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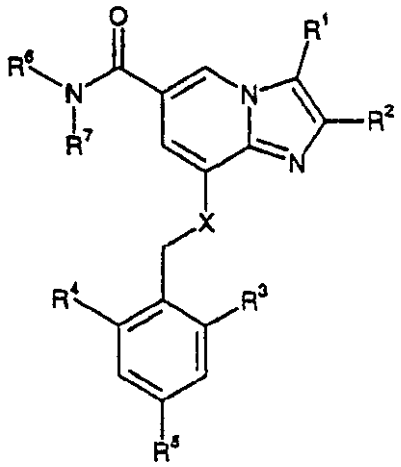
(54) Title: IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

(57) *Abstract*

The present invention relates to imidazo pyridine derivatives of formula (I), in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxyamide group in 6-position, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.



(I)

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IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

TECHNICAL FIELD

The present invention relates to novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above. The invention also relates to new intermediates for in the preparation of the novel compounds.

BACKGROUND ART

Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known in the art, e.g. from EP-B-0033094 and US 4,450,164 (Schering Corporation); from EP-B-0204285 and US 4,725,601 (Fujisawa Pharmaceutical Co.); and from publications by J. J. Kaminski et al. in the Journal of Medical Chemistry (vol. 28, 876-892, 1985; vol. 30, 2031-2046, 1987; vol. 30, 2047-2051, 1987; vol. 32, 1686-1700, 1989; and vol. 34, 533-541, 1991).

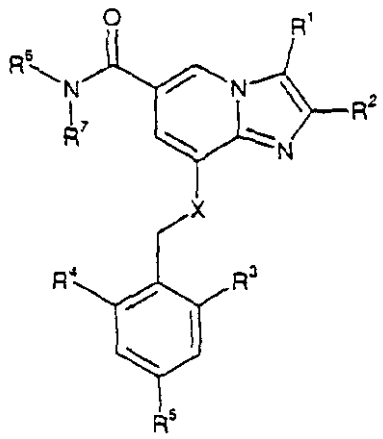
For a review of the pharmacology of the gastric acid pump (the H^+, K^+-ATPase), see Sachs et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I, which are imidazo pyridine derivatives in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxamide group in 6-position are particularly

effective as inhibitors of the gastrointestinal H^+, K^+-ATPase and thereby as inhibitors of gastric acid secretion.

In one aspect, the invention thus relates to compounds of the general Formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

(a) H,

(b) CH_3, or

(c) CH_2OH;

R^2 is

(a) CH_3

(b) CH_2CH_3

R^3 is

(a) H

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl

(d) halogen

R^4 is

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

R^5 is
(a) H, or
(b) halogen;

R^6, R^7 are the same or different
(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.

As used herein, the term "C_1–C_6 alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C_1–C_6 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.

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. 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 invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I, such as prodrugs.

It will also be appreciated by those skilled in the art, although derivatives of compounds of formula I may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of formula I are included within the scope of the invention.

Depending on the process conditions the end products of the Formula I 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.

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulphonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybensoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halogenbensenesulphonic acid, toluenesulphonic acid or naphthalenesulphonic acid.

Preferred compounds according to the invention are those of the Formula I wherein R^1 is CH_3 or CH_2OH; R^2 is CH_3 or CH_2CH_3; R^3 is CH_3 or CH_2CH_3; R^4 is CH_3 or CH_2CH_3; R^5 is H, Br, Cl, or F.

Particularly preferred compounds according to the invention are:

- 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
- 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
- 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-dimethylbenzylamino)-imidazo[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-diethylbenzylamino)-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-methylbenzylamino)-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-methylbenzylamino)-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

- 2,3-dimethyl-8-(2-ethyl-6-methylbenzyloxy)-imidazo[1,2-a]pyridine-6-carboxamide

Most preferred compounds according to the invention are:

- 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
- 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
- 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
- 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide

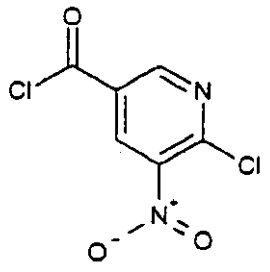
Preparation

The present invention also provides the following processes A, B and C for the manufacture of compounds with the general Formula I.

Process A

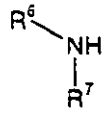
Process A for manufacture of compounds with the general Formula I wherein X is NH comprises the following steps:

a) Compounds of the general Formula II



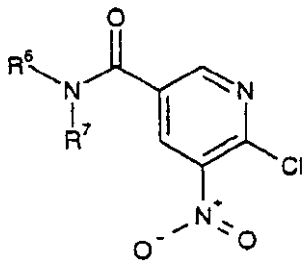
II

can be reacted with amino compounds of the general Formula III



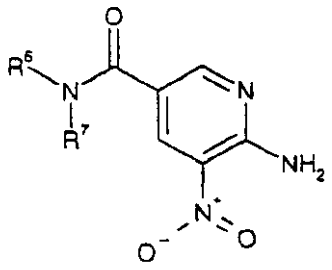
III

wherein R^6 and R^7 are as defined for Formula I, to the corresponding amide of the Formula IV. The reaction can be carried out in standard conditions in an inert solvent.



IV

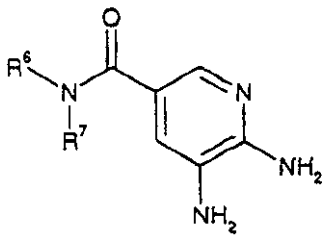
b) Compounds of the general Formula IV can be reacted with ammonia to compounds of the general Formula V



V

wherein R^6 and R^7 are as defined for Formula I. The reactions can be carried out under standard conditions in an inert solvent.

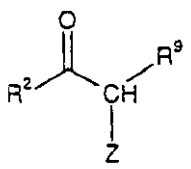
c) Compounds of the Formula V can be reduced e.g. by using hydrogen and a catalyst such as Pd/C to compounds of the Formula VI



VI

wherein R^6 and R^7 are as defined for Formula I. The reaction can be carried out under standard conditions in an inert solvent.

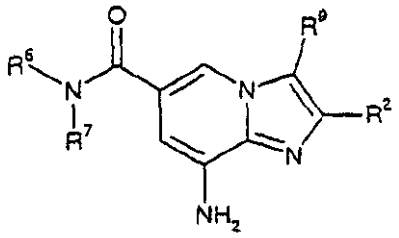
d) The imidazo[1,2-a]pyridine compounds of the Formula VIII can be prepared by reacting compounds of the general Formula VI with compounds of the general Formula VII



VII

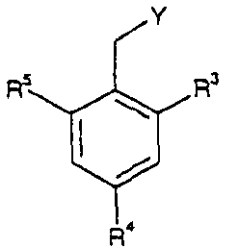
wherein R^2 is as defined for Formula I and Z is a leaving group such as halogen, mesyl, tosyl and R^9 represents H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$ etc.

The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide, etc. with or without a base.



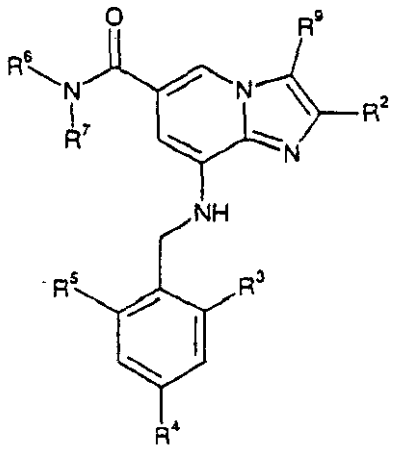
VIII

e) Compounds of the Formula VIII can be reacted with compounds of the Formula IX



IX

wherein R^3, R^4 and R^5 are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl , to the compounds of the Formula X.



X

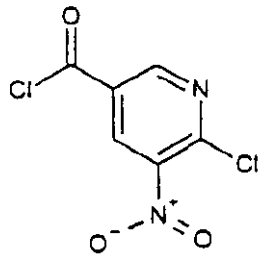
wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for Formula I and R^9 is H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc. It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

f) Reduction of compounds of the general Formula X wherein R^9 is an ester group e.g. by using lithium borohydride in an inert solvent such as tetrahydrofuran or diethyl ether, to the compounds of the general Formula I wherein R^1 is CH_2OH.

Process B

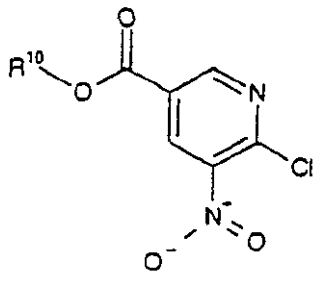
Process B for manufacture of compounds with the general Formula I wherein R^1 is H or CH_3 and X is NH comprises the following steps:

a) Compounds of the general Formula II



II

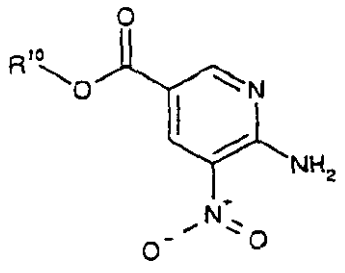
can be reacted with an alcohol compound of the general Formula R^{10}–OH, wherein R^{10} is an alkyl group such as methyl, ethyl, etc. to the corresponding ester of Formula XI.



XI

The reactions can be carried out under standard conditions .

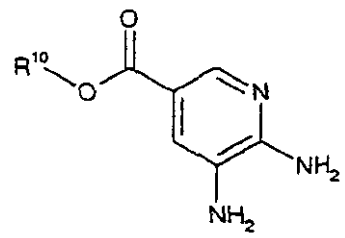
b) Compounds of the general Formula XI can be reacted with ammonia to compounds of the general Formula XII



XII

wherein R^{10} is an alkyl group such as methyl or ethyl, etc. The reactions can be carried out under standard conditions in an inert solvent.

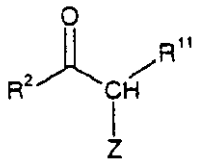
c) Compounds of the Formula XII can be reduced e.g. by using hydrogen and a catalyst such as Pd/C to compounds of the Formula XIII



XIII

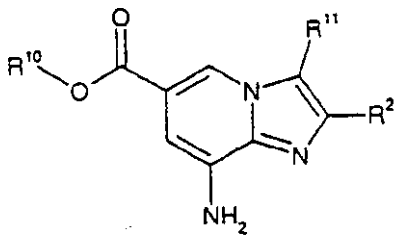
wherein R^{10} is an alkyl group such as methyl, ethyl etc. The reaction can be carried out under standard conditions in an inert solvent.

d) The imidazo[1,2-a]pyridine compounds of the Formula XV wherein R^{10} is an alkyl group such as methyl, ethyl etc. can be prepared by reacting compounds of the general Formula XIII with compounds of the general Formula XIV



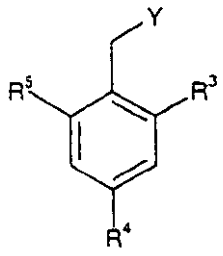
XIV

wherein R^2 is as defined for Formula I, Z is a leaving group such as halogen , mesyl or tosyl and R^{11} represents H or CH_3. The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide etc, with or without a base.



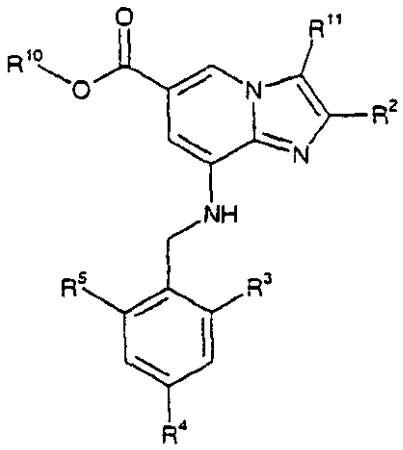
XV

e) Compounds of the Formula XV can be reacted with compounds of the Formula IX



IX

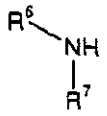
wherein R^3, R^4 and R^5 are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl, to the compounds of the Formula XVI.



XVI

wherein R^2, R^3, R^4 and R^5 are as defined for Formula I, R^{10} is an alkyl group such as methyl, ethyl, etc. and R^{11} is H, or CH_3. It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

f) Compounds of the Formula XVI can be reacted with amino compounds of the general Formula III



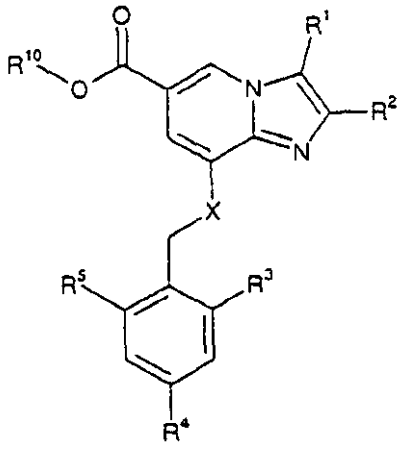
III

wherein R^6 and R^7 are as defined in Formula I to the corresponding amide of the Formula I wherein R^1 is H or CH_3 and X is NH. The reaction can be carried out by heating the reactants in the neat amino compound or in an inert solvent under standard conditions.

Process C

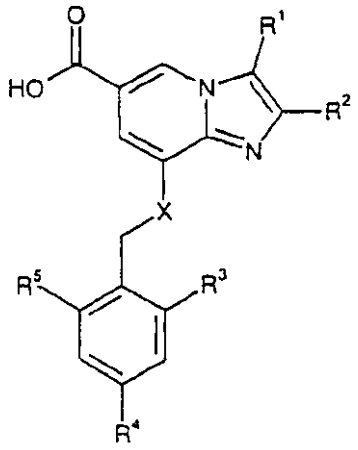
Process C for manufacture of compounds with the general Formula I comprises the following steps:

a) Treating compounds of Formula XVII



XVII

wherein R^1, R^2, R^3, R^4, R^5, and X are as defined in Formula I and R^{10} is an alkyl group such as methyl, ethyl, etc, with acid or base under standard conditions can hydrolyzed them to the corresponding carboxylic acid compounds of Formula XVIII



XVIII

b) Compounds of the Formula XVIII wherein R^1, R^2, R^3, R^4, R^5 and X are as defined in Formula I can be reacted with amino compounds of Formula III in the presence of a coupling reagent to the corresponding amide compounds of the Formula I. The reaction can be carried out in an inert solvent under standard conditions.

Medical use

In a further aspect, the invention relates to compounds of the formula I for use in therapy, in particular for use against gastrointestinal inflammatory diseases. The invention also provides the use of a compound of the formula I in the manufacture of a medicament for the inhibition of gastric acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

The compounds according to the invention may thus be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre-and postoperatively to prevent acid aspiration and stress ulceration.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

Pharmaceutical formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient.

The compounds of the invention can also be used in formulations together with other active ingredients, e.g. antibiotics such as amoxicillin.

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

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with 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 glycol waxes. The mixture is then processed into granules or pressed into tablets.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active compound. Hard gelatin capsules may also contain the active compound in combination with solid

powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

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

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.1% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring 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 compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing 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 by reconstituted with a suitable solvent extemporaneously before use.

The compounds according to the present invention can also be used in formulations, together or in combination for simultaneous, separate or sequential use, with other active ingredients, *e.g.* for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa. Such other active ingredients may be antimicrobial agents, in particular:

- β-lactam antibiotics such as amoxicillin, ampicillin, cephalothin, cefaclor or cefixime;
- macrolides such as erythromycin, or clarithromycin;
- tetracyclines such as tetracycline or doxycycline;
- aminoglycosides such as gentamycin, kanamycin or amikacin;
- quinolones such as norfloxacin, ciprofloxacin or enoxacin;
- others such as metronidazole, nitrofurantoin or chloramphenicol; or
- preparations containing bismuth salts such as bismuth subcitrate, bismuth subsalicylate, bismuth subcarbonate, bismuth subnitrate or bismuth subgallate.

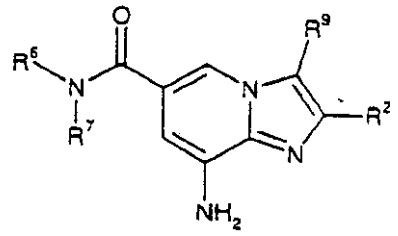
The compounds according to the present invention can also be used together or in combination for simultaneous, separate or sequential use with antacids such as aluminium hydroxide, magnesium carbonate and magnesium hydroxid or alginic acid, or together or in combination for simultaneous, separate or sequential use with pharmaceuticals which inhibit acid secretion, such as, H2-blockers (*e.g* cimetidine, ranitidine), H+/K+ - ATPase inhibitors (*e.g*. omeprazole, pantoprazole, lansoprazole or rabeprazole), or
together or in combination for simultaneous, separate or sequential use with gastroprokinetics (*e.g*. cisapride or mosapride).

Intermediates

A further aspect of the invention is new intermediate compounds which are useful in the synthesis of compounds according to the invention.

Thus, the invention includes

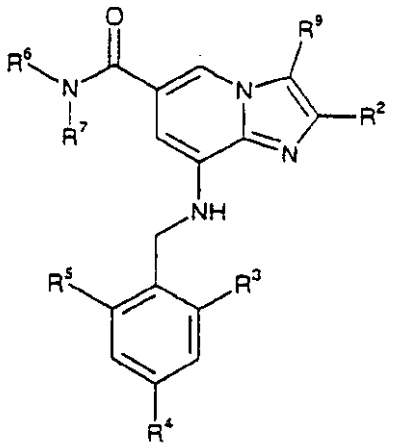
(a) a compound of the formula VIII



VIII

wherein R^2, R^6 and R^7 are as defined for Formula I. and R^9 is H, CH^3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc.:

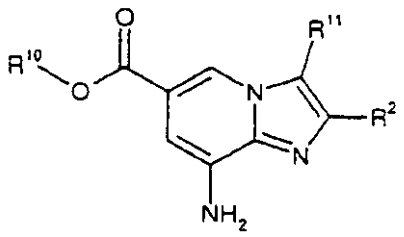
(b) a compound of the formula X



X

wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for Formula I, and R^9 is an ester group such as $COOCH_3$, $COOC_2H_5$ etc.;

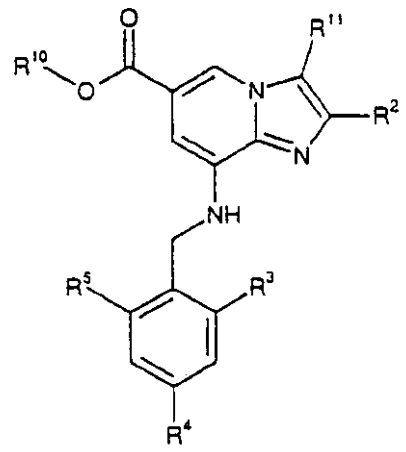
(c) a compound of the formula XV



XV

wherein R^2 is as defined for Formula I, R^{10} is an alkyl group and R^{11} is H or CH_3;

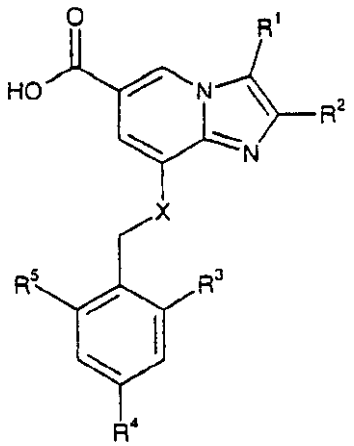
(d) a compound of the formula XVI



XVI

wherein R^2, R^3, R^4 and R^5 are as defined for Formula I, R^{10} is an alkyl group and R^{11} is H or CH_3;

(e) a compound of the formula XVIII



XVIII

wherein R^1, R^2, R^3, R^4, R^5 and X are as defined for

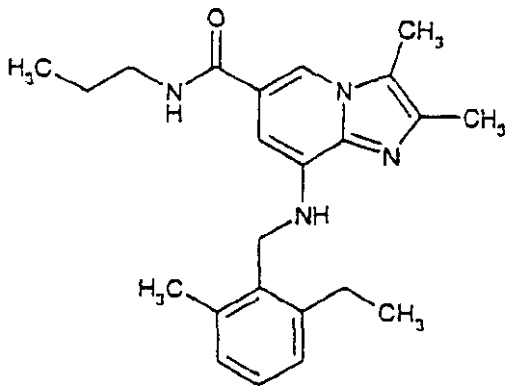
Formula I.

EXAMPLES

1. PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-propyl-imidazo[1,2-a]pyridine-6-carboxamide

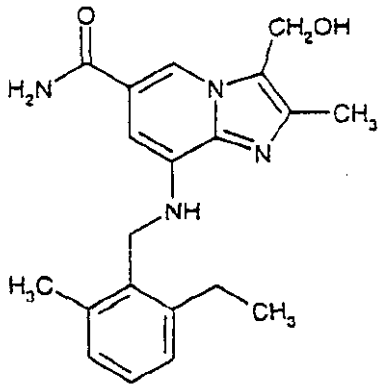


Ethyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.12 g, 0.33 mmol), propylamine (1.0 g, 17 mmol) and a cat. amount of sodium cyanide were refluxed in methanol (20 ml) for 24 h. An additional amount of propylamine (1.0 g, 17 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using dietyl ether as eluent. Crystallization from diethyl ether gave 0.053 g (42%) of the title compound.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.0 (t, 3H), 1.2 (t, 3H), 1.65-1.75 (m, 2H), 2.3 (s, 3H), 2.35 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 3.4-3.5 (m, 2H), 4.35 (d, 2H), 4.9 (bs, 1H), 6.2 (bs, 1H), 6.35 (s, 1H), 7.0-7.2 (m, 4H), 7.85 (s, 1H).

