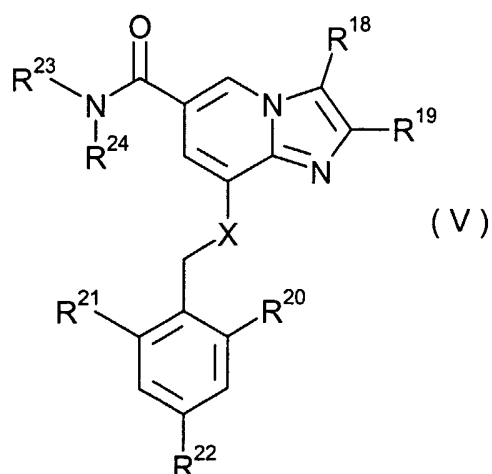
(a) NH, or

(b) O;

25

for the manufacture of a combination for the inhibition of transient lower
esophageal sphincter relaxations (TLESRs).

9. Use of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V:



or a pharmaceutically acceptable salt thereof, wherein

R^{18} is

- 15
- (a) H,
 - (b) CH_3 , or
 - (c) CH_2OH ;

R^{19} is

- 20
- (a) CH_3
 - (b) CH_2CH_3

R^{20} is

- 25
- (a) H
 - (b) C_1 - C_6 alkyl,
 - (c) hydroxylated C_1 - C_6 alkyl
 - (d) halogen

R^{21} is

- 30
- (a) H,
 - (b) C_1 - C_6 alkyl,
 - (c) hydroxylated C_1 - C_6 alkyl, or
 - (d) halogen;

R^{22} is

- (a) H, or
- (b) halogen;

R^{23} and R^{24} are the same or different, selected from any one of

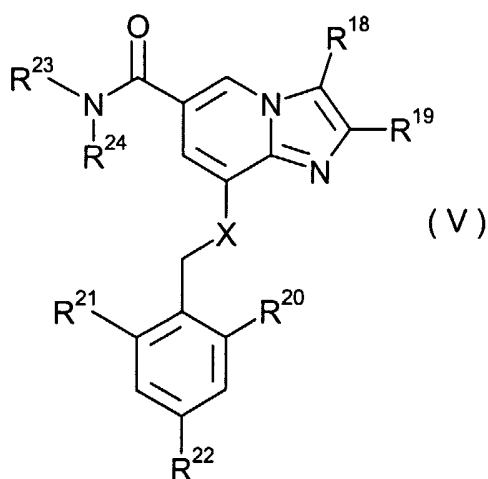
- (a) H,
- (b) C_1 - C_6 alkyl;
- (c) hydroxylated C_1 - C_6 alkyl
- (d) C_1 - C_6 alkoxy-substituted C_1 - C_6 alkyl

X is

- (a) NH, or
- (b) O;

for the manufacture of a combination for the treatment of gastro-esophageal reflux disease (GERD).

10. Use of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V:



or a pharmaceutically acceptable salt thereof, wherein

R^{18} is

- (a) H,
- (b) CH_3 , or

(c) CH₂OH;

R¹⁹ is

(a) CH₃

5 (b) CH₂CH₃

R²⁰ is

(a) H

(b) C₁-C₆ alkyl,

10 (c) hydroxylated C₁-C₆ alkyl

(d) halogen

R²¹ is

(a) H,

15 (b) C₁-C₆ alkyl,

(c) hydroxylated C₁-C₆ alkyl, or

(d) halogen;

R²² is

20 (a) H, or

(b) halogen;

R²³ and R²⁴ are the same or different, selected from any one of

(a) H,

25 (b) C₁-C₆ alkyl;

(c) hydroxylated C₁-C₆ alkyl

(d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

X is

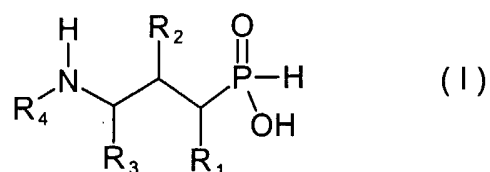
30 (a) NH, or

(b) O;

for the manufacture of a combination for the prevention of reflux.

11. Use according to any one of claims 8-10, wherein the reflux inhibitor is a GABA_B receptor agonist.

12. Use according to any one of claims 8-10, wherein the reflux inhibitor is a compound according to formula I



wherein

R₁ represents hydrogen;

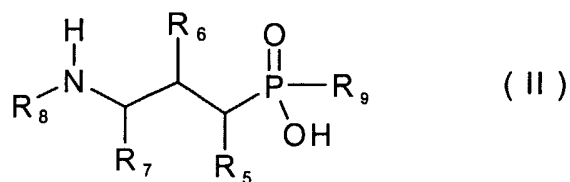
R₂ represents hydroxy, fluoro or an oxo group;

R₃ represents hydrogen;

R₄ represents hydrogen;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

13. Use according to any one of claims 8-10, wherein the reflux inhibitor is a compound according to formula II



wherein

R₅ represents hydrogen or lower alkyl;

R₆ represents a fluoro group;

5

R₇ represents hydrogen;

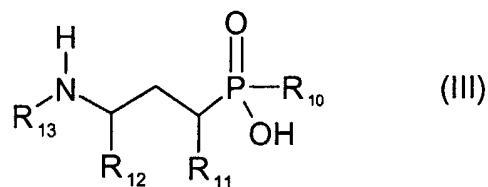
R₈ represents hydrogen;

10

R₉ represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl;
or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

14. Use according to any one of claims 8-10, wherein the reflux inhibitor is a
compound according to formula III

15



wherein

R₁₀ represents hydrogen, methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