Example 1.2

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide

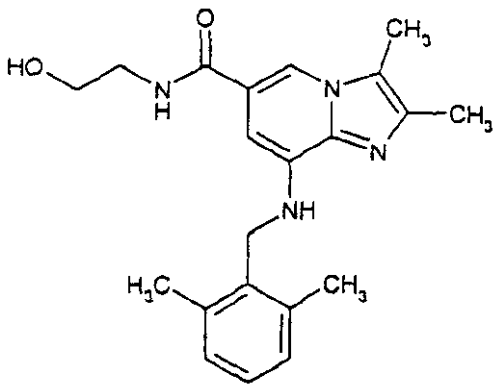


Ethyl 6-(aminocarbonyl)-8-(2-ethyl-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine-3-carboxylate (280 mg, 0.71 mmol) and lithium borohydride (16 mg, 0.71 mmol) were added to tetrahydrofuran (10 ml) and the reaction mixture was refluxed for 70 min. Additional amounts of lithium borohydride (16 mg) and methanol (45 mg, 1.42 mmol) were added and the mixture was refluxed for 80 min. Additional amounts of lithium borohydride (16 mg) and methanol (22 mg, 71 mmol) were added and the mixture was refluxed for 4 h. The reaction mixture was allowed to reach R.T. and water (1 ml) and methanol (5 ml) and was stirred for 40 min. at R.T. The solvents were evaporated under reduced pressure and the residue was added to water and was stirred for 80 min. The crystals were filtered off and washed with water, ethyl acetate/ethanol and diethyl ether to give the desired product (115 mg, 46 %).

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.15 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.35 (d,2H), 4.75 (d, 2H), 4.85 (t, 1H), 5.1 (t, 1H), 6.8 (s, 1H), 7.1-7.25 (m, 3H), 7.4 (bs, 1H), 8.05 (bs, 1H), 8.3 (s, 1H)

Example 1.3

Synthesis of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide

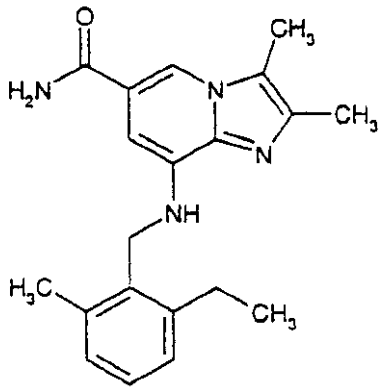


Methyl 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.12 g, 0.33 mmol), ethanolamine (0.2 g, 3.3 mmol) and sodium cyanide (10 mg, 0.2 mmol) were refluxed in dimethoxyethane (2 ml) for 20 h. The solvent was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using methylene chloride : methanol (92:8) as eluent gave the product which was washed with diethyl ether to give 103 mg (79%) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.3 (s, 6H), 2.35 (s, 6H), 3.5-3.6 (m, 2H), 3.75-3.8 (m, 2H), 4.3 (d, 2H), 4.95 (t, 1H), 6.4 (s, 1H), 6.85 (t 1H), 7.0-7.2 (m, 3H), 7.75 (s, 1H)

Example 1.4

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

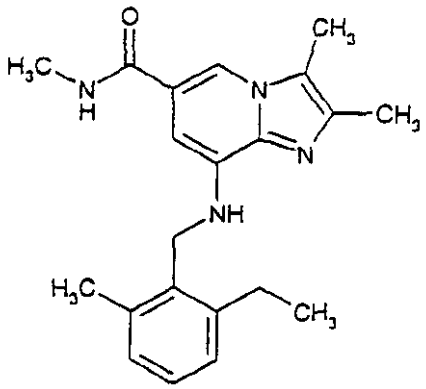


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (3.3 g, 16.2 mmol), 2-ethyl-6-methylbenzylchloride (2.73 g, 16.2 mmol), potassium carbonate (8.0 g, 58 mmol) and potassium iodide (1.1 g, 6.6 mmol) were added to acetone (150 ml) and refluxed for 20 h. An additional amount of 2-ethyl-6-methylbenzylchloride (1.0 g, 5.9 mmol) was added and the reaction mixture was refluxed for 7 h. Methylene chloride (60 ml) and methanol (30 ml) were added. The reaction mixture was filtered and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride: methanol (100:7) as eluent. Crystallization from ethyl acetate gave 2.8 g (50%) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 4.4 (d, 2H), 4.9 (bs, 1H), 6.0 (bs, 2H), 6.45 (s, 1H), 7.0-7.2 (m, 3H), 7.9, (s, 1H).

Example 1.5

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide

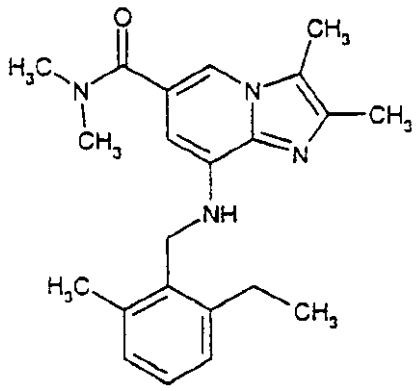


2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.14 g, 0.44 mmol) were added to methylene chloride (10 ml) and the reaction mixture was stirred at room temperature for 15 min. Methylamine (0.1 g, 3.2 mmol) was added and the reaction mixture was stirred at ambient temperature for 1.5 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using ethylacetate : methylene chloride (1:1) as eluent. The yield was treated with diethyl ether to give 40 mg (26 %) of the desired product .

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 3.05 (d, 3H), 4.35 (d, 2H), 4.9 (t, 1H), 6.3 (bs, 1H), 6.4 (s, 1H), 7.0-7.2 (m, 3H), 7.85 (s, 1H)

Example 1.6

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N,N,2,3-tetramethylimidazo[1,2-a]pyridine-6-carboxamide

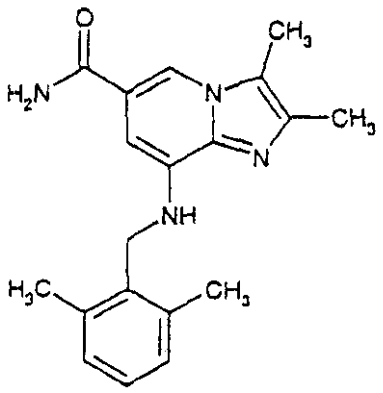


2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). Dimethylamin (0.063 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 4 h. An additional amount of dimethylamin (0.1 ml) was added and the mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using methylene chloride : methanol (9:1) as eluent. The oily product was treated with heptane and the solid that formed was filtered off to give 0.1 g (62 %) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.35 (s, 6H), 2.4 (s, 3H), 2.7 (q, 2H), 3.15 (s, 6H), 4.4 (d, 2H), 4.9 (t, 1H), 6.25 (s, 1H), 7.0-7.2 (m, 3H), 7.45 (s, 1H)

Example 1.7

Synthesis of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

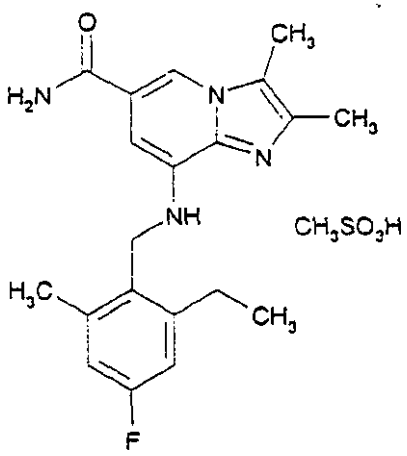


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (0.6 g, 2.9 mmol), 2,6-dimethylbenzylchloride (0.45 g, 2.9 mmol), sodium carbonate (1.0 g, 9.4 mmol) and potassium iodide (0.2 g, 1.3 mmol) were added to acetone (25 ml) and refluxed for 19 h. Methylene chloride was added and inorganic salts were filtered off. The solution was washed with a bicarbonate solution, the organic layer was separated, dried and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride : methanol (100 : 5) as eluent and the product was washed with diethyl ether to give 0.78 g (82 %) of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.4 (s, 6H), 2.42 (s, 3H), 4.4 (d, 2H), 2.95 (bs, 1H), 6.45 (s, 1H), 7.05-7.15 (m, 3H), 7.95 (s, 1H)

Example 1.8

Synthesis of 2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate

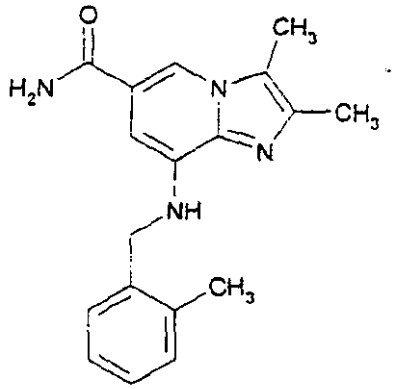


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (0.7 g, 1.9 mmol), 2-ethyl-4-fluoro-6-methylbenzylchloride (0.26 g, 1.9 mmol) and diisopropylethylamin (0.54 g, 4.2 mmol) were added to dimethylformamide (5 ml) and stirred at room temperature for 1 h. Methylene chloride and water were added to the reaction mixture, the organic layer was separated, dried and evaporated under reduced pressure. The residue was solved in ethylacetate and ethanol and metanesulfonic acid (0.2 g, 2 mmol) was added. The product was filtred off and was solved in methylene chloride:methanol (2:1) and an excess of potassium carbonate. The solids were filtred off and the solvent was evaporated under reduced pressure.The residue was purified by column chromatography on silica gel using methylene chloride: methanol (10:1) as eluent. The residue was solved in ethylacetate and methansulfonic acid (0.04 g, 0.4 mmol) was added. The salt was filtred off to give 0.2 g (23 %) of the title compound.

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.15 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 2.45 (s, 3H), 2.6 (q, 2H), 4.35 (d, 2H), 6.15 (bs, 1H), 6.95-7.05 (m, 2H), 7.4 (s, 1H), 7.8 (bs, 1H), 8.3 (bs, 1H), 8.45 (s, 1H)

Example 1.9

Synthesis of 2,3-dimethyl-8-(2-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

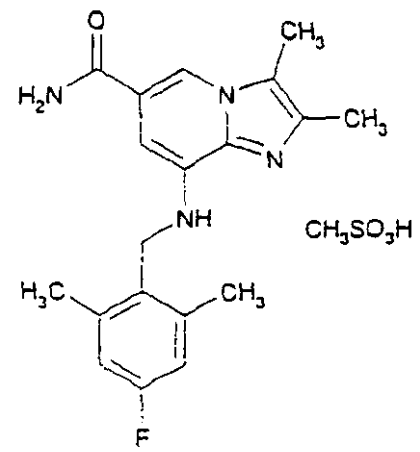


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.0 g, 2.7 mmol), α-chloro-o-xylene (0.38 g, 2.7 mmol) and diisopropylethylamin (0.76 g, 5.9 mmol) in dimethylformamide (7 ml) were stirred at 50 °C for 7 h and at room temperature for 72 h. The solvent was evaporated and the residue was treated with a mixture of methylene chloride, water and a small amount of diisopropylethylamin. The solid that formed was isolated by filtration and washed with ethylacetate to give 0.11 g (13 %) of the title compound.

^{1}H-NMR (300 MHz,DMSO-d_6): δ 2.3 (s, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 4.45 (d, 2H), 6.3-6.4 (m, 2H), 7.1-7.25 (m, 4H), 7.3 (bs, 1H), 7.85 (bs, 1H), 8.05 (s, 1H)

Example 1.10

Synthesis of 2,3-dimethyl-8-(2,6-dimethyl-4-fluoro-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate

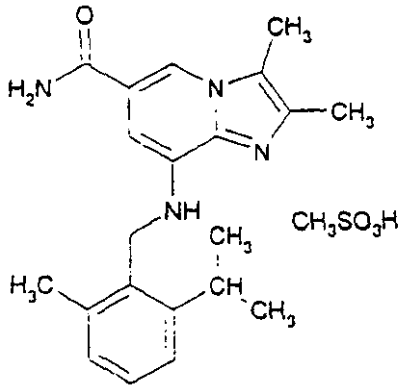


8-Amino-2,3-dimethylimidazo[1.2-a]pyridine-6-carboxamide mesylate (5.0 g, 13.4 mmol), 2,6-dimethyl-4-fluorobenzylbromide (2.91g, 13.4 mmol), diisopropylethylamin (3.8 g, 29.5 mmol) and a cat. amount of potassium iodide were stirred in dimethylformamide (20 ml) at room temperature overnight. Water (70 ml) and methylene chloride (2 x 50 ml) were added to the reaction mixture and the organic layer was separated, dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. The product was solved in isopropanol and methansulfonic acid (0.3 g) was added. The salt that formed was isolated by filtration and washed with isopropanol and diethyl ether to give 1.4 g (24 %) of the title compound.

^{1}H-NMR (500 MHz,DMSO-d_6): δ 2.25 (s, 3H), 2.35 (s, 6H), 2.4 (s, 3H), 2.5 (s, 3H), 4.4 (d, 2H), 6.1 (bs, 1H), 7.0 (d, 2H), 7.35 (s, 1H), 7.8 (bs, 1H), 8.3 (bs, 1H), 8.45 (s, 1H)

Example 1.11

Synthesis of 2,3-dimethyl-8-(2-methyl-6-isopropylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate

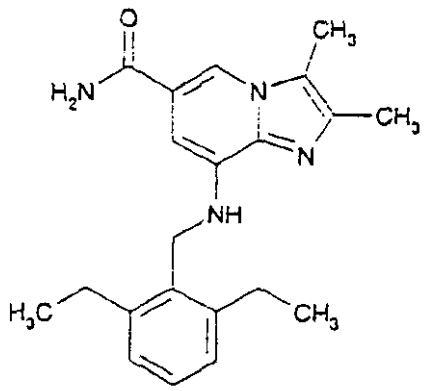


8-Amino-2,3-dimethylimidazo[1.2-a]pyridine-6-carboxamide mesylate (3.0 g, 8.0 mmol), 2-methyl-6-isopropylbenzylchloride (1.47 g, 8.0 mmol), diisopropylethylamin (2.4 g, 18.6 mmol) and a cat. amount of potassium iodide in dimethylformamide (15 ml).
The title compound were prepared according to Example 1.10 (Yield: 1.3 g, 36 %)

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.2 (d, 6H), 2.25 (s, 3H), 2.4 (s, 3H), 2.45 (s, 3H), 2.5 (s, 3H), 3.2 (m, 1H), 4.45 (d, 2H), 6.15 (bs, 1H), 7.15-7.3 (m, 3H), 7.4 (s, 1H), 7.85 (bs, 1H), 8.35 (bs, 1H), 8.45 (s, 1H)

Example 1.12

Synthesis of 2,3-dimethyl-8-(2,6-diethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

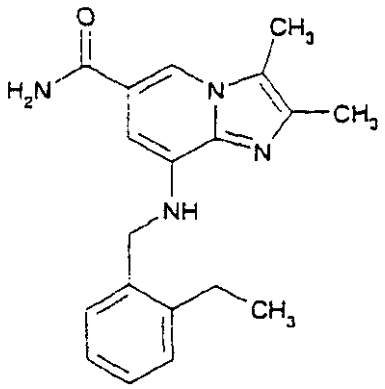


8-Amino-2,3-dimethylimidazo[1.2-a]pyridine-6-carboxamide mesylate (4.0 g, 10.7 mmol), 2,6-diethylbenzylchloride (1.8 g, 9.9 mmol), diisopropylethylamin (3.0 g, 23.3 mmol) were stirred in dimethylformamide (20 ml) at 50 °C overnight and at 70 °C for 3 h. Water (60 ml) and methylene chloride were added and the organic layer was separated, dried and evaporated under reduced pressure. The residue was treated with diethyl ether and the product was filtred off to give 1.7 g (45 %) of the title compound.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.2 (t, 6H), 2.35 (s, 3H), 2.4 (s,3H), 2.7 (q, 4H), 4.4 (d, 2H), 4.95 (bs, 1H), 6.15 (bs, 2H), 6.5 (s, 1H), 7.05-7.25 (m, 3H), 7.95 (s, 1H)

Example 1.13

Synthesis of 2,3-dimethyl-8-(2-ethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide



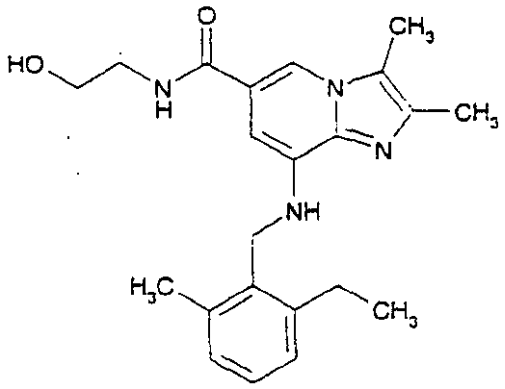
8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (4.0 g, 10.7 mmol), 2-ethylbenzylchloride (1.65 g, 10.7 mmol), diisopropylethylamin (3.0 g, 23.3 mmol) in diemethylformamide (20 ml).

The title compound was prepared according to Example 1.12 (Yield: 1.15 g, 26 %)

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.2 (t, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 4.5 (d, 2H), 6.3 (t, 1H), 6.4 (s, 1H), 7.05-7.25 (m, 4H), 7.3 (bs, 1H), 7.85 (bs, 1H), 8.05 (s, 1H)

Example 1.14

Synthesis of 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide



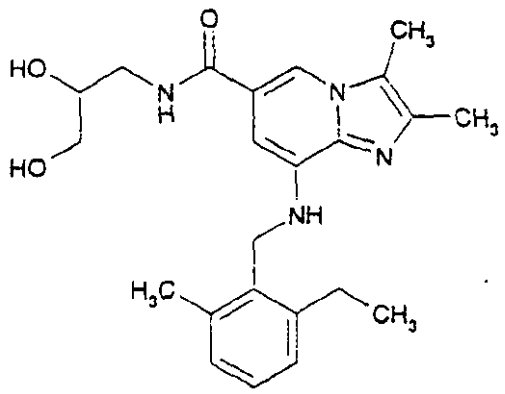
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.29 g, 0.90 mmol) were added to methylene chloride (15 ml)

and the mixture was stirred for 5 min. Ethanolamin (0.11g, 1.8 mmol) was added and the reaction mixture was stirred at ambient temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent. Crystallization from diethyl ether gave 0.2 (59 %) of the desired product.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.2 (t, 3H), 2.3 (s,6H), 2.35 (s,3H), 2.7 (q, 2H), 3.55-3.6 (m,2H), 3.8-3.85 (m, 2H), 4.35 (d, 2H), 4.9 (t, 1H), 6.4 (s, 1H), 6.85 (t, 1H), 7.05-7.2 (m, 3H), 7.75 (s, 1H)

Example 1.15

Synthesis of N-(2,3-dihydroxypropyl)-2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-[1.2-a]pyridine-6-carboxamide



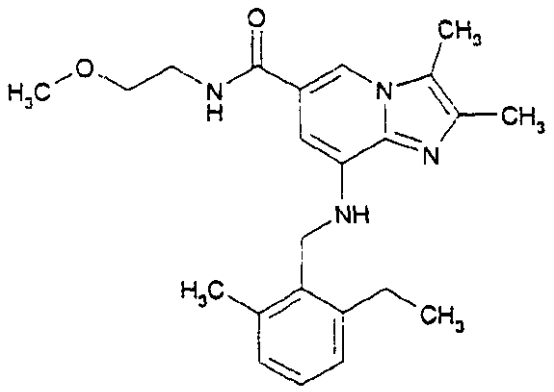
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.29 g, 0.90 mmol) and 3-amino-1,2-propanediol (0.16 g, 1.81 mmol) in dimethylformamide (10 ml).

The title compound was prepared according to Example 1.14 (Yield: 0.2 g, 54 %)

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1,2 (t,3H), 1.82-1.85 (m, 1H), 2.32 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 2.7 (q, 2H), 3.5-3.65 (m, 4H), 3.72-3.77 (m,1H), 3.85-3.91 (m,1H), 4.34 (d, 2H), 5.04 (t, 1H), 6.4 (d, 1H), 6.89 (t, 1H), 7.04-7.12 (m, 2H), 7.18 (t, 1H), 7.78 (d, 1H)

Example 1.16

Synthesis of 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide

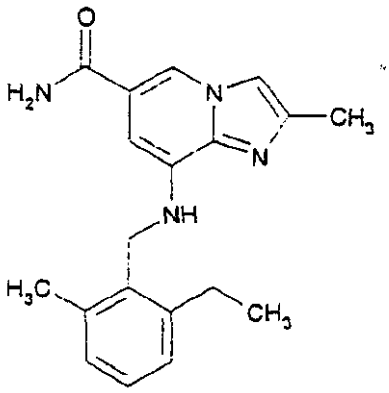


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) and 2-methoxyethylamin (0.11 g, 1.4 mmol) in methylene chloride (10 ml).
The title compound were prepared according to Example 1.14
Crystallization from hexane:ethylacetate. (Yield: 0.09 g, 53 %)

^{1}H-NMR (400 MHz,$CDCl_3$): δ 1.22 (t, 3H), 2.34 (s, 3H), 2.38 (s, 3H), 2.39 (s, 3H), 2.71 (q, 2H), 3.42 (s, 3H), 3.6-3.72 (m, 4H), 4.38 (d, 2H), 4.91 (t, 1H), 6.42 (s, 1H), 6.58 (t, 1H), 7.04-7.2 (m, 3H), 7.88 (s, 1H)

Example 1.17

Synthesis of 2-methyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

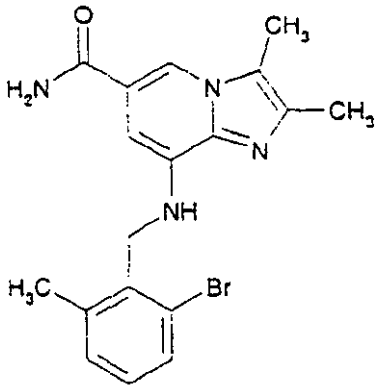


8-Amino-2-methylimidazo[1,2-a]pyridine-6-carboxamide (3.8 g, 20 mmol), 2-ethyl-6-methylbenzylchloride (2.8 g, 17 mmol), potassium carbonate (5.5 g, 40 mmol) and sodium iodide (0.1 g, 0.6 mmol) were added to dimethylformamide (75 ml) and the mixture was stirred at 50 °C for 4 h. and at room temperature for 48 h. The reaction mixture was filtred through silica gel and the gel was washed with methylene chloride. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Crystallization from a mixture of methylene chloride and hexane gave 0.13 g (2 %) of the title compound.