20

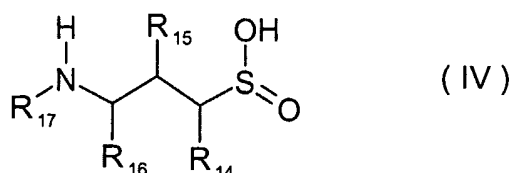
R₁₁ represents hydrogen, hydroxy, C₁-C₇ alkyl, C₁-C₇ alkoxy or halogen;

R₁₂ represents hydrogen, C₁-C₇ alkyl (optionally substituted by hydroxy, mercapto,
C₁-C₇ alkoxy, C₁-C₇ thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

25

R₁₃ represents hydrogen, C₁-C₇ alkyl (optionally substituted by aryl or heteroaryl),
aryl or heteroaryl;
or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

15. Use according to any one of claims 8-10, wherein the reflux inhibitor is a compound according to formula IV



5 wherein

R_{14} represents hydrogen, hydroxy, C_1 - C_7 alkyl, C_1 - C_7 alkoxy or halogen;

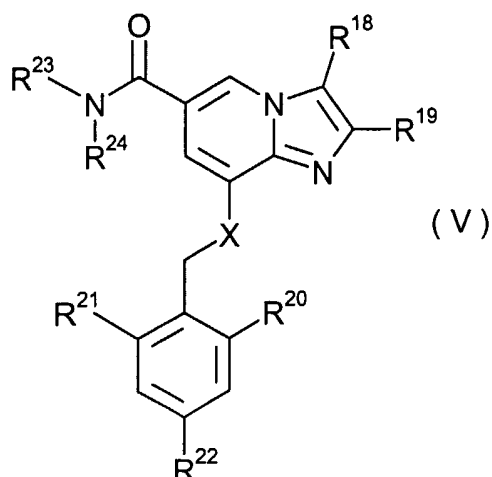
R_{15} represents hydrogen, hydroxy, mercapto, halogen, or an oxo group;

10 R_{16} represents hydrogen or C_1 - C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1 - C_7 alkoxy, C_1 - C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R_{17} represents hydrogen, C_1 - C_7 alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

15 or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

16. A method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of (i) at least one reflux inhibitor; and (ii) at least one imidazopyridine of formula V:



20

25

or a pharmaceutically acceptable salt thereof, wherein

R^{18} is

- 5 (a) H,
(b) CH_3 , or
(c) CH_2OH ;

R^{19} is

- 10 (a) CH_3
(b) CH_2CH_3

R^{20} is

- 15 (a) H
(b) C_1 - C_6 alkyl,
(c) hydroxylated C_1 - C_6 alkyl
(d) halogen

R^{21} is

- 20 (a) H,
(b) C_1 - C_6 alkyl,
(c) hydroxylated C_1 - C_6 alkyl, or
(d) halogen;

R^{22} is

- 25 (a) H, or
(b) halogen;

R^{23} and R^{24} are the same or different, selected from any one of

- 30 (a) H,
(b) C_1 - C_6 alkyl;
(c) hydroxylated C_1 - C_6 alkyl
(d) C_1 - C_6 alkoxy-substituted C_1 - C_6 alkyl

X is

- 35 (a) NH, or

(b) O;

is administered to a subject in need of such inhibition.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01008

A. CLASSIFICATION OF SUBJECT MATTER

C07F 9/30; C07C 211/03, 313/04, 229/08; C07D 233/64, 307/52, 401/12, 213/65, 213/68, 213/69;
IPC7: 235/28, 471/04; A61K 31/66, 31/185, 31/197, 31/4439, 31/4184, 31/437; 4375, 4188; A61P 1/04
 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)

IPC7: C07D, C07C, 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)

CHEM. ABS DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6313136 B1 (KOSRAT AMIN ET AL), 6 November 2001 (06.11.01), abstract; column 1, lines 38-44; column 10, lines 19-30; example; claim --	1-16
Y	WO 9811885 A1 (ASTRA AKTIEBOLAG), 26 March 1998 (26.03.98), page 1, lines 5-7; page 2, lines 17-25; page 3, line 29 - page 6, line 6; page 13, table 1; page 14-16, claim --	1-16
Y	WO 0142252 A1 (ASTRAZENECA AB), 14 June 2001 (14.06.01), pages 15-20, examples 1-4; page 29, lines 12-15; pages 30-39, claim --	1-16

☒ 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

15 Sept 2003

Date of mailing of the international search report

16 -09- 2003

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01008

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 0141743 A1 (ASTRAZENECA AB), 14 June 2001 (14.06.01), pages 16-18, examples 1-4; page 29, lines 12-15; pages 30-39, claim -- -----	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01008

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.: **16**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☒ Claims Nos.: **1-2, 7-11, 16**
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:
see next sheet
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 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.
☐ No protest accompanied the payment of additional search fees.

Box I.1

Claim 16 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/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/compositions.

Box I.2

Present claims 1-2, 7-11 och 16 relate to compounds defined by reference to desirable properties, namely reflux inhibiting properties (claims 1-2, 7-11 och 16) and agonism at GABA_B-receptors (claim 11). The claims cover combinations, and the use of combinations, comprising all compounds having these properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such combinations.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define compounds by reference to a result to be achieved. This lack of clarity is such as to render a meaningful search over the whole of the claimed scope impossible.

The search has been carried out only for the compounds with the formula V in the present claim 1 (and 8-10 and 16), in combination with the compounds with the formulas I-IV in the present claims 3-6 (and 12-15), GABA or its derivative baclofen

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

International application No.

PCT/SE 03/01008

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INTERNATIONAL SEARCH REPORT
Information on patent family members

26/07/03

International application No.
PCT/SE 03/01008

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