^{1}H-NMR (400 MHz,$CDCl_3$): δ 1.15 (t, 3H), 2.31 (s, 6H), 2.64 (q, 2H), 4.32 (d, 2H), 4.89 (bs, 1H), 6.36 (s, 1H), 7.0-7.15 (m, 3H), 7.23 (s, 3H), 8.03 (s, 1H)

Example 1.18

Synthesis of 2,3-dimethyl-8-(2-bromo-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

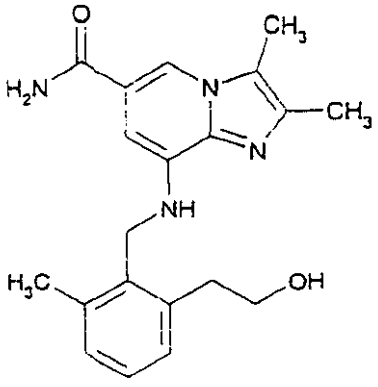


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.0 g, 5.0 mmol), 2-bromo-6-methylbenzylchloride (45%)(3.0 g, 5.0 mmol) and diisopropylethylamin (2.2 g, 17 mmol) were added to dimethylformamide (50 ml) and stirred at 50 °Cfor 48 h. Methylene chloride and water were added to the reaction mixture, the organic layer was separated, washed with saturated sodium chloride, dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue twice by column chromatography on silica gel using methylene chloride: methanol (10:1) and ethylacetate as eluent gave 0.18 g (1 %) of the desired product.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 2.28 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 4.48 (d, 2H), 5.0 (bs, 1H), 6.05 (bs, 2H), 6.41 (d, 1H), 6.95-7.1 (m, 2H), 7.37 (d, 1H), 7.87 (d, 1H)

Example 1.19

Synthesis of 2,3-dimethyl-8-(2-(2-hydroxyethyl)-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

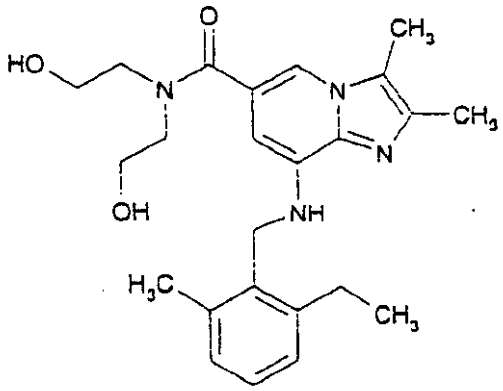


2,3-dimethyl-8-(2-(2-(benzyloxy)ethyl)-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide (0.13 g, 0.29 mmol), cyclohexene (1 ml), $Pd(OH)_2$ cat. (25 mg) were added to ethanol (5 ml) and the mixture was refluxed overnight. An additional amount of cyclohexene (1 ml) and $Pd(OH)_2$ cat. (25 mg) were added and the mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Treating the residue with chloroform and filtration gave 0.1 g (99 %) of the title compound.

^{1}H-NMR (400 MHz, CD_3OD): δ 2.29 (s, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 2.94 (t, 2H), 3.74 (t, 2H), 4.47 (s, 2H), 6.83 (d, 1H), 711-7.20 (m, 3H), 8.12 (d, 1H)

Example 1.20

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N,N-bis(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide



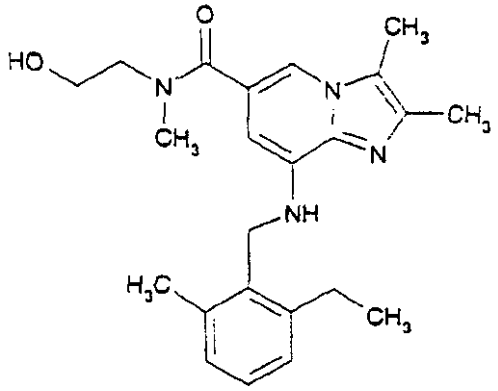
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.3 g, 0.94 mmol) and diethanolamine (0.2 g, 1.9 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.14 (Yield: 0.19 g, 50 %)

^{1}H-NMR (400 MHz,$CDCl_3$): δ 1.2 (t, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 2.7 (q, 2H), 3.65 (bs, 4H), 3.9 (bs, 4H), 4.35 (d, 2H), 4.95 (bs, 1H), 6.35 (s, 1H), 7.0-7.2 (m, 3H), 7.7 (s, 1H)

Example 1.21

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N-(2-hydroxyethyl)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide



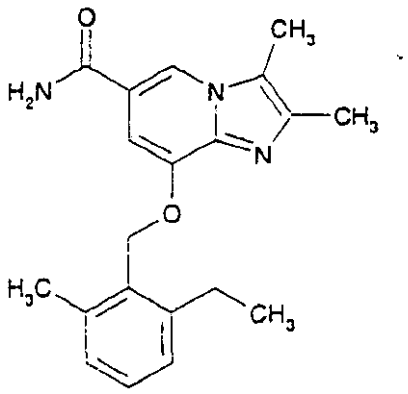
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.3 g, 0.94 mmol) and 2-(methylamino)ethanol (0.2 g, 2.66 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.14 (Yield: 0.25 g, 71 %)

^{1}H-NMR (600 MHz,$CDCl_3$): δ 1.2 (t, 3H), 2.25 (s, 6H), 2.35 (s, 3H), 2.7 (q, 2H), 3.15 (s, 3), 3.65 (bs, 2H), 3.9 (bs, 2H), 4.35 (d, 2H), 5.0 (bs, 1H), 6.25 (bs, 1H), 7.0-7.25 (m., 3H), 7.45 (bs, 1H)

Example 1.22

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyloxy)-imidazo[1,2-a]pyridine-6-carboxamide



6-amino-5-(2-ethyl-6-methylbenzyloxy)nicotinamide (0.14 g, 0.49 mmol), 3-bromo-2-butanone (0.075 g, 0.49 mmol) and sodium bicarbonate (0.1 g, 1.2 mmol) was added to acetonitrile (3 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Crystallization from acetonitrile gave 0.058 g (35 %) of the title compound.

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.14 (t, 3H), 2.24 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 2.69 (q, 2H), 5.25 (s, 2H), 7.1-7.3 (m, 4H), 7.51 (bs, 1H), 8.08 (bs, 1H), 8.42 (s, 1H)

2. PREPARATION OF INTERMEDIATES

Example 2.1

Synthesis of methyl 6-amino-5-nitronicotinate

6-Chloro-5-nitronicotinoyl chloride (22.0 g, 0.1 mol) was cooled to +5°C. Methanol was added dropwise during 30 min and the reaction mixture was stirred for 60 min. The temperature was not allowed to raise over +10°C. Ammonium hydroxide (25%, 400 ml) was added dropwise to the reaction mixture and the mixture was stirred at room temperature for 20 h. The product was filtered off, washed with water and dried to give 9.0 g (45.9%) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 3H), 6.3 (bs, 1H), 8.0 (bs, 1H), 8.95 (s, 1H), 9.05 (s, 1H)

Example 2.2

Synthesis of methyl 5,6-diaminonicotinate

Methyl 6-amino-5-nitronicotinate (9.0 g, 46 mmol) and a small amount of Pd/C cat. were added to methanol (200 ml) and the mixture was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased. Following filtration through celite, the methanol was evaporated under reduced pressure to give the title compound, 7.0 g (92%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.3 (s, 2H), 3.9 (s, 3H), 4.75 (s, 2H), 7.45 (s, 1H), 8.35 (s, 1H)

Example 2.3

Synthesis of methyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

Methyl 5,6-diaminonicotinate (0.9 g, 5.4 mmol) and 3-bromo-2-butanon (0.9 g, 6.0 mmol) were added to acetonitril (30 ml) and refluxed for 24 h. Upon cooling some of the product was filtered off as hydrobromide salt. 20 ml of the filtrate was evaporated under reduced pressure and diethyl ether was added. More product was filtrated off as hydrobromide salt. The salt was dissolved in methylene chloride and washed with a bicarbonate solution. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure to give 0.7 g (59%) of the desired compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.4 (s, 6H), 3.9 (s, 3H), 4.5 (s, 2H), 6.85 (s, 1H), 8.1 (s, 1H)

Example 2.4

Synthesis of methyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate

Methyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (0.7 g, 3.2 mmol), 2-ethyl-6-methylbenzylchloride (0.54 g, 3.2 mmol), potassium carbonate (0.9 g, 6.4 mmol) and a cat. amount of potassium iodide were added to acetonitrile (20 ml) and were refluxed for 6 h. Following filtration, the acetonitrile was evaporated under reduced pressure to give an oil. The oily residue was solved in methylene chloride and washed with water. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure to give a solid. Purification by column chromatography on silica gel using methylene chloride : ethylacetate (10 : 1) as eluent gave 0.42 g (38%) of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.15 (t, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 2.43 (s, 3H), 2.75 (q, 2H), 4.0 (s, 3H), 4.25 (d, 2H), 4.9 (bs, 1H), 6.8 (s,1H), 7.05-7.2 (m, 3H), 8.1 (s, 1H)

Example 2.5

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid

Methyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.4 g, 1.1 mmol) was added to a mixture of 1,4-dioxane (6 ml) and 2 M NaOH (6 ml) and was refluxed for 30 min. The dioxane was evaporated under reduced pressure and the aqueous solution was made acidic by addition of 2 M HCl. The acidic aqueous was basified by the addition of a saturated bicarbonate solution and the solid that formed was isolated by filtration to give 0.35 g (91%) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.15 (t, 3H), 2.2 (s, 3H), 2.35 (s, 6H), 2.7 (q, 2H), 4.35 (d, 2H), 4.65 (t, 1H), 6.8 (s, 1H), 7.05-7.2 (m, 3H), 7.95 (s, 1H)

Example 2.6

Synthesis of ethyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

Ethyl 5,6-diaminonicotinate (1.4 g, 7.7 mmol) and 3-bromo-2-butanon (1.16 g, 7.2 mmol) were added to 1,2-dimethoxyethan (50 ml) and refluxed for 20 h. The solvent was evaporated under reduced pressure and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with saturated sodium bicarbonate and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride : methanol (10 : 1) as eluent to give 0.3 g (17 %) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.4 (t, 3H), 2.4 (s, 6H), 4.35 (q, 2H), 4.6 (s, 2H), 6.75 (s, 1H), 8.2 (s, 1H)

Example 2.7

Synthesis of ethyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate

Ethyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (0.7 g, 3.0 mmol), 2-ethyl-6-methylbenzylchloride (0.5 g, 3.0 mmol), sodium carbonate (0.64 g, 6.0 mmol) and a cat. amount of potassium iodide were added to acetone (50 ml) and were refluxed for 20 h. Following filtration, the acetone was evaporated under reduced pressure to give an oil. The oily product was purified by column chromatography on silica gel using diethyl ether : petroleum ether (1:1) as eluent to give 0.12 g (9%) of the title product.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (t, 3H), 1.5 (t, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 2.75 (q, 2H), 4.45-4.5 (m, 4H), 4.9 (bs, 1H), 6.8 (s, 1H), 7.05-7.2 (m, 3H), 8.1 (s, 1H)

Example 2.8

Synthesis of 6-amino-5-nitronicotinamide

A solution of 6-chloro-5-nitronicotinoyl chloride (38 g, 0.2 mol) in tetrahydrofuran (500 ml) was stirred at +5°C and ammonia was bubbled into the solution. After 1 h the reaction mixture was allowed to warm to room temperature and ammonia was bubbled into the solution for additional 2.5 h. The reaction mixture was stirred at room temperature for 20 h. The solids were removed by filtration, washed thoroughly with water and were dried under reduced pressure to give 18.5 g (51%) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.4 (s, 1H), 8.05 (s, 1H), 8.3 (s, 2H), 8.8 (s, 2H)

Example 2.9

Synthesis of 5,6-diaminonicotinamide

A suspension of 6-amino-5-nitronicotinamide (18 g, 99 mmol) and a cat. amount of Pd/C in methanol (600 ml) and the mixture was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased. Following filtration through celite, the methanol was evaporated under reduced pressure to give the title compound, 14.5 g (96%).

^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.0 (bs, 2H), 6.1 (bs, 2H), 6.9 (bs, 1H), 7.15 (s, 1H), 7.55 (bs, 1H), 7.9 (s, 1H)

Example 2.10

Synthesis of 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

5,6-Diaminonicotinamide (12.5 g, 82 mmol), 3-bromo-2-butanon (13.6, 90 mmol) and acetonitrile (150 ml) were refluxed for 20 h. Additional 3-bromo-2-butanon (4.0 g, 26.5 mmol) was added and the reaction mixture was refluxed for 5 h. Upon cooling the solids were removed by filtration. The solids were added to methylene chloride (150 ml), methanol (150 ml) and potassium carbonate (22 g, 160 mmol) and were stirred for 30 min. The solids were removed by filtration and evaporation of the solvents under reduced pressure gave an oily residue. Purification by column chromatography on silica gel eluting with methylene chloride : methanol (5:1) gave 3.3 g (20%) of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H), 2.35 (s, 3H), 5.6 (s, 2H), 6.65 (s, 1H), 7.15 (bs, 1H), 7.85 (bs, 1H), 8.05 (s, 1H)

Example 2.11

Synthesis of ethyl 8-amino-6-(aminocarbonyl)-2-methylimidazo[1,2-a]pyridine-3-carboxylate

5,6-Diaminonicotinamide (2.0 g, 13.4 mmol), ethyl-2-chloroacetoacetate (2.38 g, 14.4 mmol) and ethanol (40 ml) were refluxed for 20 h. The precipitate was isolated by filtration and washed with ethanol and diethyl ether. The solids were suspended in water, basified with a sodium hydroxide solution and isolated by filtration. Washing the solids with water and diethyl ether gave 0.42 g (12%) of the desired product.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.4 (t, 3H), 2.6 (s, 3H), 4.35 (q, 2H), 5.95 (bs, 2H), 6.9 (s, 1H), 7.35 (bs, 1H), 8.0 (bs, 1H), 9.0 (s, 1H)

Example 2.12

Synthesis of ethyl 6-(aminocarbonyl)-8-(2-ethyl-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine-3-carboxylate

Ethyl 8-amino-6-(aminocarbonyl)-2-methylimidazo[1,2-a]pyridine-3-carboxylate (0.41 g, 1.6 mmol), 2-ethyl-6-methylbenzylchloride, sodium carbonate (0.7 g, 6.6 mmol), sodium iodide (0.15 g, 1.0 mmol) and acetone (20 ml) were refluxed for 44 h. Methylene chloride was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel eluting with methylene chloride : methanol (100 : 4) gave 0.35 g (56%) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H), 1.45 (t, 3H), 2.35 (s, 3H), 3.65 (s, 3H), 2.7 (q, 2H), 4.4-4.45 (m, 4H), 5.0 (t, 1H), 6.95 (s, 1H), 7.0-7.2 (m, 3H), 9.2 (s, 1H)

Example 2.13

Synthesis of 8-amino-2-methylimidazo[1,2-a]pyridine-6-carboxamide mesylate

5,6-diaminonicotinamide (10 g, 66 mmol), chloroacetone (6.1 g, 66 mmol) and sodium bicarbonate (11.2 g, 132 mmol) were added to dimethylformamide (200 ml) and the mixture was stirred for 72 h. at room temperature. Most of the solvent was evaporated under reduced pressure and methanesulfonic acid (6 g, 63 mmol) was added. More solvent was evaporated under reduced pressure and ethanol was added to the residue. Upon warming the mixture to 60 °C. the product crysstallized as salt and was filtred off to give 6 g (32 %) of the title compound.

^{1}H-NMR (400 MHz,$CDCl_3$): δ 2.3 (s, 6H), 7.25 (s,1H), 7.4 (s, 1H), 7.6 (s, 1H), 7.75 (s,1H), 7.85 (s,1H), 7.9 (s, 1H), 8.15 (s,1H), 8.6 (s,1H)

Example 2.14

Synthesis of 1-bromo-2-isopropyl-6-methylbenzene

2-isopropyl-6-methylanilin (14.9 g, 0.1 mol) was solved in conc hydrobromic acid (40 ml) and the mixture was cooled to 5 °C. Sodium nitrite (7.0 g, 0.1 mol) in water (15 ml) was added so that the temperature was below 10 °C. A solution of copper(I)bromide in conc hydrobromic acid (10 ml) was added to the reaction mixture and the temperature was allowed to raise to room temperature. The mixture was stirred for 1h. at room temperature and 30 min at 40 °C Hexane was added and the organic layer was separated and evaporated under reduced pressure. Purification by column chromatography on silica gel using hexane as eluent gave 6.9 g (32 %) of the title compound as an oil.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.23 (d, 6H), 2.43 (s, 3H), 3.4-3.55 (m, 1H), 7.05-7.2 (m, 3H)

Example 2.15

Synthesis of 2-isopropyl-6-methylbenzaldehyd

To a solution of 1-bromo-2-isopropyl-6-methylbenzene (6.9 g, 32.4 mmol) in diethyl ether (50 ml) was added magnesium turnings (0.9 g, 37 mmol) and the mixture was refluxed in nitrogen atmosphere until the reaction was started and was then stirred overnight at room temperature. Dimethylformamide (4 ml) was added dropwise during 10 min. and the mixture was stirred for 30 min. Saturated ammmoniumchloride solution (30 ml) was added and the mixture was stirred for 1h. The organic layer was separated, filtrated and evaporated under reduced pressure. Purification by column chromatography on silica gel using hexane:methylene chloride (3:2) as eluent gave 1.75 g (33 %) of the title compound .

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.25 (d, 6H), 2.55 (s, 3H), 3.7-3.8 (m, 1H), 7.1-7.4 (m, 3H), 10.65 (s, 1H)

Example 2.16

Synthesis of 2-isopropyl-6-methylbenzylalcohol

To a solution of 2-isopropyl-6-methylbenzaldehyd (1.75 g, 10.8 mmol) in methanol (15 ml) was added sodium borohydride (0.35 g, 9.5 mmol) and the mixture was stirred 1 h. at room temperature. The solvent was evaporated under reduced pressure and to the residue was added hexane and water. The organic layer was separated and evaporated under reduced pressure to give 1.73 g (98 %) of the title compound as an oil.

^{1}H-NMR (500 MHz.$CDCl_3$): δ 1.25 (d, 6H), 2.45 (s, 3H), 3.3-3.4 (m, 1H), 4.8 (s, 2H), 7.05- 7.2 (m, 3H)

Example 2.17

Synthesis of 2-isopropyl-6-methylbenzylchloride

To a solution of 2-isopropyl-6-methylbenzylalcohol (1.7 g, 10.4 mmol) in methylene chloride (20 ml) was added thionyl chloride (1.7 g, 14 mmol) and the reaction was stirred for 1 h. at room temperature. The solvent was evaporated under reduced pressure and the residue was filrated through silica gel using methylenechloride as eluent. The solvent was evaporated under reduced pressure to give 1.83 g (96 %) of the title compound as an oil.

^{1}H-NMR (500 MHz.$CDCl_3$): δ 1.25 (d, 6H), 2.45 (s, 3H), 3.25-3.35 (m, 1H), 4.75 (s, 2H), 7.05-7.25 (m, 3H)

Example 2.18

Synthesis of 2-bromo-6-methylbenzylbromide

A mixture of 3-bromo-o-xylene (15 g, 81 mmol), N-bromo succinimid (15.1 g, 85.1 mmol), dibenzoylperoxid (0.65 g) and tetrachloromethane (150 ml) was refluxed for 5 hours. After filtration the filtrate was washed with sodium hydrogensulfite and water.The organic layer was dried over sodium sulfate and evaporated *in vacuo*. Chromatography (SiO_2) (petroleum ether: ethyl acetate, 100:4) gave a 16.8 g fraction of a mixture containing 45 % of the title compound. This mixture was used without further purification.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 2.5 (s, 3H), 4.65 (s, 2H), 7.05-7.45 (m, 3H)

Example 2.19

Synthesis of 2-(2-bromo-3-methylphenyl)acetonitril

2-bromo-1-(bromomethyl)-3-methylbenzene (15 g, 0.057 mmol) and potassium cyanide (9.6 g, 0.148 mol) were added to dimethylformamide (75 ml) and stirred at 90 °C overnight. The solvent was evaporated under reduced pressure and the residue partitioned between water (150 ml) and methylene chloride. The aqueous layer was extracted twice with methylene chloride, the organic extracts was separated, washed twice with water and was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using heptane:methylene chloride (3:7) as eluent gave 8.0 g (67 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 2.44 (s, 3H), 3.86 (s, 2H), 7.22-7.37 (m, 3H)

Example 2.20

Synthesis of 2-(2-bromo-3-methylphenyl)acetic acid

2-(2-bromo-3-methylphenyl)acetonitril (8.0 g, 0.038 mol) was added to a mixture of water (60 ml) and sulfuric acid (50 ml) and the mixture was refluxed overnight. After cooling to room temperature water (200 ml) was added and the mixture was extracted twice with methylene chloride. The methylene chloride extracts were combined, washed twice with water, dried and evaporated under reduced pressure to give 7.9 g (90.8 %) of the title compound.

^{1}H-NMR (400 MHz,$CDCl_3$): δ 2.42 (s, 3H), 3.86 (s, 2H), 7.09-7.18 (m, 3H)

Example 2.21

Synthesis of ethyl 2-(2-bromo-3-methylphenyl)acetate

2-(2-bromo-3-methylphenyl)acetic acid (7.9 g, 0.034 mol) and sulfuric acid (0.1ml) were added to ethanol (25 ml) and the mixture was refluxed overnight. The solvent was evaporated and to the residue was added saturated sodium carbonate. The aqueous solution was extracted twice with diethyl ether, the organic extracts were combiened, washed twice with water, dried and evaporated under reduced pressure to give the desired product as an oil. (8.5 g, 97.7%).

^{1}H-NMR (400 MHz,$CDCl_3$): δ 1.24 (t, 3H), 2.40 (s, 3H), 3.78 (s, 3H), 4.16 (q,2H), 7.06-7.14 (m, 3H)

Example 2.22

Synthesis of 2-(2-bromo-3-methylphenyl)-1-ethanol

LiAlH4 (3.1 g, 0.083 mol) was suspended in dry tetrahydrofuran (100 ml) in argon atmosphere. Ethyl 2-(2-bromo-3-methylphenyl)acetate (8.5 g, 0.033 mol) solved in dry tetrahydrofuran (50 ml) was added and the mixture was stirred at room temperature for 4 h. The mixture was cooled on ice and 3.1 ml of water was added dropwise, followed by 3.1 ml of 15% sodium hydroxide and then 9.3 ml of water. After 15 h. the solids were removed by filtration and washed thoroughly with tetrahydrofuran. The filtrate was removed under reduced pressure. Purification of the residue by filtrating through silica gel using methylene chloride : methanol (9:1) as eluent gave 7.0 g (98.6 %) of the title compound as an oil.

^{1}H-NMR (400 MHz,$CDCl_3$): δ 2.39 (s, 3H), 3.00 (t, 2H), 3.81 (t, 2H), 7.04-7.10 (m, 3H)

Example 2.23

Synthesis of benzyl 2-bromo-3-methylphenethyl ether

Sodium hydride (50 % in oil) (1.7 g, 0.036 mol) was suspended in dry tetrahydrofuran (75 ml) in argon atmosphere. 2-(2-bromo-3-methylphenyl)-1-ethanol (7.0 g, 0.033 mol) solved in tetrahydrofuran (25 ml) was added dropwise during 30 min at room temperature. Benzyl bromide (6.2 g, 0.036 mol) was added and the reaction mixture was stirred at room temperature over night. Water (1.0 ml) was added carefully and the solvent was evaporated

under reduced pressure. The residue was partitioned between water and diethyl ether and the water layer was extracted twice with diethyl ether. The ether extracts were combined, washed twice with water, and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using heptane:methylene chloride (7:3) as eluent gave 7.5 g (74.3 %) of the title compound.

^{1}H-NMR (400 MHz,$CDCl_3$): δ 2.38 (s, 3H), 3.10 (t, 2H), 3.69 (t, 2H), 4.51 (s, 2H), 7.04-7.08 (m, 3H), 7.21-7.30 (m, 5H)

Example 2.24

Synthesis of 2-[2-(benzyloxy)ethyl]-6-methylbenzaldehyde

To a solution of benzyl 2-bromo-3-methylphenethyl ether (3.2 g, 0.0105 mol) in dry tetrahydrofuran in a nitrogen atmosphere at -65 °C was added tert-butyllithium (1.7 M in pentane)(10.5 ml, 0.018 mol) and the mixture was stirred at -20 °C for 30 min. Dimethylformamide (1.5 g, 0.021 mol) was added dropwise at -65 °C and the mixture was stirred at -20 °C for 30 min and at room temperature for 1 h. To the solution was water added carefully and 2M HCl to make it acidic and the mixture was stirred for 30 min. To the mixture was added diethyl ether (50 ml), the organic layer was separated, washed with saturated sodium carbonate and water. The organic layer was separated, dried and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using heptane:methylene chloride (2:8) as eluent gave 1.0 g (38.5 %) of the title compound.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 2.55 (s, 3H), 3.23 (t, 2H), 3.66 (t, 2H), 4.46 (s, 2H), 7.05-7.31 (m, 8H), 10.54 (s, 1H)

Example 2.25

Synthesis of 8-((2-[2-(benzyloxy)ethyl]-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

To a solution of 8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate 1.4 g (0.0038 mol) in methanol (20 ml) in a nitrogen atmosphere was added zinc chloride (1.0

g, 0.0039 mol) solved in methanol(10 ml) and the mixture was stirred for 30 min. To the mixture were added 2-[2-(benzyloxy)ethyl]-6-methylbenzaldehyde (1.0 g, 0.0039 mol) and sodium cyano borohydride (0.48 g, 0.0076 mol) and the mixture was refluxed overnight. The reation mixture was cooled to room temperature, triethylamine (4 ml) was added, the mixture was stirred for 30 min. and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent.The residue was solved in diethyl ether, treated with diethyl ether/HCl and the precipitated product as HCl salt was filtered off . The salt was soloved in methylene chloride and washed with saturated sodium carbonate. The organic layer was separated, washed with water, dried and evaporated under reduced pressure to give 0.13 g (7.7 g) of the title compound.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 2.31 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 2.98 (t, 2H), 3.66 (t, 2H), 4.37 (d, 2H), 4.46 (s, 2H), 5.02 (bs, 1H), 6.29 (bs, 2H), 6.47 (s, 1H), 7.03-7.26 (m, 8H), 7.91 (s, 1H)

Example 2.26

Synthesis of 2-ethyl-6-methylbenzyl 5-(2-ethyl-6-methylbenzyloxy)-6-nitronicotinate

5-hydroxy-6-nitronicotinic acid (1 g, 5 mmol), 2-ethyl-6-methylbenzylchloride (1.85 g, 11 mmol), N,N-diisopropylamine (1.75 g, 14 mmol) and tetrabutylammonium iodide (0.1 g) was added to acetonitrile (10 ml) and was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was solved in methylene chloride and washed with water. The organic layer was separated , dried and evaporated under reduced pressure. Purification of the residue by column chromatograhy on silica gel using n-hexane:methylene chloride (1:1) as eluent gave 0.7 g (29 %) of the title compound.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.2 (t, 3H), 1.25 (t, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 2.7 (q, 2H), 2.8 (q, 2H), 5.25 (s, 2H), 5.55 (s, 2H), 7.05-7.3 (m, 6H), 8.2 (s, 1H), 8.65 (s, 1H)

Example 2.27

Synthesis of 6-amino-5-(2-ethyl-6-methylbenzyloxy)nicotinamide

2-ethyl-6-methylbenzyl 5-(2-ethyl-6-methylbenzyloxy)-6-nitronicotinate (0.7 g, 2 mmol) was added to a solution of ammonia in methanol (5-10 %)(40 ml) and the mixture was stirred at 35 °C for 96 h. The solvent was evaporated under reduced pressure. Purification of the residue twice by column chromatography on silica gel using ethylacetate:methylene chloride (1:1) and methanol:methylene chloride (1:9) as eluent gave 0.14 g (31 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.21 (t, 3H), 1.87 (s, 2H), 2,37 (s, 3H), 2.72 (q, 2H), 5.11 (s, 2H), 5.99 (bs, 2H), 7.1-7.3 (m, 3H), 7.67 (d, 1H), 8.09 (d, 1H)

BIOLOGICAL TESTS

1. In vitro experiments

Acid secretion inhibition in isolated rabbit gastric glands

Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglindh et al. (1976) Acta Physiol. Scand. 97, 401-414.

Determination of H^+,K^+-ATPase activity

Membrane vesicles (2.5 to 5 µg) were incubated for 15 min at +37°C in 18 mM Pipes/Tris buffer pH 7.4 containing 2 mM $MgCl_2$, 10 mM KCl and 2 mM ATP. The ATPase activity was estimated as release of inorganic phosphate from ATP, as described by LeBel et al. (1978) Anal. Biochem. 85, 86-89.

2. In vivo experiments

Inhibiting effect on acid secretion in female rats

Female rats of the Sprague-Dawly strain are used. They are equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of

gastric secretions and administration of test substances, respectively. A recovery period of 14 days after surgery is allowed before testing commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula with tap water (+37°C), and 6 ml Ringer-Glucose given subcutaneously. Acid secretion is stimulated with infusion during 2.5-4 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg·h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substances or vehicle are given either at 60 min after starting the stimulation (intravenous and intraduodenal dosing, 1 ml/kg), or 2 h before starting the stimulation (oral dosing, 5 ml/kg, gastric cannula closed). The time interval between dosing and stimulation may be increased in order to study the duration of action. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 M, and acid output calculated as the product of titrant volume and concentration.

Further calculations are based on group mean responses from 4-6 rats. In the case of administration during stimulation; the acid output during the periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. In the case of administration before stimulation; percentage inhibition is calculated directly from acid output recorded after test compound and vehicle.

Bioavailability in rat

Adult rats of the Sprague-Dawley strain are used. One to three days prior to the experiments all rats are prepared by cannulation of the left carotid artery under anaesthesia. The rats used for intravenous experiments are also cannulated in the jugular vein (Popovic (1960) J. Appl. Physiol. 15, 727-728). The cannulas are exteriorized at the nape of the neck.

Blood samples (0.1 - 0.4 g) are drawn repeatedly from the carotid artery at intervals up to 5.5 hours after given dose. The samples are frozen until analysis of the test compound.

Bioavailability is assessed by calculating the quotient between the area under blood/plasma concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

The area under the blood concentration vs. time curve, AUC, is determined by the log/linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following intraduodenal or oral administration is calculated as F(%) = (AUC (p.o. or i.d.) / AUC (i.v.)) x 100.

Inhibition of gastric acid secretion and bioavailability in the conscious dog.

Labrador retriever or Harrier dogs of either sex are used. They are equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhaim-pouch for the collection of gastric secretion.

Before secretory tests the animals are fasted for about 18 h but water is freely allowed. Gastric acid secretion is stimulated for up to 6.5 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle is given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenham-pouch dog.

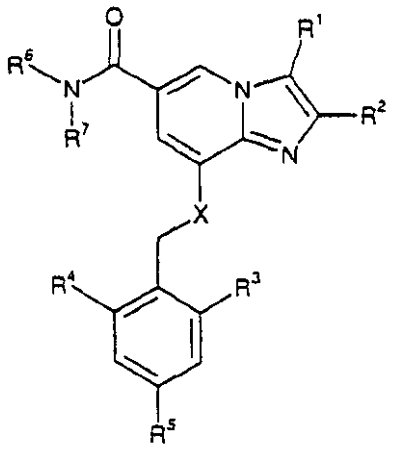
The acidity of the gastric juice samples are determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the

fraction preceding administration to 1.0. Percentage inhibition is calculated from fractional responses elicited by test compound and vehicle.

Blood samples for the analysis of test compound concentration in plasma are taken at intervals up to 4 h after dosing. Plasma is separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability (F%) after oral or i.d. administration is calculated as described above in the rat model.

CLAIMS

1. A compound of the formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is
(a) H,
(b) CH_3, or
(c) CH_2OH;

R^2 is
(a) CH_3
(b) CH_2CH_3

R^3 is (a) H
(b) C_1-C_6 alkyl,
(c) hydroxylated C_1-C_6 alkyl
(d) halogen

R^4 is
(a) H,
(b) C_1-C_6 alkyl,

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

R^5 is
(a) H, or
(b) halogen;

R^6, R^7 are the same or different
(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 compound according to claim 1 wherein R^1 is CH_3 or CH_2OH; R^2, R^3 and R^4 independently are CH_3 or CH_2CH_3; and R^5 is H, Br, Cl, or F.

3. The compound according to claim 1 or 2 being

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,

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,

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,

N-[2-(dimethylamine)-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,

2,3-dimethyl-8-(2-ethyl-6-methylbenzyloxy)-imidazo[1,2-a]pyridine-6-carboxamide,

or

a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 or 2 being;

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,

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,

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,

2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide,

2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide,

or

a pharmaceutically acceptable salt thereof.

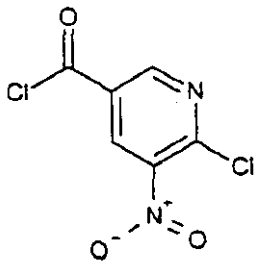
5. A compound according to any of claims 1-4as a hydrochloride or mesylate salt.

6. Products containing at least one compound according to any of claims 1-4 and at least one antimicrobial agent as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

7. Products containing at least one compound according to any of claims 1-4 and at least one proton pump inhibitor as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

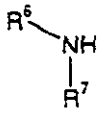
8. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH, comprising

(a) reacting a compound of the Formula II



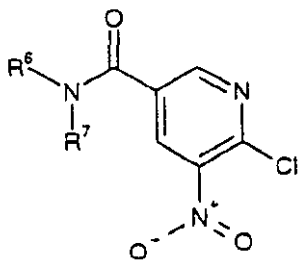
II

with a compound of the Formula III



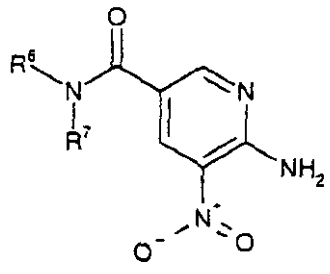
III

wherein R^6 and R^7 are as defined in claim 1, in an inert solvent, to a compound of the Formula IV,



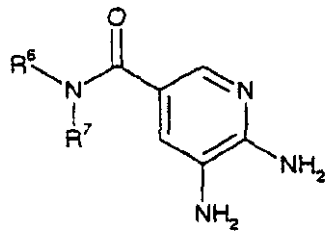
IV

(b) reacting a compound of the Formula IV wherein R^6 and R^7 are as defined in claim 1, with ammonia in an inert solvent to a compound of the Formula V



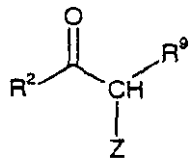
V

(c) reducing a compound of the Formula V wherein R^6 and R^7 are as defined in claim 1 in an inert solvent under standard conditions to a compound of the Formula VI



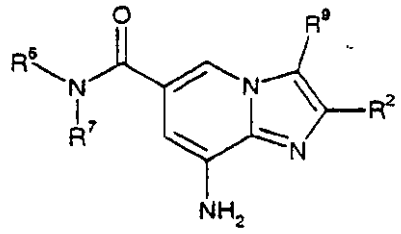
VI

(d) reacting a compound of the Formula VI wherein R^6 and R^7 are as defined in claim 1 with a compound of Formula VII



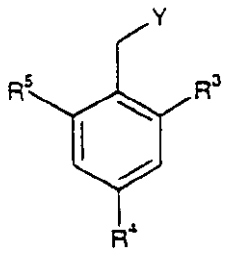
VII

wherein R^2 is as defined in claim 1, Z is a leaving group and R^9 represent H, CH_3 or an ester group, in an inert solvent with or without a base to a compound of the Formula VIII



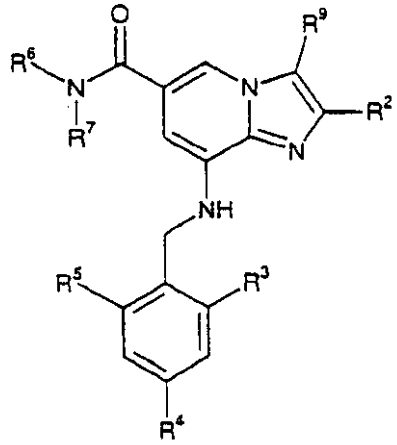
VIII

(e) reacting a compound of the Formula VIII wherein R^6, R^7 and R^2 are as defined in claim 1, and R^9 is H, CH_3 or an ester group with a compound of Formula IX



IX

wherein R^3, R^4, and R^5 are as defined in claim 1, and Y is a leaving group in an inert solvent with or without a base, to a compound of the Formula X

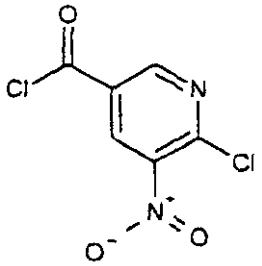


X

(f) reducing a compound of Formula X wherein R^9 is an ester group in an inert solvent to a compound of the Formula I wherein R^1 is CH_2OH and X is NH.

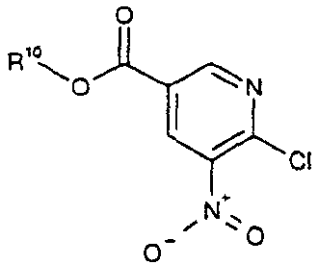
9. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH and R^1 is H or CH_3, comprising

(a) reacting a compound of the Formula II



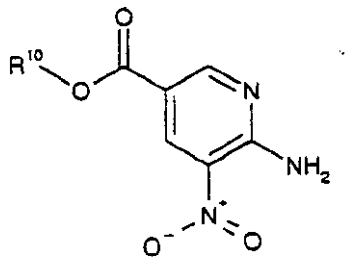
II

with an alcohol compound of the general formula R^{10}-OH, wherein R^{10} is an alkyl group under standard conditions, to a compound of the Formula XI



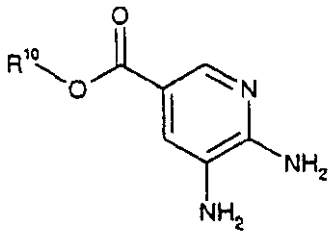
XI

(b) reacting a compound of the Formula XI wherein R^{10} is an alkyl group, with ammonia in an inert solvent under standard conditions to a compound of the Formula XII



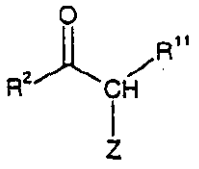
XII

(c) reducing a compound of the Formula XII wherein R^{10} is an alkyl group in an inert solvent under standard conditions to a compound of the Formula XIII



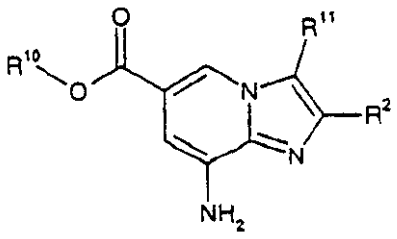
XIII

(d) reacting a compound of the Formula XIII wherein R^{10} is an alkyl group with a compound of Formula XIV



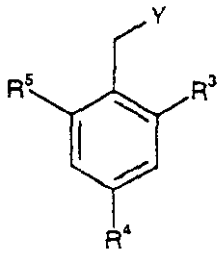
XIV

wherein R^2 is as defined in claim 1, Z is a leaving group and R^{11} represent H or CH_3, in an inert solvent with or without a base to a compound of the Formula XV



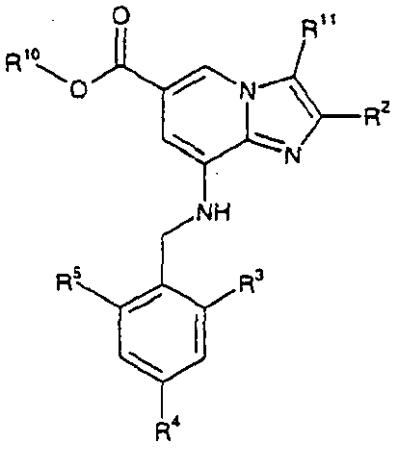
XV

(e) reacting a compound of the Formula XV wherein R^{10} is an alkyl group, R^2 are as defined in claim 1 and R^{11} is H or CH3 with a compound of Formula IX



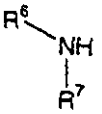
IX

wherein R^3, R^4, and R^5 are as defined in claim 1 and Y is a leaving group in an inert solvent with or without a base to a compound of the Formula XVI



XVI

(f) reacting a compound of Formula XVI wherein R^2, R^3, R^4 and R^5 are as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3 with a compound of Formula III

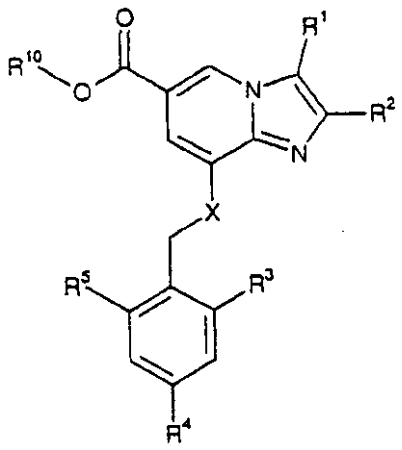


III

wherein R^6 and R^7 are as defined in claim 1, under standard conditions, to a compound of Formula I wherein R^1 is H or CH_3 and X is NH.

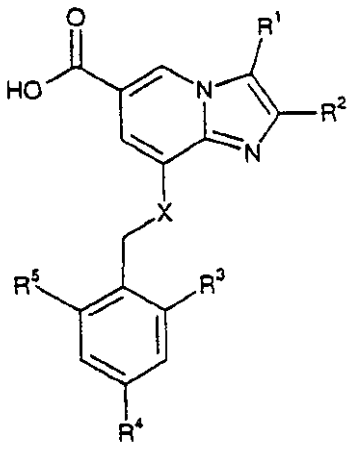
10. A process for the preparation of a compound according to any one of claims 1 to 5 comprising

(a) treating a compound of Formula XVII



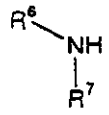
XVII

wherein R^1, R^2, R^3, R^4, R^5 and X are as defined in claim 1 and R^{10} is an alkyl group, with acid or base under standard conditions to a compound of Formula XVIII



XVIII

(b) reacting a compound of Formula XVIII wherein R^1, R^2, R^3, R^4, R^5 and X is defined in claim 1 with a compound of Formula III



III

wherein R^6 and R^7 are as defined in claim 1, in the presence of a coupling reagent in an inert solvent under standard conditions, to a compound of Formula I.

11. A compound according to any one of claims 1 to 5 for use in therapy.

12. A pharmaceutical formulation containing a compound according to any one of claims 1 to 5 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.

13. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the inhibition of gastric acid secretion.

14. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases.

15. Use of a compound according to any one of claims 1 to 5 the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the said salt is adapted to be administered in combination with at least one antimicrobial agent.

16. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including man, in need of such inhibition an effective amount of a compound according to any one of claims 1 to 5.

17. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 5.

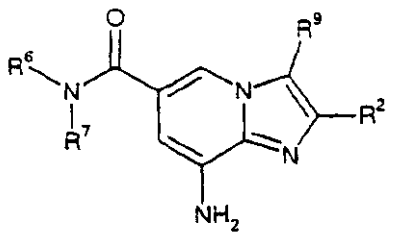
18. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 5, wherein the said salt is administered in combination with at least one antimicrobial agent.

19. A pharmaceutical formulation for use in the inhibition of gastric acid secretion wherein the active ingredient is a compound according to any one of claims 1 to 5.

20. A pharmaceutical formulation for use in the treatment of gastrointestinal inflammatory diseases wherein the active ingredient is a compound according to any one of claims 1 to 5.

21. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the active ingredient is a compound according to any one of claims 1 to 5 in combination for simultaneous, separate or sequential use or together with at least one antimicrobial agent.

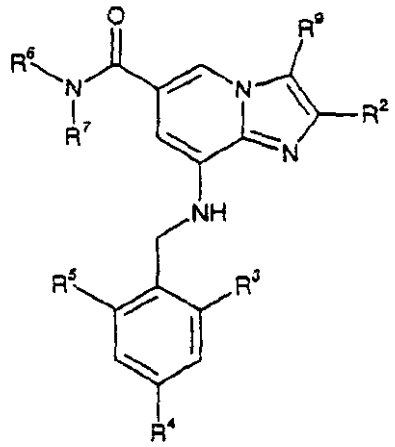
22. A compound of the formula VIII



VIII

wherein R^2, R^6 and R^7 are as defined in claim 1, and R^9 is H, CH_3 or an ester group.

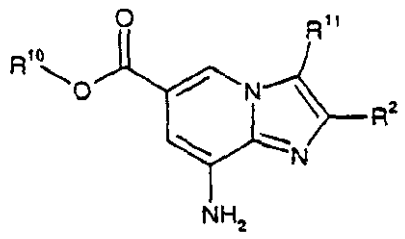
23. A compound of the formula X



X

wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1, and R^9 is an ester group.

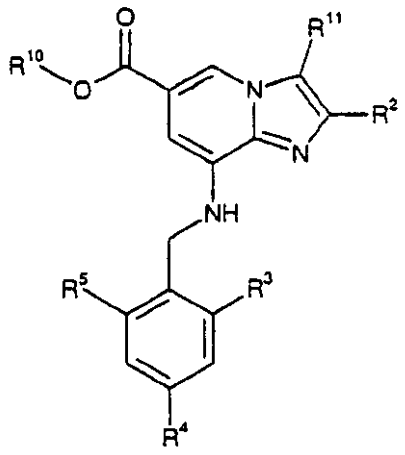
24. A compound of the formula XV



XV

wherein R^2 is as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3.

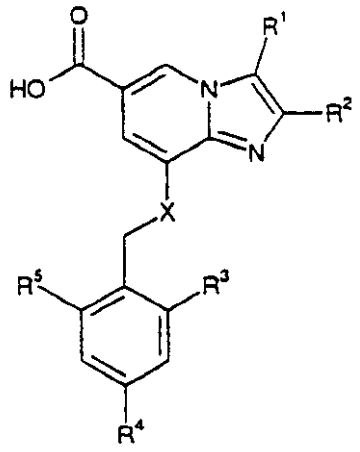
25. A compound of the formula XVI



XVI

wherein R^2, R^3, R^4 and R^5 are as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3.

26. A compound of the formula



XVIII

wherein R^1, R^2, R^3, R^4 R^5 and X are as defined in claim 1.

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A61K 31/435

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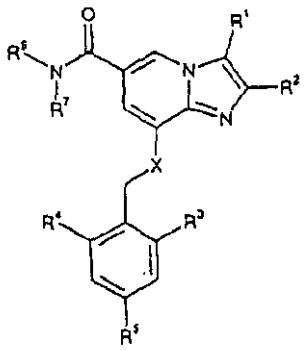
代理人 罗才希

权利要求书12页 说明书48页 附图页数0页

[54]发明名称 抑制胃酸分泌的咪唑并吡啶衍生物

[57]摘要

本发明涉及式(Ⅰ)的咪唑并吡啶衍生物衍生物,其中所述苯基部分被取代,其中所述咪唑并吡啶部分在6-位上由甲酰胺基取代,该衍生物可抑制外源性或内源性刺激的胃酸分泌,因此可用于预防和治疗胃肠炎性疾病。



Ⅰ

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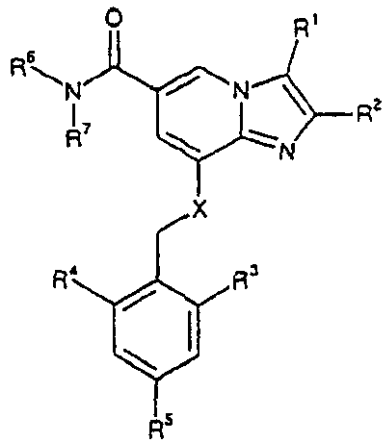
权 利 要 求 书

1. 式 I 化合物或其药学上可接受的盐，



I

其中

R^1 是

(a)H，

(b)CH_3，或

(c)CH_2OH；

R^2 是

(a)CH_3，

(b)CH_2CH_3，

R^3 是

(a)H，

(b)C_1-C_6 烷基，

(c)羟基化的 C_1-C_6 烷基，

(d)卤素；

R^4 是

(a)H，

(b)C_1-C_6 烷基，

(c)羟基化的 C_1-C_6 烷基，或

(d)卤素；

R^5是

(a)H，或

(b)卤素；

R^6, R^7是相同或不同的

(a)H，

(b)C_1-C_6烷基，

(c)羟基化的C_1-C_6烷基，

(d)C_1-C_6烷氧基-取代的C_1-C_6烷基；

X是

(a)NH，或

(b)O。

2. 根据权利要求1的化合物，其中R^1是CH_3或CH_2OH；R^2、R^3和R^4独立为CH_3或CH_2CH_3；R^5是H、Br、Cl或F。

3. 根据权利要求1或2的化合物或其药学上可接受的盐是

2,3-二甲基-8-(2-乙基-6-甲基苄基氨基)-N-丙基-咪唑并[1,2-a]吡啶-6-甲酰胺，

8-(2-乙基-6-甲基苄基氨基)-3-羟基甲基-2-甲基咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2,6-二甲基苄基氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-6-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

8-(2-乙基-6-甲基苄基氨基)-N,2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺，

8-(2-乙基-6-甲基苄基氨基)-N,N,2,3-四甲基咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2,6-二甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰

胺，

N-[2-(二甲基胺)-2-氧代乙基]-8-(2-乙基-6-甲基苄基氨基)-N,2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-4-氟代-6-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐，

2,3-二甲基-8-(2-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2,6-二甲基-4-氟代-苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐，

2,3-二甲基-8-(2-甲基-6-异丙基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐，

2,3-二甲基-8-(2,6-二乙基-苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-6-甲基-苄基氨基)- N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺，

N-(2,3-二羟基丙基)-2,3-二甲基-8-(2-乙基-6-甲基苄基氨基)-[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-6-甲基-苄基氨基)-N-(2-甲氧基乙基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2-甲基-8-(2-乙基-6-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-溴代-6-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-(2-羟乙基)-6-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

8-(2-乙基-6-甲基苄基氨基)-N,N-双(2-羟乙基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺，

8-(2-乙基-6-甲基苄基氨基)-N-(2-羟乙基)-N,2,3-三甲基咪唑并

[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-6-甲基苄氧基)-咪唑并[1,2-a]吡啶-6-甲酰胺。

4. 根据权利要求 1 或 2 的化合物或其药学上可接受的盐是：

8-(2-乙基-6-甲基苄基氨基)-3-羟基甲基-2-甲基咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2,6-二甲基苄基氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-6-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

8-(2-乙基-6-甲基苄基氨基)-N,2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2,6-二甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-4-氟代-6-甲基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2,6-二甲基-4-氟代-苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2,6-二乙基苄基氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-6-甲基苄基氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺，

2,3-二甲基-8-(2-乙基-6-甲基苄基氨基)-N-(2-甲氧基乙基)-咪唑并[1,2-a]吡啶-6-甲酰胺。

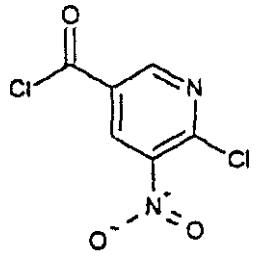
5. 根据权利要求 1-4 中任一项的化合物为盐酸盐或甲磺酸盐。

6. 含有至少一种根据权利要求 1-4 中任一项的化合物和至少一种抗菌剂作为同时、分别或顺序用于预防或治疗胃肠炎性疾病的组合制剂的产物。

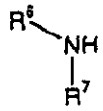
7. 含有至少一种根据权利要求 1-4 中任一项的化合物和至少一种质子泵抑制剂作为同时、分别或顺序用于预防或治疗胃肠炎性疾病的组合制剂的产物。

8. 根据权利要求 1-5 中任一项的化合物的制备方法，其中 X 是 NH，包括:

(a)使式 II 化合物与式 III 化合物

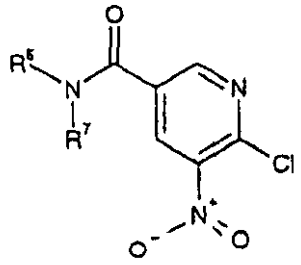


II



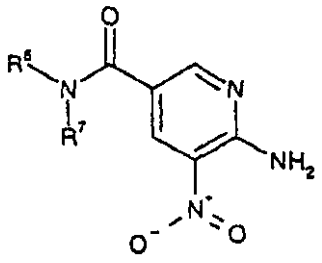
III

其中 R^6 和 R^7 如权利要求 1 中所定义，在惰性溶剂中反应得到式 IV 化合物，



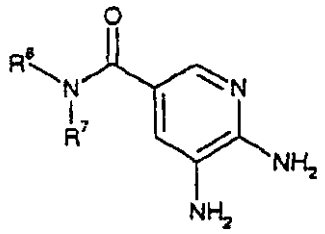
IV

b)使式 IV 化合物，其中 R^6 和 R^7 如权利要求 1 中所定义，在惰性溶剂中与氨反应得到式 V 化合物，



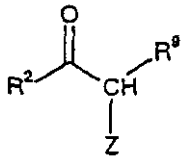
V

c)将式 V 化合物，其中 R^6 和 R^7 如权利要求 1 中所定义，在惰性溶剂中，在标准条件下还原，得到式 VI 化合物，



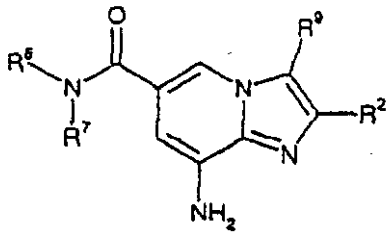
VI

(d)使式 VI 化合物，其中 R^6 和 R^7 如权利要求 1 中所定义，与式 VII 化合物



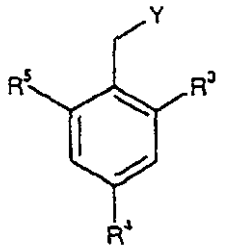
VII

其中 R^2 如权利要求 1 所定义，Z 是离去基团和 R^9 代表 H、CH_3 或酯基团，在惰性溶剂中，在有碱或没有碱存在下反应，得到式 VIII 化合物，



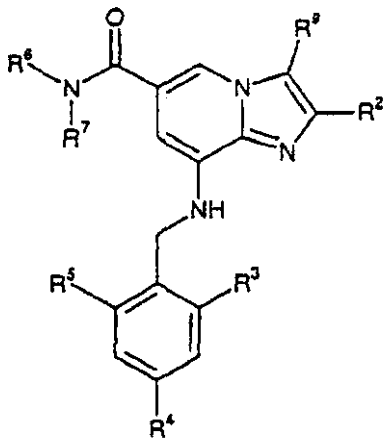
VIII

(e)使式 XIII 化合物，其中 R^6、R^7 和 R^2 如权利要求 1 中所定义和 R^9 是 H、CH_3 或酯基团，与式 IX 化合物



IX

其中 R^3、R^4 和 R^5 如权利要求 1 中所定义，Y 是离去基团，在惰性溶剂中，在有碱或没有碱存在下反应，得到式 X 化合物，

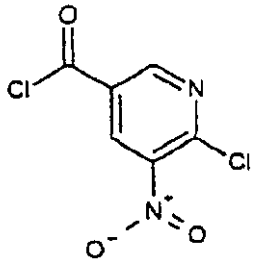


X

(f)将式 X 化合物，其中 R^9 是酯基团，在惰性溶剂中还原得到式 I 化合物，其中 R^1 是 CH_2OH 和 X 是 NH。

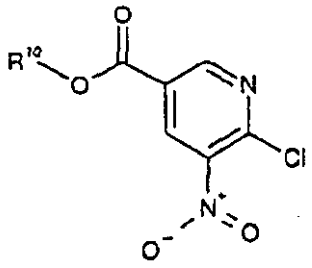
9. 用于制备根据权利要求 1-5 中任一项的化合物的方法，其中 X 是 NH 和 R^1 是 H 或 CH_3，包括:

(a)使式 II 化合物



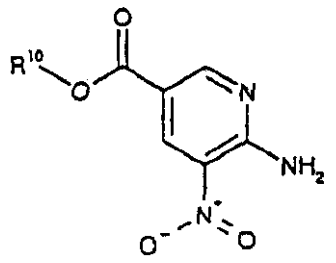
II

与通式 R^{10}-OH 的醇化合物，其中 R^{10} 是烷基，在标准条件下反应，得到式 XI 化合物，



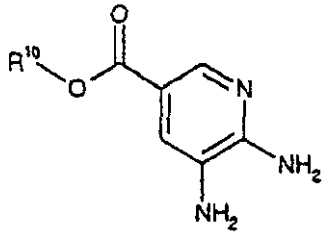
XI

(b)使式 XI 化合物，其中 R^{10} 是烷基，在惰性溶剂中，在标准条件下，与氨反应得到式 XII 化合物，



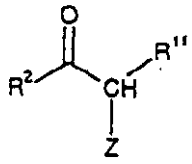
XII

(c)将式 XII 化合物，其中 R^{10} 是烷基，在惰性溶剂中，在标准条件下还原，得到式 XIII 化合物，



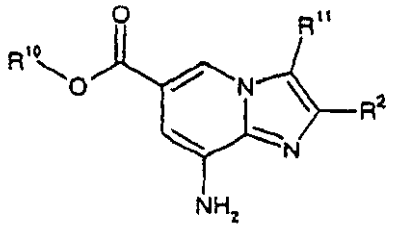
XIII

(d)使式 XIII 化合物，其中 R^{10} 是烷基，与式 XIV 化合物



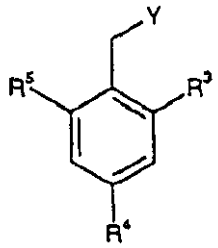
XIV

其中 R^2 如权利要求 1 中所定义，Z 是离去基团和 R^{11} 代表 H 或 CH_3，在惰性溶剂中，在有碱或没有碱存在下反应，得到式 XV 化合物，



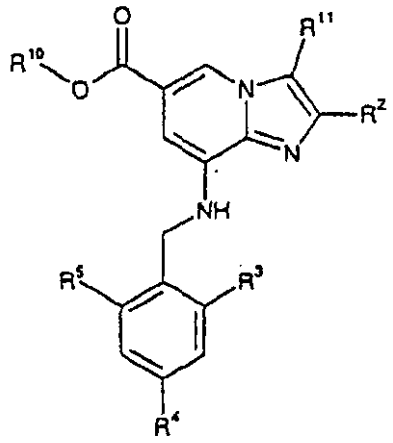
XV

(e)使式 XV 化合物，其中 R^{10} 是烷基，R^2 如在权利要求 1 中所定义和 R^{11} 是 H 或 CH_3，与式 IX 化合物



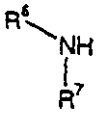
IX

其中 R^3、R^4和 R^5如权利要求 1 中所定义，Y 是离去基团，在惰性溶剂中，在有碱或没有碱存在下反应，得到式 XVI 化合物，



XVI

(f)使式 XVI 化合物,其中 R^2、R^3、R^4和 R^5如在权利要求 1 中所定义，R^{10}是烷基和 R^{11}是 H 或 CH_3，与式 III 化合物

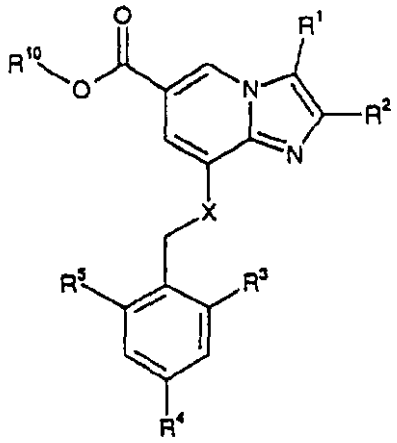


III

其中 R^6和 R^7如在权利要求 1 中所定义，在标准条件下反应，得到式 I 化合物，其中 R^1是 H 或 CH_3和 X 是 NH。

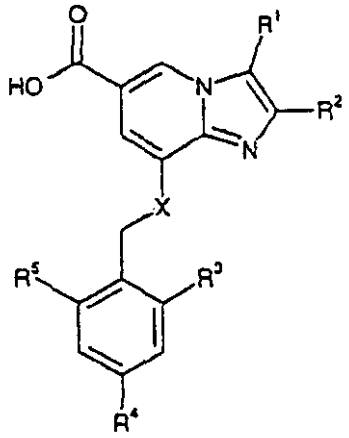
10. 用于制备根据权利要求 1-5 中任一项的化合物的方法，包括:

(a)在标准条件下，用酸或碱处理式 XVII 化合物



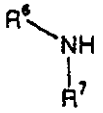
XVII

其中 R^1、R^2、R^3、R^4、R^5和 X 如在权利要求 1 中所定义，R^{10}是烷基，得到式 XVIII 化合物，



XVIII

(b)使式 XVIII 化合物，其中 R^1、R^2、R^3、R^4、R^5和 X 如在权利要求 1 中所定义，与式 III 化合物



III

其中 R^6和 R^7如在权利要求 1 中所定义，在偶合试剂存在下，在惰性溶剂中，在标准条件下反应，得到式 I 化合物.

11. 根据权利要求 1-5 中任一项的化合物用于治疗.

12. 含有作为活性组分的根据权利要求 1-5 中任一项的化合物并结合药学上可接受的稀释剂或载体的药用制剂.

13. 根据权利要求 1-5 中任一项的化合物在制备用于抑制胃酸分泌的药物中的用途.

14. 根据权利要求 1-5 中任一项的化合物在制备用于治疗胃肠炎性疾病的药物中的用途.

15. 根据权利要求 1-5 中任一项的化合物，在制备用于治疗或预防由人胃粘膜幽门螺旋菌(Helicobater pylori)感染所引起的疾病的药物中的用途，其中所述盐与至少一种抗菌剂组合给药.

16. 用于抑制胃酸分泌的方法，该方法包括给予需要此抑制的哺乳动物包括人有效量的根据权利要求 1-5 中任一项的化合物.

17.用于治疗胃肠炎性疾病的方法，该方法包括给予需要此治疗的哺乳动物包括人有效量的根据权利要求 1-5 中任一项的化合物.

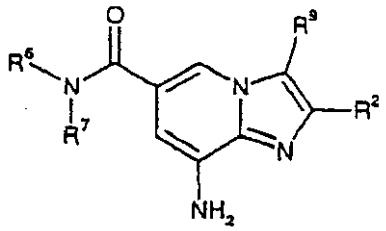
18. 用于治疗或预防由人胃粘膜幽门螺旋菌感染所引起的疾病的方法，该方法包括给予需要此治疗的哺乳动物包括人有效量的根据权利要求 1-5 中任一项的化合物，其中所述盐与至少一种抗菌剂组合给药。

19. 用于抑制胃酸分泌的药用制剂，其中所述活性组分是根据权利要求 1-5 中任一项的化合物。

20. 用于治疗胃肠炎性疾病的药用制剂，其中所述活性组分是根据权利要求 1-5 中任一项的化合物。

21. 用于治疗或预防由人胃粘膜幽门螺旋菌感染所引起的疾病的药用制剂，其中所述活性组分是根据权利要求 1-5 中任一项的化合物并与至少一种抗菌剂组合以同时、分别或顺序或者一起使用。

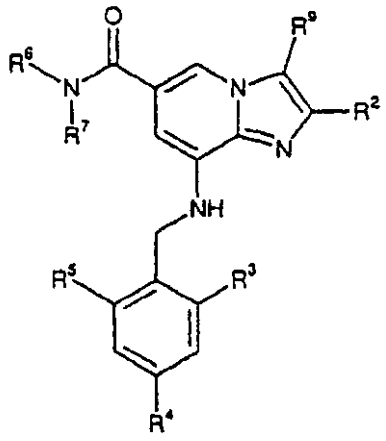
22. 式 VIII 化合物



VIII

其中 R^2、R^6和 R^7如在权利要求 1 中所定义，R^9是 H 、CH_3或酯基团。

23. 式 X 化合物

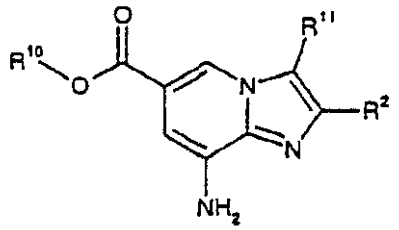


X

其中 R^2、R^3、R^4、R^5、R^6和 R^7如在权利要求 1 中所定义，R^9是

酯基团.

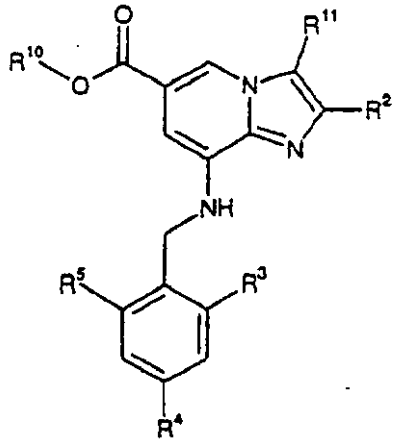
24. 式 XV 化合物



XV

其中 R^2 如在权利要求 1 中所定义，R^{10} 是烷基和 R^{11} 是 H 或 CH_3.

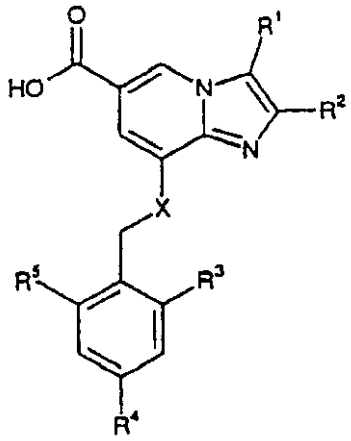
25. 式 XVI 化合物



XVI

其中 R^2、R^3、R^4 和 R^5 如在权利要求 1 中所定义，R^{10} 是烷基和 R^{11} 是 H 或 CH_3.

26. 下式化合物



XVIII

其中 R^1、R^2、R^3、R^4、R^5 和 X 如在权利要求 1 中所定义.

00.12.25

说　明　书

抑制胃酸分泌的咪唑并吡啶衍生物

技术领域

本发明涉及新的化合物和其治疗学上可接受的盐，其可抑制外源性或内源性刺激的胃酸分泌，因此可用于预防和治疗胃肠的炎性疾病。另一方面，本发明涉及本发明化合物在治疗中的用途；制备这些新化合物的方法；含有至少一种作为活性组分的本发明化合物或其治疗上可接受的盐的药用组合物；和该活性化合物在制备用于上述医疗用途的药物中的用途。本发明还涉及用于制备所述新化合物中的新的中间体。

背景技术

用于治疗消化性溃疡疾病的取代的咪唑并[1,2-a]吡啶为本领域内已知的化合物，例如可从 EP-B-0033094 和 US 4,450,164 (Schering Corporation)中；从 EP-B-0204285 和 US 4,725,601(Fujisawa Pharmaceutical Co.)中；和从 J.J.Kaminski 等在*药物化学杂志*(28 卷, 876-892, 1985; 30 卷, 2031-2046, 1987; 30 卷, 2047-2051, 1987; 32 卷, 1686-1700, 1989 和 34 卷, 533-541, 1991)中所发表的内容得知。

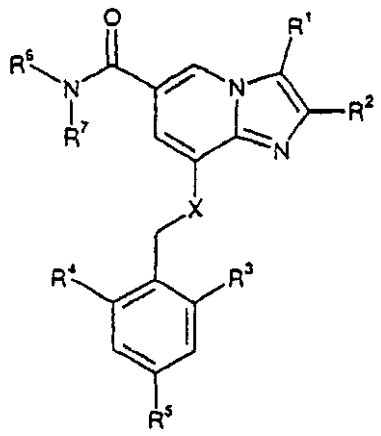
关于胃酸泵(H^+, K^+-ATP 酶)的药理学的述评，参见 Sachs 等(1995) Annu. Rev. Pharmacol. Toxicol. 35:277-305 .

本发明的公开

已惊奇地发现，为咪唑并吡啶衍生物(其中苯基部分被取代和其中咪唑并吡啶部分在 6-位被甲酰胺基取代)的式 I 化合物为特别有效的胃肠 H^+, K^+-ATP 酶抑制剂，因此可作为胃酸分泌的抑制剂。

因此，一方面，本发明涉及通式 I 的化合物或其药学上可接受的

盐:



I

其中

R^1是

(a) H,

(b) CH_3, 或

(c) CH_2OH;

R^2是

(a) CH_3,

(b) CH_2CH_3;

R^3是

(a) H,

(b) C_1-C_6烷基,

(c) 羟基化的 C_1-C_6烷基,

(d) 卤素;

R^4是

(a) H,

(b) C_1-C_6烷基,

(c) 羟基化的 C_1-C_6烷基, 或

(d) 卤素;

R^5是

(a) H，或

(b) 卤素；

R^6、R^7为相同或不同的

(a) H，

(b) C_1-C_6烷基，

(c) 羟基化的 C_1-C_6烷基，

(d) C_1-C_6烷氧基取代的 C_1-C_6烷基；

X是

(a) NH，或

(b) O．

这里所用术语“C_1-C_6烷基”意指具有1-6个碳原子的直链或支链烷基．所述 C_1-C_6烷基的实例包括甲基、乙基、n-丙基、异-丙基、n-丁基、异-丁基、仲-丁基、t-丁基和直-和支链戊基和己基．

术语“卤素”包括氟、氯、溴和碘．

纯的对映异构体、外消旋混合物和两种对映异构体的不等量混合物都在本发明范围内．应该知道，所有可能的非对映形式(纯的对映异构体、外消旋混合物和两种对映异构体的不等量混合物)都在本发明范围内．具有式I化合物的生物功能的式I化合物的衍生物(例如前体药物)也包括在本发明中．

本领域技术人员也将理解，虽然式I化合物的衍生物可能不具有如此的药理活性，但它们经肠胃外或口服给药，经体内代谢后形成具有药理活性的本发明的化合物．因此，这些衍生物可称作“前体药物”．所有式I化合物的前体药物都包括在本发明范围内．

根据工艺条件，式I的最终产物可以中性或盐的形式获得．这些终产物的游离碱和盐都在本发明的范围内．

新化合物的酸加成盐，可用本身已知的方法，用碱试剂如碱或通过离子交换法转换成游离碱．获得的游离碱也可与有机或无机酸形成盐．

在酸加成盐的制备中，优选使用适合形成治疗上可接受的盐的酸。这些酸的实例是氢卤酸例如盐酸、 硫酸、磷酸、硝酸、脂族、脂环族、芳族或杂环羧基或磺酸，例如甲酸、乙酸、丙酸、琥珀酸、乙醇酸、乳酸、苹果酸、酒石酸、柠檬酸、抗坏血酸、马来酸、羟基马来酸、丙酮酸、 P-羟基苯甲酸、扑酸(embonic)、甲磺酸、乙磺酸、羟基乙磺酸、卤代苯磺酸、甲苯磺酸或萘磺酸.

根据本发明优选化合物是式I化合物，其中R^1是CH_3或CH_2OH；R^2是CH_3或CH_2CH_3； R^3是CH_3或CH_2CH_3； R^4是CH_3或CH_2CH_3；R^5是H、 Br、 Cl或F.

根据本发明特别优选的化合物是:

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-N-丙基-咪唑并[1,2-a]吡啶-6-甲酰胺

8-(2-乙基-6-甲基苄氨基)-3-羟基甲基-2-甲基咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2,6-二甲基苄氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

8-(2-乙基-6-甲基苄氨基)-N-2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺

8-(2-乙基-6-甲基苄氨基)-N,N,2,3-四甲基咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2,6-二甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-4-氟代-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐

2,3-二甲基-8-(2-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2,6-二甲基-4-氟代-苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐

2,3-二甲基-8-(2-甲基-6-异丙基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰

胺甲磺酸盐

2,3-二甲基-8-(2,6-二乙基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺

N-(2,3-二羟基丙基)-2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-N-(2-甲氧基乙基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2-甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-溴代-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-(2-羟乙基)-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

8-(2-乙基-6-甲基苄氨基)-N,N-双(2-羟乙基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺

8-(2-乙基-6-甲基苄氨基)-N-(2-羟乙基)-N-2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-6-甲基苄氧基)-咪唑并[1,2-a]吡啶-6-甲酰胺.

根据本发明最优选的化合物是:

8-(2-乙基-6-甲基苄氨基)-3-羟基甲基-2-甲基咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2,6-二甲基苄氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

8-(2-乙基-6-甲基苄氨基)-N,2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2,6-二甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-4-氟代-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2,6-二甲基-4-氟代-苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2,6-二乙基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-N-(2-甲氧基乙基)-咪唑并[1,2-a]吡啶-6-甲酰胺.

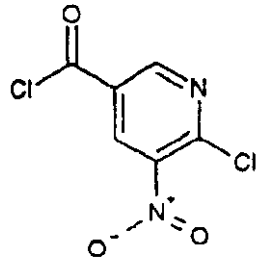
制备

本发明也提供下列用于制备通式I化合物的方法A、B和C.

方法A

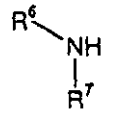
方法A用于制备通式I化合物，其中X是NH，该方法包括以下步骤:

a) 通式II化合物



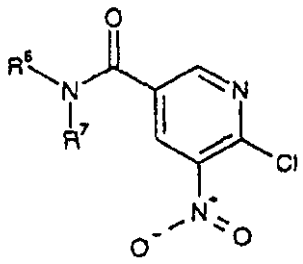
II

可与通式III的氨基化合物反应，



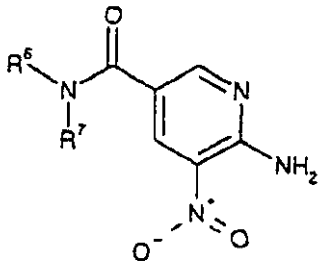
III

其中R^6和R^7如式I所定义，得到相应的式IV酰胺. 该反应可在标准条件下，在惰性溶剂中进行.



IV

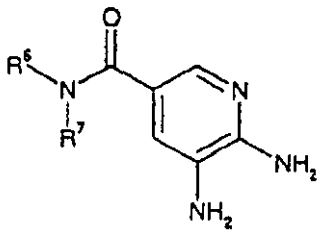
b) 通式 IV 化合物可与氨反应,得到通式 V 化合物



V

其中 R^6 和 R^7 如通式 I 所定义. 该反应可在标准条件下, 在惰性溶剂中进行.

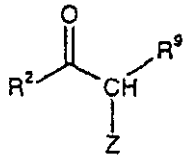
c) 式 V 化合物可通过例如用氢和催化剂如 Pd/C 还原得到式 VI 化合物



VI

其中 R^6 和 R^7 如式 I 所定义. 该反应可在标准条件下, 在惰性溶剂中进行.

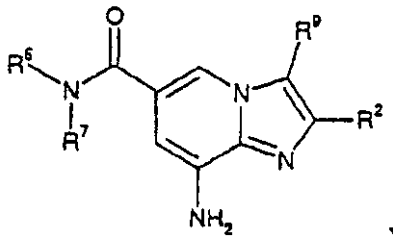
d) 式 VIII 的咪唑并[1,2-a]吡啶化合物, 可通过使通式 VI 化合物与通式 VII 化合物反应制备



VII

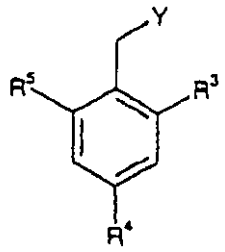
其中 R^2 如式 I 所定义和 Z 是离去基团如卤素、甲磺酰基、甲苯磺酰基和 R^9 代表 H、 CH_3 或酯基团如 $COOCH_3$、 $COOC_2H_5$ 等. 该反应可在

标准条件下，在惰性溶剂如丙酮、乙腈、醇、二甲基甲酰胺等中，在有碱或没有碱存在下进行.



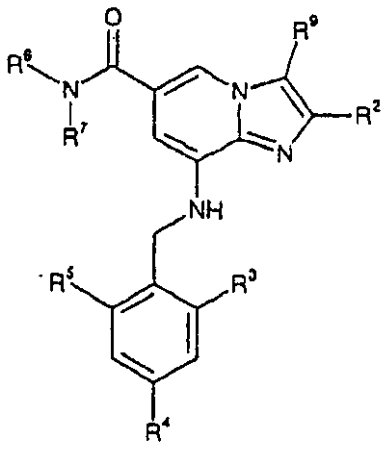
VIII

e) 式 XIII 化合物可与式 IX 化合物反应



IX

其中 R^3、R^4和 R^5如式 I 所定义，Y 是离去基团，例如卤素、甲苯磺酰基或甲磺酰基，得到式 X 化合物.



X

其中 R^2、R^3、R^4、R^5、R^6和 R^7如式 I 所定义，R^9是 H、CH_3或酯基团如 $COOCH_3$、$COOC_2H_5$等. 可方便地在惰性溶剂(例如丙酮、乙腈、二甲氧基乙烷、甲醇、乙醇或二甲基甲酰胺)中，在有碱或没有碱存在下进行该反应. 所述碱例如是碱金属氢氧化物如氢氧化钠和氢氧化钾、碱金属碳酸盐如碳酸钾和碳酸钠或有机胺例如三乙胺.

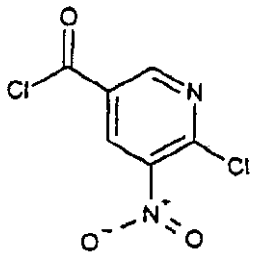
f) 例如通过利用溶于惰性溶剂如四氢呋喃或乙醚中的硼氢化锂

还原通式 X 化合物，其中 R^9 是酯基团得到通式 I 化合物，其中 R^1 是 CH_2OH .

方法 B

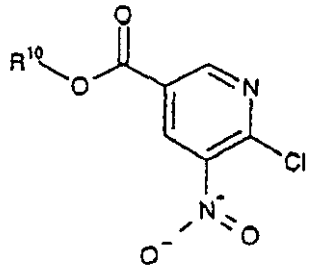
方法 B 用于制备通式 I 的化合物，其中 R^1 是 H 或 CH_3 和 X 是 NH，该方法包括以下步骤:

a) 通式 II 化合物



II

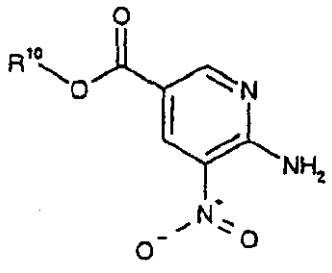
可与通式 R^{10}-OH 的醇化合物反应，其中 R^{10} 是烷基如甲基、乙基等，得到相应的式 XI 酯.



XI

该反应可在标准条件下进行.

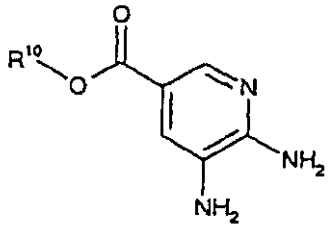
b) 通式 XI 化合物可与氨反应得到通式 XII 化合物



XII

其中 R^{10} 是烷基例如甲基或乙基等. 该反应可在标准条件下，在惰性溶剂中进行.

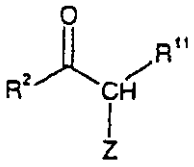
c) 式XII化合物可例如通过用氢和催化剂如Pd/C还原得到式XIII化合物



XIII

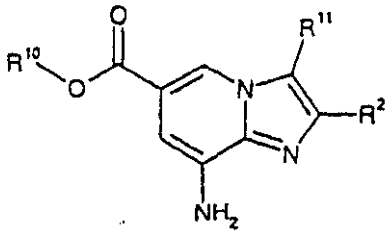
其中 R^{10} 是烷基例如甲基、乙基等. 该反应可在标准条件下，在惰性溶剂中进行.

d) 式 XV 的咪唑并[1,2-a]吡啶化合物，其中 R^{10} 是烷基例如甲基、乙基等，可通过使通式 XIII 化合物与通式 XIV 化合物反应制备



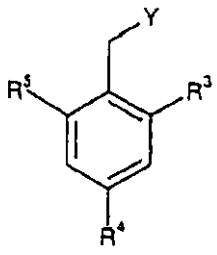
XIV

其中 R^2 如式 I 所定义，Z 是离去基团例如卤素、甲磺酰基或甲苯磺酰基和 R^{11} 代表 H 或 CH_3. 该反应在标准条件下，在惰性溶剂例如丙酮、乙腈、醇、二甲基甲酰胺等中，在有碱或没有碱存在下进行.



XV

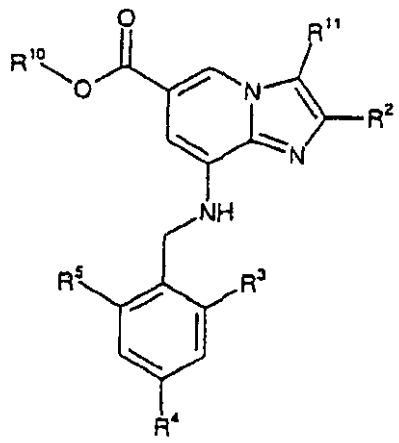
e) 式 XV 化合物可与式 IX 化合物反应



IX

其中 R^3、R^4 和 R^5 如式 I 所定义和 Y 是离去基团例如卤素、甲苯磺酰

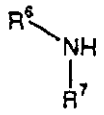
基或甲磺酰基，得到式 XVI 化合物。



XVI

其中 R^2、R^3、R^4和 R^5如式 I 所定义，R^{10}是烷基例如甲基、乙基等，R^{11}是 H 或 CH_3。可方便地在惰性溶剂(例如丙酮、乙腈、二甲氧基乙烷、甲醇、乙醇或二甲基甲酰胺)中，在有碱或没有碱存在下进行该反应。所述碱例如是碱金属氢氧化物如氢氧化钠和氢氧化钾、碱金属碳酸盐如碳酸钾和碳酸钠或有机胺例如三乙胺。

f) 式 XVI 化合物可与通式 III 氨基化合物反应



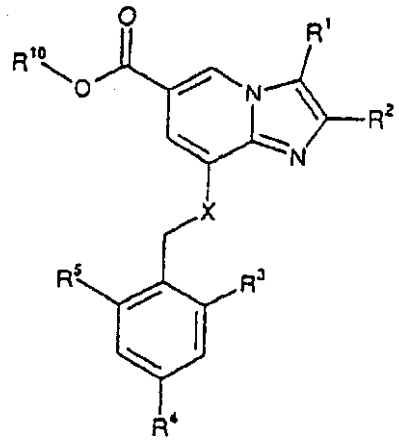
III

其中 R^6、R^7如在式 I 中所定义，得到相应的式 I 的酰胺，其中 R^1是 H 或 CH_3，X 是 NH。该反应可通过在单纯的氨基化合物中或在标准条件下，在惰性溶剂中加热所述反应物进行。

方法 C

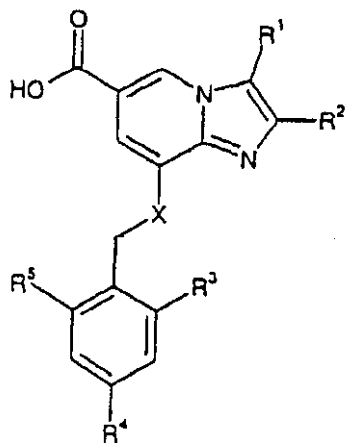
方法 C 用于制备通式 I 的化合物，该方法包括以下步骤:

a) 在标准条件下用酸或碱处理式 XVII 化合物



XVII

其中 R^1、R^2、R^3、R^4、R^5和X如在式I中所定义，R^{10}是烷基如甲基、乙基等，可以水解所述化合物得到相应的式XVIII的羧酸化合物.



XVIII

b)式XVIII化合物，其中 R^1、R^2、R^3、R^4、R^5和X如在式I中所定义，在偶合剂的存在下，可与式III的氨基化合物反应得到相应的式I的酰胺化合物. 该反应可在标准条件下，在惰性溶剂中进行.

医疗用途

另一方面，本发明涉及式I化合物在治疗中的用途，尤其用于治疗胃肠炎性疾病. 本发明也提供式I化合物在制备用于抑制胃酸分泌或用于治疗胃肠炎性疾病的药物中的用途.

因此，根据本发明的化合物可用于预防和治疗哺乳动物包括人的胃肠炎性疾病和与胃酸有关的疾病例如胃炎、胃溃疡、十二指肠溃疡、

回流性食管炎和佐林格-埃利森综合征．另外，该化合物也可用于治疗其它需要胃的抗分泌作用的胃肠疾病，例如胃泌素瘤的病人和急性上胃肠道出血的病人。该化合物也可用于加强护理下的病人，以及用于手术前和手术后防止胃酸吸入和应激溃疡形成．

该活性物质一般日剂量变动的范围很大并取决于许多因素例如每个病人的个体需求、给药途径和疾病本身．一般来说，口服和肠胃外的剂量为每天 5-1000 mg 活性物质．

药用制剂

再一方面，本发明涉及含有至少一种作为活性组分的本发明化合物或其治疗上可接受的盐的药用组合物．

本发明化合物也与其它活性成分例如抗生素如阿莫西林一起在制剂中使用。

对于临床应用而言，将本发明化合物配制成供口腔、直肠、肠胃外或其它给药方式的药用制剂．该药用制剂含有至少一种与一种或多种药学上可接受的成分组合的本发明化合物．所述载体可是固体、半固体或液体稀释剂或胶囊形式．这些药用制剂是本发明的另一个目的．通常活性化合物的量占所述制剂重量的 0.1-95 %，对于肠胃外给药，优选占所述制剂重量的 0.1-20 %，对于口服给药，优选占所述制剂重量的 0.1-50 %。

在制备以供口服给药的剂量单位形式的含有本发明化合物的药用制剂中，可将所选择的化合物与固体、粉末成分例如乳糖、蔗糖、山梨醇、甘露糖醇、淀粉、支链淀粉、纤维素衍生物、明胶或与其它合适的成分以及崩解剂和润滑剂如硬脂酸镁、硬脂酸钙、硬脂基富马酸钠和聚乙二醇蜡混合．然后将该混合物加工成颗粒状或压制成片剂．

软的明胶胶囊可用含有活性化合物或本发明化合物、植物油、脂肪或其它对于软明胶胶囊合适的溶媒的混合物的胶囊制备．硬明胶胶

囊可含有活性化合物的颗粒。硬明胶胶囊也可含有在与固体粉末状成分如乳糖、蔗糖、山梨醇 、甘露糖醇、马铃薯淀粉、玉米淀粉、支链淀粉、纤维素衍生物或明胶混合的活性化合物。

用于直肠给药的剂量单位可制备为(i)含有与中性脂肪基混合的活性物质的栓剂形式; (ii)含有与植物油、石蜡油或其它对明胶直肠胶囊合适的溶媒混合的活性物质的明胶直肠胶囊形式; (iii)预制的微量灌肠剂形式; 或(iv)可在给药前，在合适的溶剂中复制的干燥的微量灌肠剂形式。

可以糖浆或悬浮液形式制备供口服给药的液体制剂，例如含有0.1%-20%(重量)的活性成分和由糖或糖醇和乙醇、水、甘油、丙二醇和聚乙二醇的混合物组成的其余部分的溶液或悬浮液。如果需要，该液体制剂可含有着色剂、调味剂、糖精和羧甲基纤维素或其它增稠剂。供口服给药的液体制剂也可配制成在服用前与合适的溶剂重新复制的干粉形式。

供肠胃外给药的溶液，可制备成溶于药学上可接受的溶剂中，优选浓度为 0.1-10 % (重量)的本发明化合物的溶液。该溶液也可含有稳定成分和/或缓冲成分并以安瓿或管形瓶形式分散成单位剂量。供肠胃外给药的溶液也可制备成干制剂以便在使用前用合适的溶剂重新复制。

根据本发明的化合物可用于制剂中，并与其它活性成分一起或以组合的形式同时、分别或按顺序使用，例如用于治疗或预防人胃粘膜幽门螺旋菌(Helicobater pylori)感染引起的疾病。其它活性成分可以是抗菌素，尤其是:

β-内甲酰胺抗生素例如阿莫西林、氨苄西林、头孢噻吩、头孢克洛或头孢克肟;

大环内酯类例如红霉素或克拉霉素;

四环素类例如四环素或多西环素;

氨基糖甙类例如庆大霉素、卡那霉素或阿米卡星;

喹诺酮类例如诺氟沙星、环丙沙星或依诺沙星;
其它例如甲硝唑、呋喃妥因或氯霉素; 或
含有铋盐例如碱式柠檬酸铋、碱式水杨酸铋、碱式碳酸铋、硝酸氧铋或碱式没食子酸铋的制剂.

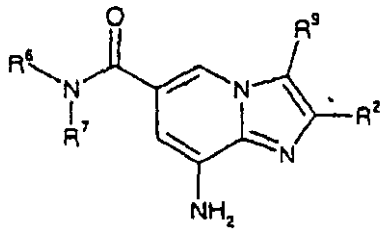
根据本发明的化合物可与解酸药例如氢氧化铝、碳酸镁和氢氧化镁或藻酸一起或以组合的形式同时、分别或按顺序使用，或者与抑制胃酸分泌的药物例如 H2-受体阻断剂(例如西米替丁、雷尼替丁)、H+/K+-ATP 酶抑制剂(例如奥美拉唑、泮托拉唑、兰索拉唑或雷贝拉唑)一起或以组合的形式同时、分别或按顺序使用,或者与胃动力药(gastroprokinetics) (例如西沙必利、莫沙必利) 一起或以组合的形式同时、分别或按顺序使用.

中间体

本发明的另一方面是用于合成本发明化合物的新的中间体化合物.

因此，本发明包括:

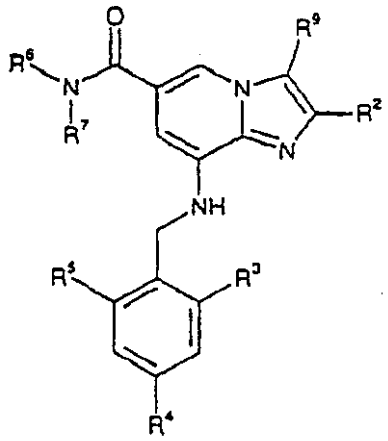
(a) 式 VIII 化合物



VIII

其中 R^2、R^6和 R^7如式 I 所定义，R^9是 H、CH_3或酯基团例如 $COOCH_3$、$COOC_2H_5$等;

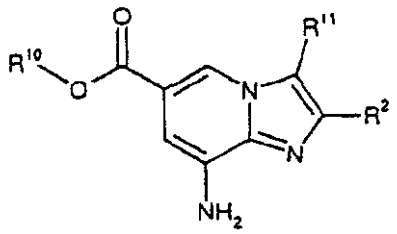
(b) 式 X 化合物



X

其中 R^2、R^3、R^4、R^5、R^6和 R^7如式 I 所定义，R^9是酯基团例如 $COOCH_3$、$COOC_2H_5$等；

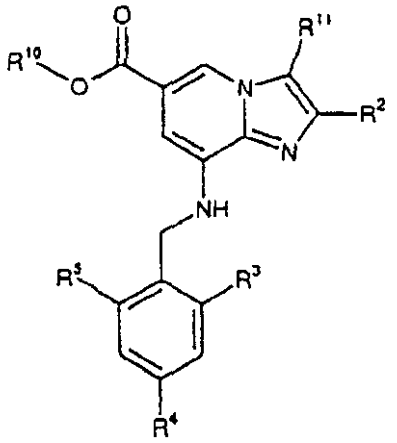
(c) 式 XV 化合物



XV

其中 R^2如式 I 所定义，R^{10}是烷基和 R^{11}是 H 或 CH_3；

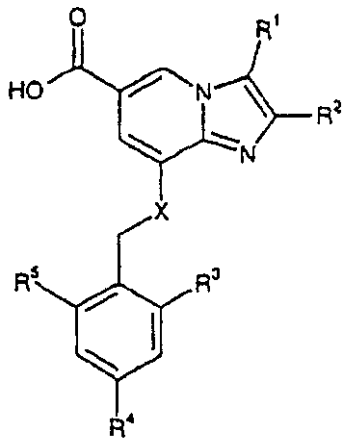
(d) 式 XVI 化合物



XVI

其中 R^2、R^3、R^4和 R^5如式 I 所定义，R^{10}是烷基和 R^{11}是 H 或 CH_3；

(e) 式 XVIII 化合物



XVIII

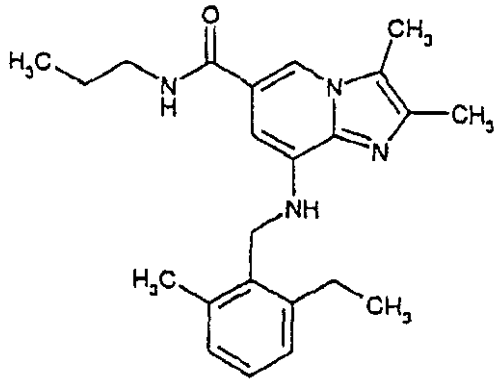
其中 R^1、R^2、R^3、R^4、R^5和X如式I所定义.

实施例

1.本发明化合物的制备

实施例 1.1

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-N-丙基-咪唑并[1,2-a]吡啶-6-甲酰胺的合成

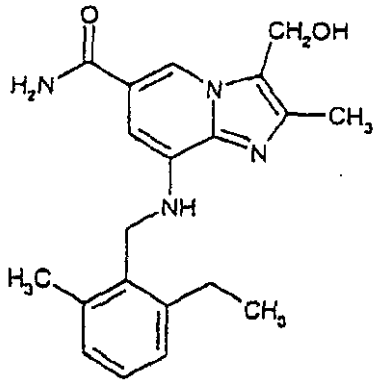


将2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酸乙酯(0.12 g, 0.33 mmol)、丙胺(1.0 g, 17 mmol)和催化量的氰化钠在甲醇(20 ml)中回流24小时. 加入额外量的丙胺(1.0 g, 17 mmol)并将该反应混合物回流24小时. 在减压下蒸发溶剂并用乙醚为洗脱剂, 在硅胶上用柱层析纯化该残余物. 从乙醚中结晶得到0.053g (42%)的标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.0 (t, 3H), 1.2(t, 3H), 1.65-1.75 (m, 2H), 2.3 (s, 3H,), 2.35 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 3.4-3.5(m, 2H), 4.35(d, 2H), 4.9(bs, 1H), 6.2 (bs, 1H), 6.35 (s, 1H), 7.0-7.2 (m, 4H), 7.85 (s, 1H).

实施例 1.2

8-(2-乙基-6-甲基苄氨基)-3-羟基甲基-2-甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成

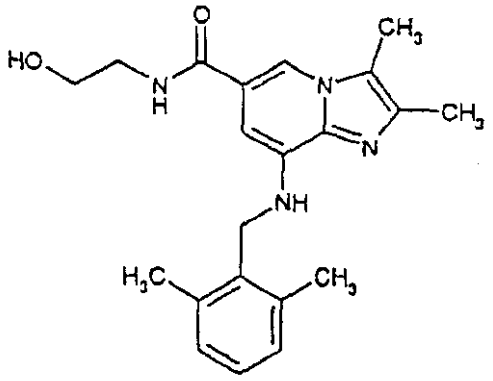


将 6-(氨基羰基)-8-(2-乙基-6-甲基苄氨基)-2-甲基咪唑并[1,2-a]吡啶-3-甲酸乙酯(280 mg, 0.71 mmol)和硼氢化锂(16mg, 0.71 mmol)加入到四氢呋喃(10 ml)中并将该反应混合物回流 70 分钟. 加入额外量的硼氢化锂(16 mg)和甲醇(45 mg, 1.42 mmol)并回流该混合物 80 分钟. 加入额外量的硼氢化锂(16 mg)和甲醇(22 mg, 71 mmol)并回流该混合物 4 小时. 将该反应混合物达到室温, 在室温下, 将该混合物和水(1 ml)、甲醇(5 ml)搅拌 40 分钟. 在减压下蒸发溶剂并将残余物加入到水中并搅拌 80 分钟. 滤除催化剂并用水、乙酸乙酯/乙醇和乙醚洗涤, 得到所需的产物(115 mg, 46 %).

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.15 (t, 3H), 2.25 (s, 3H,), 2.35 (s, 3H), 2.7 (q, 2H), 4.35(d, 2H), 4.75 (d, 2H), 4.85(t, 1H), 5.1 (t, 1H), 6.8 (s, 1H), 7.1-7.25 (m, 3H), 7.4 (bs, 1H), 8.05 (bs, 1H), 8.3 (s, 1H).

实施例 1.3

2,3-二甲基-8-(2,6-二甲基苄氨基)-N-羟基乙基-咪唑并[1,2-a]吡啶-6-甲酰胺的合成

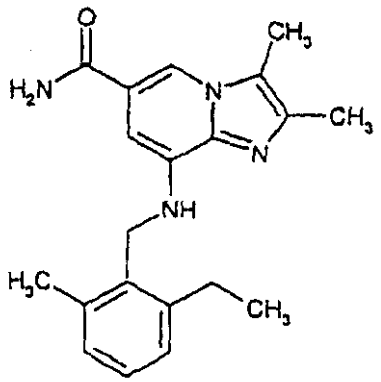


将 2,3-二甲基-8-(2,6-二甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酸甲酯(0.12 g, 0.33 mmol)、乙醇胺(0.2 g , 3.3 mmol)和氰化钠(10mg, 0.2 mmol)在二甲氧基乙烷(2 ml)中回流 20 小时. 在减压下蒸发溶剂. 用二氯甲烷:甲醇(92:8)作为洗脱剂，在硅胶上用柱层析纯化该残余物得到产物，用乙醚洗涤该产物得到 103 mg (79 %)标题化合物.

^{1}H-NMR (300MHz, $CDCl_3$): δ 2.3 (s, 6H,), 2.35 (s, 6H), 3.5-3.6(m, 2H), 3.75-3.8 (m, 2H), 4.3(d, 2H), 4.95(t, 1H), 6.4 (s, 1H), 6.85 (t, 1H), 7.0-7.2 (m, 3H), 7.75 (s, 1H).

实施例 1.4

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成

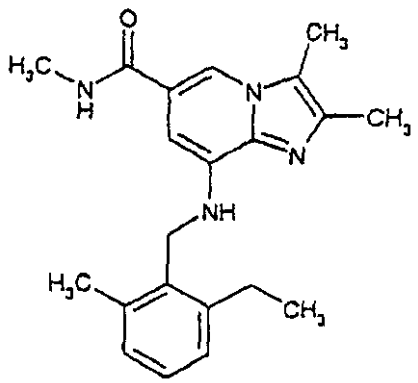


将 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺(3.3 g, 16.2 mmol)、2-乙基-6-甲基苄基氯 (2.73 g , 16.2 mmol)、碳酸钾(8.0 g, 58 mmol)和碘化钾(1.1g, 6.6 mmol)加入到丙酮(150 ml)中并回流 20 小时. 加入额外量的 2-乙基-6-甲基苄基氯(1.0 g, 5.9 mmol)并回流该反应混合物 7 小时. 加入二氯甲烷(60 ml)和甲醇(30 ml). 过滤该反应混合物并在减压下蒸发溶剂. 用二氯甲烷:甲醇(100:7)作为洗脱剂, 在硅胶上用柱层析纯化该残余物. 从乙酸乙酯中结晶得到 2.8 g (50%)标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.34 (s, 3H), 2.36(s, 3H), 2.38(s, 3H), 2.7(q, 2H), 4.4 (d, 2H), 4.9 (bs, 1H), 6.0 (bs, 2H), 6.45 (s, 1H), 7.0-7.2(m, 3H), 7.9(s, 1H).

实施例 1.5

8-(2-乙基-6-甲基苄氨基)-N,2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成

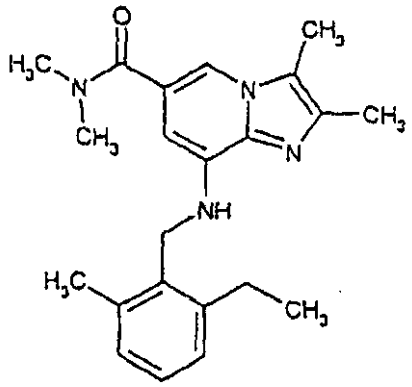


将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.15 g, 0.44 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓(uronium)四氟硼酸盐(TBTU) (0.14g, 0.44 mmol)加入到二氯甲烷(10 ml)中并在室温下搅拌该反应混合物 15 分钟. 加入甲基胺(0.1 g, 3.2 mmol), 在室温下搅搅拌该反应混合物 1.5 小时. 在减压下蒸发溶剂并用乙酸乙酯:二氯甲烷(1:1)作为洗脱剂, 在硅胶上经柱层析纯化该残余物. 经乙醚处理该产物得到 40mg (26%)所需产物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.33 (s, 3H), 2.36(s, 3H), 2.38(s, 3H), 2.7(q, 2H), 3.05 (d, 3H), 4.35 (d, 2H), 4.9 (t, 1H), 6.3 (bs, 1H), 6.4 (s, 1H), 7.0-7.2(m, 3H), 7.85(s, 1H).

实施例 1.6

8-(2-乙基-6-甲基苄氨基)-N,N,2,3-四甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成



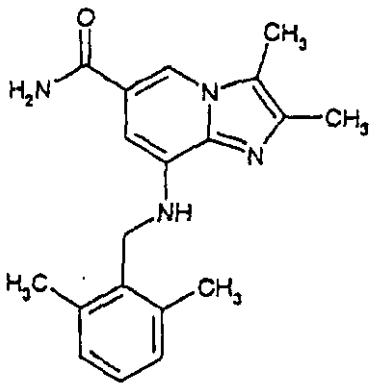
将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸 (0.15 g, 0.44 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU) (0.14g, 0.44 mmol)加入到二氯甲烷(10 ml)中. 加入二甲基胺(0.063 g, 1.4 mmol)并在室温下搅拌该反应混合物 4 小时. 加入额外量的二甲胺(0.1 ml)并在室温下搅拌该混合物 20 小时. 在减压下蒸发溶剂并用二氯甲烷:甲醇(9:1)作为洗脱剂通过柱层析纯化该残余物. 经庚烷处理该油性产物并过滤形成的固体得到 0.1g (62 %)标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.35 (s, 6H), 2.4(s, 3H), 2.7(q, 2H), 3.15(s, 6H), 4.4 (d, 2H), 4.9 (t, 1H), 6.25 (s, 1H), 7.0-7.2(m, 3H), 7.45(s, 1H).

00.12.25

实施例 1.7

2,3-二甲基-8-(2,6-二甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成



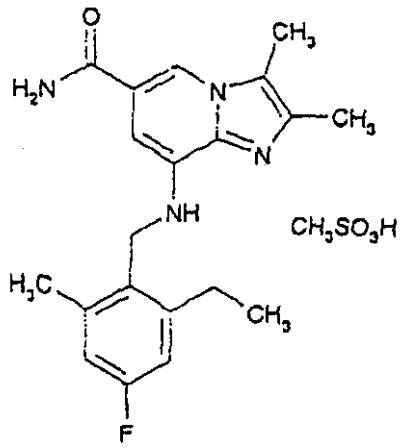
将 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺(0.6 g, 2.9 mmol)、 2,6-二甲基苄基氯(0.45 g, 2.9 mmol)、碳酸钠(1.0 g, 9.4 mmol)和碘化钾(0.2g, 1.3 mmol)加入到丙酮(25 ml)中并回流 19 小时. 加入二氯甲烷并滤出无机盐. 用碳酸氢钠洗涤该溶液, 分离有机层、干燥并在减压下蒸发溶剂. 用二氯甲烷:甲醇(100:5)作为洗脱剂, 在硅胶上经柱层析纯化该残余物. 经乙醚洗涤该产物得到 0.78g (82%)标题化合物.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.4 (s, 6H), 2.42(s, 3H), 4.4 (d, 2H), 2.95 (bs, 1H), 6.45 (s, 1H),7.05-7.15(m, 3H), 7.95(s, 1H).

00.12.25

实施例 1.8

2,3-二甲基-8-(2-乙基-4-氟代-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐的合成



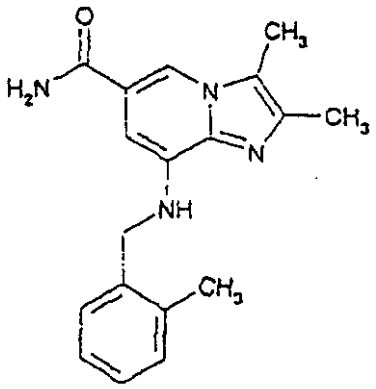
将 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(0.7 g, 1.9 mmol)、 2-乙基-4-氟代-6-甲基苄基氯(0.26 g, 1.9 mmol)和二异丙基乙胺(0.54, 4.2 mmol)加入到二甲基甲酰胺(5 ml)中并在室温下搅拌 1 小时. 将二氯甲烷和水加入到该反应混合物中, 分离有机层、干燥并在减压下蒸发溶剂. 将该残余物溶于乙酸乙酯中并加入乙醇和甲磺酸(0.2 g, 2 mmol). 滤出产物并溶于二氯甲烷:甲醇(2:1)和过量的碳酸钾中. 滤出固体并在减压下蒸发溶剂. 用二氯甲烷:甲醇(10:1)作为洗脱剂, 在硅胶上经柱层析纯化该残余物. 将该残余物溶于乙酸乙酯中并加入甲磺酸(0.04 g, 0.4 mmol). 滤出盐得到 0.2g (23%)的标题化合物.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.15 (t, 3H), 2.25 (s, 3H), 2.35(s, 3H), 2.4 (s, 3H), 2.45 (s, 3H), 2.6 (q, 2H), 4.35 (d, 2H), 6.15 (bs, 1H), 6.95-7.05(m, 2H), 7.4(s, 1H) , 7.8(bs, 1H), 8.3(bs, 1H), 8.45(s, 1H).

00.12.25

实施例 1.9

2,3-二甲基-8-(2-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成



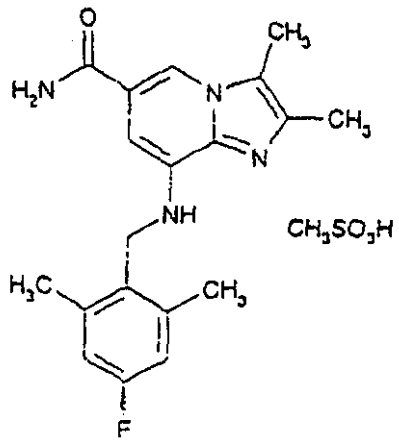
将溶于二甲基甲磺酰(7 ml)中的 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(1.0 g, 2.7 mmol)、α-氯代-邻-二甲苯(0.38 g, 2.7 mmol)和二异丙基乙胺(0.76 g, 5.9 mmol)的溶液在 50 ℃下搅拌 7 小时并在室温下搅拌 72 小时. 蒸发溶剂并用二氯甲烷、水和少量二异丙基乙胺的混合物处理该残余物. 经过滤分离所形成的固体并用乙酸乙酯洗涤得到 0.11g (13%)标题化合物.

^{1}H-NMR (300 MHz, DMSO-d_6): δ2.3 (s, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 4.45 (d, 2H), 6.3-6.4(m, 2H), 7.1-7.25(m, 4H), 7.3(bs, 1H), 7.85(bs, 1H), 8.05(s, 1H).

00.12.25

实施例 1.10

2,3-二甲基-8-(2,6-二甲基-4-氟代-苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐的合成

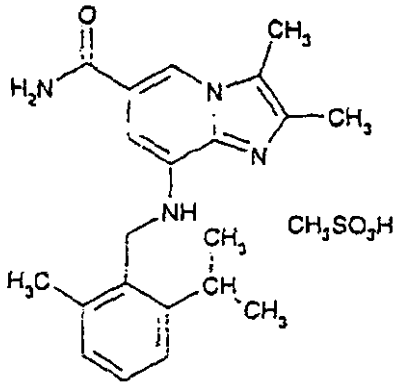


将溶于二甲基甲酰胺(20 ml)中的 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(5.0 g, 13.4 mmol)、2,6-二甲基-4-氟代苄基溴(2.91 g, 13.4 mmol)、二异丙基乙胺(3.8 g, 29.5 mmol)和催化量的碘化钾的溶液在室温下搅拌过夜. 将水(70 ml)和二氯甲烷(2 x 50 ml)加入到该反应混合物中并分离有机层、干燥并在减压下蒸发. 用二氯甲烷:甲醇(9:1)作为洗脱剂, 在硅胶上经柱层析纯化该残余物. 将该产物溶于异丙醇中并加入甲磺酸(0.3 g). 经过滤分离所形成的盐并用异丙醇和乙醚洗涤得到 1.4g (24%)标题化合物.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.25 (s, 3H), 2.35 (s, 6H), 2.4 (s, 3H), 2.5 (s, 3H), 4.4(d, 2H), 6.1(bs, 1H), 7.0(d, 2H), 7.35(s, 1H), 7.8(bs, 1H), 8.3(bs, 1H), 8.45(s, 1H).

实施例 1.11

2,3-二甲基-8-(2-甲基-6-异丙基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐的合成

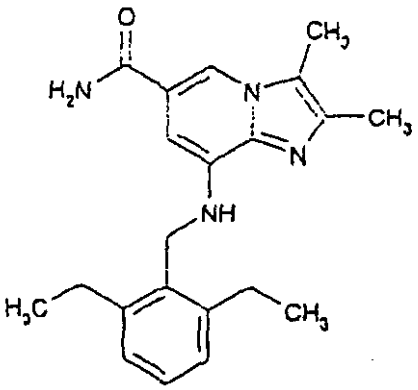


溶于二甲基甲酰胺(15 ml)中的 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(3.0 g, 8.0 mmol)、2-甲基-6-异丙基苄基氯(1.47 g, 8.0 mmol)、二异丙基乙胺(2.4 g, 18.6 mmol)和催化量的碘化钾的溶液. 根据实施例 1.10 制备标题化合物(得量:1.3 g, 36 %).

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.2 (d, 6H), 2.25 (s, 3H), 2.4 (s, 3H), 2.45 (s, 3H), 2.5 (s, 3H), 3.2(m, 1H), 4.45 (d, 2H), 6.15(bs, 1H), 7.15-7.3(m, 3H), 7.4(s, 1H), 7.85(bs, 1H), 8.35(bs, 1H), 8.45(s, 1H).

实施例 1.12

2,3-二甲基-8-(2,6-二乙基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成



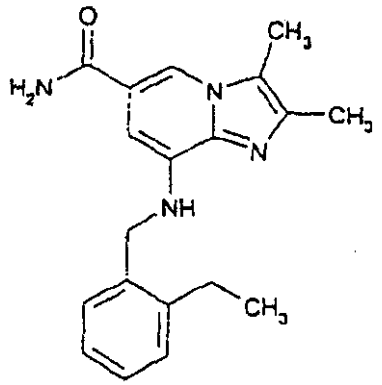
将 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(4.0 g,

10.7 mmol)、2,6-二乙基苄基氯(1.8 g, 9.9 mmol)、二异丙基乙胺(3.0 g, 23.3 mmol)在二甲基甲酰胺(20 ml)中的溶液在 50 ℃下搅拌过夜并在 70 ℃下搅拌 3 小时. 加入水(60 ml)和二氯甲烷并分离有机层、干燥并在减压下蒸发. 用乙醚处理该残余物并滤出产物得到 1.7 g (45 %)的标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 6H), 2.35 (s, 3H), 2.4 (s, 3H), 2.7 (q, 4H), 4.4 (d, 2H), 4.95 (bs, 1H), 6.15(bs, 1H), 6.5(s, 1H), 7.05-7.25(m, 3H), 7.95(s, 1H).

实施例 1.13

2,3-二甲基-8-(2-乙基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成



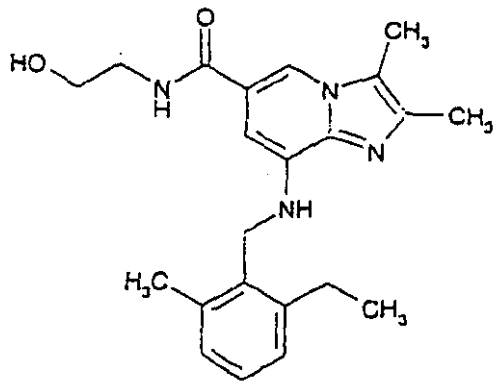
溶于二甲基甲酰胺(20 ml)中的 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(4.0 g, 10.7 mmol)、2-乙基苄基氯(1.65 g, 10.7 mmol)、二异丙基乙胺(3.0 g, 23.3 mmol).

根据实施例 1.12 制备标题化合物(得量:1.15 g, 26 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 4.5 (d, 2H), 6.3(t, 1H), 6.4(s, 1H), 7.05-7.25(m, 4H), 7.3(bs, 1H), 7.85(bs, 1H), 8.05(s, 1H).

实施例 1.14

2,3 二甲基-8-(2-乙基-6-甲基苄氨基)-N-羟乙基-咪唑并[1,2-a]吡啶-6-甲酰胺的合成



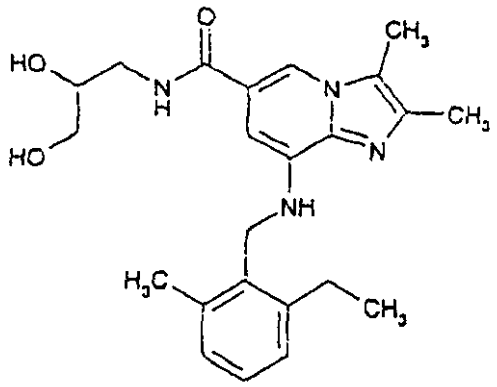
将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.3 g, 0.88 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU) (0.29g, 0.90 mmol)加入到二氯甲烷(15 ml)中并将该混合物搅拌 5 分钟. 加入乙醇胺(0.11 g, 1.8 mmol)并在室温下搅拌该反应混合物 2 小时. 在减压下蒸发溶剂并用二氯甲烷:甲醇(9:1)作为洗脱剂, 在硅胶上通过柱层析纯化该残余物. 从乙醚中结晶得到 0.2g (59 %)所需产物.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.3 (s, 6H), 2.35(s, 3H), 2.7(q, 2H), 3.55-3.6(m, 2H), 3.8-3.85(m, 2H), 4.35 (d, 2H), 4.9 (t, 1H), 6.4 (s, 1H), 6.85(t, 1H), 7.05-7.2(m, 3H), 7.75(s, 1H).

00.12.25

实施例 1.15

N-(2,3-二羟基丙基)-2,3 二甲基-8-(2-乙基-6-甲基苄氨基)-[1,2-a]吡啶-6-甲酰胺的合成



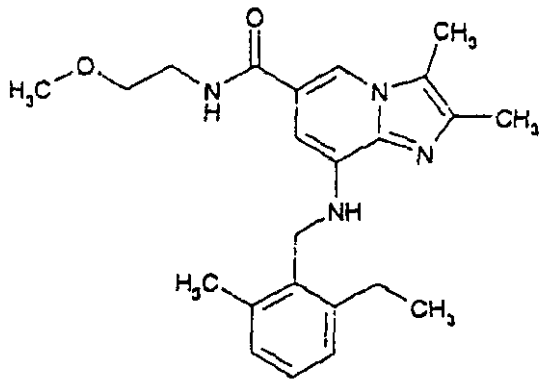
溶于二甲基甲酰胺(10 ml)中的 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.3 g, 0.88 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.29g, 0.90 mmol)和 3-氨基-1,2-丙二醇(0.16 g, 1.81 mmol).

根据实施例 1.14 制备标题化合物(得量: 0.2 g, 54 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.2 (t, 3H), 1.82-1.85(m, 1H), 2.32 (s, 3H), 2.33 (s, 3H), 2.36(s, 3H), 2.7 (q, 2H), 3.5-3.65(m, 4H), 3.72-3.77(m, 1H), 3.85-3.91(m, 1H) , 4.34 (d, 2H), 5.04(t, 1H), 6.4(t, 1H), 6.89(t, 1H), 7.04-7.12(m, 2H), 7.18(t, 1H), 7.78(d, 1H).

实施例 1.16

2,3 二甲基-8-(2-乙基-6-甲基苄氨基)-N-(2-甲氧基乙基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成



溶于二氯甲烷(10 ml)中的 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.15 g, 0.44 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.14g, 0.44 mmol)和 2-甲氧基乙胺(0.11 g, 1.4 mmol).

根据实施例 1.14 制备标题化合物

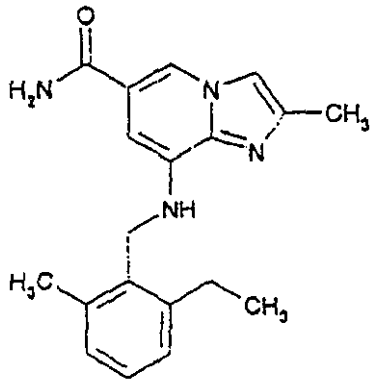
从己烷:乙酸乙酯中结晶. (得量: 0.09 g, 53 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 3H), 2.34(s, 3H), 2.38 (s, 3H), 2.39(s, 3H), 2.71(q, 2H), 3.42(s, 3H), 3.6-3.72(m, 4H), 4.38 (d, 2H), 4.91(t, 1H), 6.42 (s, 1H), 6.58(t, 1H), 7.04-7.2(m, 3H), 7.88(s, 1H).

00.12.25

实施例 1.17

2-甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成

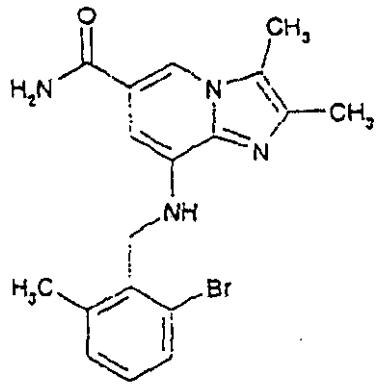


将 8-氨基-2-甲基咪唑并[1,2-a]吡啶-6-甲酰胺(3.8 g, 20 mmol)、2-乙基-6-甲基苄基氯(2.8 g, 17 mmol)、碳酸钾(5.5 g, 40 mmol)和碘化钠(0.1 g, 0.6 mmol)加入到二甲基甲酰胺(75 ml)中并将该混合物在 50 ℃下搅拌 4 小时，在室温下搅拌 48 小时。通过硅胶过滤该反应混合物并用二氯甲烷洗涤该硅胶。在减压下蒸发溶剂并用二氯甲烷:甲醇(9:1)作为洗脱剂，在硅胶上经柱层析纯化该残余物。从二氯甲烷和己烷的混合物中结晶得到 0.13 g (2 %)的标题化合物。

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H), 2.31 (s, 6H), 2.64 (q, 2H), 4.32 (d, 2H), 4.89 (bs, 1H), 6.36(s, 1H), 7.0-7.15(m, 3H), 7.23(s, 3H) 8.03(s, 1H).

实施例 1.18

2,3-二甲基-8-(2-溴代-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成

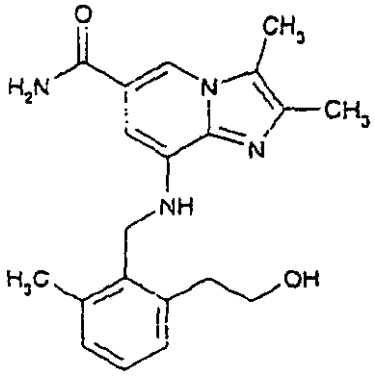


将 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(1.0 g, 5.0 mmol)、 2-溴代-6-甲基苄基氯(45 %) (3.0 g, 5.0 mmol)和二异丙基乙胺(2.2 g, 17 mmol)加入到二甲基甲酰胺(50 ml)中并在 50 ℃下搅拌 48 小时. 将二氯甲烷和水加入到该反应混合物中, 分离有机层, 用饱和的氯化钠洗涤, 干燥(Na_2SO_4)并在减压下蒸发. 用二氯甲烷:甲醇(10:1)和乙酸乙酯作为洗脱剂, 在硅胶上经柱层析纯化该残余物两次, 得到 0.18 g (1 %)的所需产物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 4.48 (d, 2H), 5.0 (bs, 1H), 6.05(bs, 2H), 6.41(d, 1H), 6.95-7.1(m, 2H), 7.37(d, 1H), 7.87(d, 1H).

实施例 1.19

2,3-二甲基-8-(2-(2-羟乙基)-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成

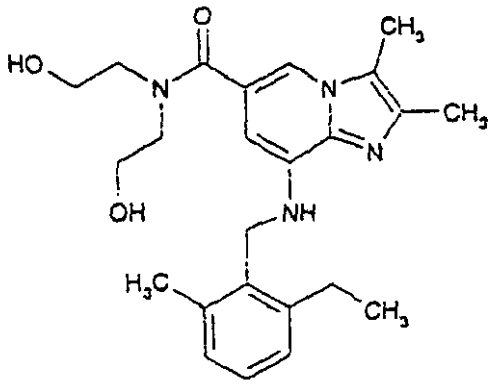


将 2,3-二甲基-8-(2-(2-苄氧基)乙基)-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酰胺(0.13 g, 0.29 mmol)、环己烯(1ml)、$Pd(OH)_2$ 催化剂(25 mg)加入到乙醇(5 ml)中并将该混合物回流过夜. 加入额外量的环己烯(1 ml)和催化量的 $Pd(OH)_2$ (25 mg)并将该混合物回流 4 小时. 减压下蒸发溶剂并用二氯甲烷:甲醇(9:1)作为洗脱剂, 在硅胶上经柱层析纯化该残余物. 用氯仿处理该残余物并过滤得到 0.1 g (99 %)的标题化合物.

^{1}H-NMR (400 MHz, CD_3OD): δ 2.29 (s, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 2.94 (t, 2H), 3.74 (t, 2H), 4.47 (s, 2H), 6.83(d, 1H), 7.11-7.20(m, 3H), 8.12(d, 1H) .

实施例 1.20

8-(2-乙基-6-甲基苄氨基)-N,N-双(2-羟乙基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成



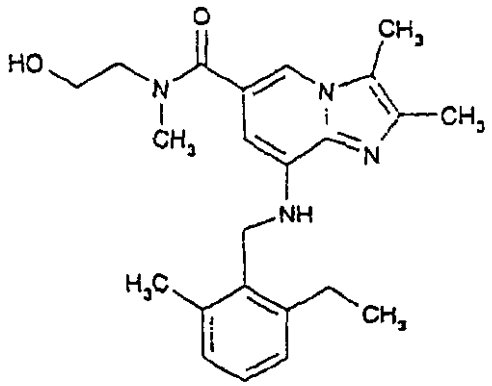
溶于二氯甲烷(10 ml)中的 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.3 g, 0.88 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU) (0.3g, 0.94 mmol)和二乙醇胺(0.2 g, 1.9 mmol).

根据实施例 1.14 制备标题化合物(得量: 0.19 g, 50 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.3 (s, 3H), 2.35(s, 3H), 2.4(s, 3H), 2.7 (q, 2H), 3.65(bs, 4H), 3.9(bs, 4H), 4.35 (d, 2H), 4.95(bs, 1H), 6.35(s, 1H), 7.0-7.2(m, 3H), 7.7(s, 1H).

实施例 1.21

8-(2-乙基-6-甲基苄氨基)-N-(2-羟乙基)-N,2,3-三甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成



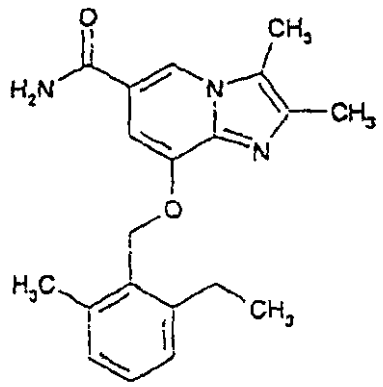
溶于二氯甲烷(10 ml)中的 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.3 g, 0.88 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU) (0.3g, 0.94 mmol)和 2-(甲基氨基)乙醇(0.2 g, 2.66 mmol).

根据实施例 1.14 制备标题化合物(得量: 0.25 g, 71 %).

^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.25 (s, 6H), 2.35(s, 3H), 2.7 (q, 2H), 3.15(s, 3H), 3.65(bs, 2H), 3.9(bs, 2H), 4.35 (d, 2H), 5.0(bs, 1H), 6.25(bs, 1H), 7.0-7.25(m, 3H), 7.45(bs, 1H).

实施例 1.22

2,3-二甲基-8-(2-乙基-6-甲基苄氧基)-咪唑并[1,2-a]吡啶-6-甲酰胺的合成



将 6-氨基-5-(2-乙基-6-甲基苄氧基)烟酰胺(0.14 g, 0.49 mmol)、 3-溴代-2-丁酮(0.075 g, 0.49 mmol)和碳酸氢钠(0.1 g, 1.2 mmol)加入到乙腈(3 ml)中并回流 20 小时. 减压下蒸发溶剂, 用二氯甲烷:甲醇(9:1)作为洗脱剂, 在硅胶上经柱层析纯化该残余物. 从乙腈中结晶得到 0.058 g (35 %)的标题化合物.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.14 (t, 3H), 2.24 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 2.69 (q, 2H), 5.25(s, 2H), 7.1-7.3(m, 4H), 7.51(bs, 1H), 8.08(bs, 1H), 8.42(s, 1H).

2. 中间体的制备

实施例 2.1

6-氨基-5-硝基烟酸甲酯的合成

将 6-氯代-5-硝基烟酰氯(22.0 g, 0.1 mol)冷却至+5 ℃. 在 30 分钟内滴加入甲醇并将该反应混合物搅拌 60 分钟. 温度不可高于+10 ℃. 将氢氧化铵(25% , 400 ml)滴加入该反应混合物中并在室温下搅拌该混合物 20 小时. 滤出产物, 用水洗涤并干燥得到 9.0 g (45.9 %)的标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 3H), 6.3 (bs, 1H), 8.0 (bs, 1H), 8.95 (s, 1H), 9.05 (s, 1H).

实施例 2.2

5,6-二氨基烟酸甲酯的合成

将 6-氨基-5-硝基烟酸甲酯(9.0 g, 46 mmol)和少量Pd/C催化剂加入到甲醇(200 ml)中并在室温和大气压下氢化该混合物直到停止摄取氢气. 然后通过硅藻土过滤, 在减压下蒸发甲醇得到 7.0 g (92 %)的标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.3 (s, 2H), 3.9 (s, 3H), 4.75 (s, 2H), 7.45 (s, 1H), 8.35 (s, 1H).

实施例 2.3

8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酸甲酯的合成

将 5,6-二氨基烟酸甲酯(0.9 g, 5.4 mmol)和 3-溴代-2-丁酮(0.9 g, 6.0 mmol)加入到乙腈(30 ml)中并回流 24 小时. 冷却后, 滤出部分为氢溴酸盐的产物. 在减压下蒸发 20ml 的滤液并加入乙醚. 又滤出为氢溴酸盐的产物. 将该盐溶于二氯甲烷中并用碳酸氢盐溶液洗涤. 分离有机层, 经 Na_2SO_4 干燥并在减压下蒸发得到 0.7 g (59 %)的所需化合物.

^{1}H-NMR (300 MHz,$CDCl_3$): δ 2.4 (s, 6H), 3.9 (s, 3H), 4.5 (s, 2H),

6.85 (s, 1H), 8.1 (s, 1H).

实施例 2.4

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酸甲酯的合成

将 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酸甲酯 (0.7 g, 3.2 mmol)、2-乙基-6-甲基苄基氯(0.54 g, 3.2 mmol)、碳酸钾(0.9 g, 6.4 mmol)和催化量的碘化钾加入到乙腈(20 ml)中并回流 6 小时. 然后过滤, 在减压下蒸发乙腈得到一种油. 将该油状残余物溶于二氯甲烷中并用水洗涤. 分离有机层, 经 Na_2SO_4 干燥并在减压下蒸发得到一种固体. 用二氯甲烷:乙酸乙酯(10:1)作为洗脱剂, 在硅胶上经柱层析纯化得到 0.42 g (38 %)的标题化合物.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.15 (t, 3H), 2.35(s, 3H), 2.4 (s, 3H), 2.43 (s, 3H), 2.75(q, 2H), 4.0(s, 3H), 4.25(d, 2H), 4.9(bs, 1H), 6.8 (s, 1H), 7.05-7.2(m, 3H), 8.1 (s, 1H).

实施例 2.5

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸的合成

将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酸甲酯(0.4 g, 1.1 mmol)加入到 1,4-二噁烷(6 ml)和 2M NaOH(6 ml)的混合物中并回流 30 分钟. 在减压下蒸发二噁烷, 通过加入经 2M HCl 使该水溶液显酸性. 通过加入饱和的碳酸氢盐溶液使酸性的水溶液碱化并经过滤分离形成的固体得到 0.35 g (91 %)的标题化合物.

^{1}H-NMR (400 MHz,DMSO-d_6): δ 1.15 (t, 3H), 2.2(s, 3H), 2.35 (s, 6H), 2.7 (q, 2H), 4.35(d, 2H), 4.65(t, 1H), 6.8 (s, 1H), 7.05-7.2(m, 3H), 7.95 (s, 1H).

实施例 2.6

8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酸乙酯的合成

将 5,6-二氨基烟酸乙酯(1.4 g, 7.7 mmol)和 3-溴代-2-丁酮(1.16 g, 7.2 mmol)加入到 1,2-二甲氧基乙烷(50 ml)中并回流 20 小时. 在减压下蒸发溶剂并将该残余物溶于二氯甲烷中. 用饱和的碳酸氢钠洗涤该二氯甲烷溶液并经 Na_2SO_4 干燥. 在减压下蒸发溶剂, 用二氯甲烷:甲醇(10:1)作为洗脱剂, 在硅胶上经柱层析纯化得到 0.3 g (17 %)的标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.4 (t, 3H), 2.4 (s, 6H), 4.35 (q, 2H), 4.6(s, 2H), 6.75 (s, 1H), 8.2 (s, 1H).

实施例 2.7

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-甲酸乙酯的合成

将 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酸乙酯(0.7 g, 3.0 mmol)、2-乙基-6-甲基苄基氯(0.5 g, 3.0 mmol)、碳酸钠(0.64 g, 6.0 mmol)和催化量的碘化钾加入到丙酮(50 ml)中并回流 20 小时. 然后过滤, 在减压下蒸发丙酮得到一种油. 用乙醚:石油酯(1:1)作为洗脱剂, 在硅胶上经柱层析纯化该油性产物得到 0.12 g (9 %)的标题产物.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.25 (t, 3H), 1.5(t, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 2.44(s, 3H), 2.75(q, 2H), 4.45-4.5(m, 4H), 4.9(bs, 1H), 6.8 (s, 1H), 7.05-7.2(m, 3H), 8.1(s, 1H).

实施例 2.8

6-氨基-5-硝基烟酰胺的合成

将溶于四氢呋喃(500 ml)中的 6-氯代-5-硝基烟酰氯(38 g, 0.2 mol)溶液在+5 ℃下搅拌并将氨气起泡通入该溶液. 1 小时后, 将该反应混合物加热至室温并将氨气再起泡通入该溶液 2.5 小时. 在室温下搅拌

该反应混合物 20 小时. 过滤滤出固体, 用水充分洗涤并在减压下干燥得到 18.5 g (51 %)的标题化合物.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.4 (s, 1H), 8.05 (s, 1H), 8.3 (s, 2H), 8.8 (s, 2H).

实施例 2.9

5,6-二氨基烟酰胺的合成

将溶于甲醇(600 ml)中的 6-氨基-5-硝基烟酰胺(18 g, 99 mmol)和催化量的 Pd/C 的悬浮液在室温下和大气压下氢化直到停止摄取氢气. 然后经硅藻土过滤, 在减压下蒸发甲醇得到 14.5 g (96 %)的标题化合物.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.0 (bs, 2H), 6.1 (bs, 2H), 6.9 (bs, 1H), 7.15 (s, 1H) ,7.55(bs, 1H), 7.9(s, 1H).

实施例 2.10

8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成

将 5,6-二氨基烟酰胺(12.5 g, 82 mmol)、 3-溴代-2-丁酮(13.6 g, 90 mmol)和乙腈(150 ml)回流 20 小时. 加入额外量的 3-溴代-2-丁酮(4.0 g, 26.5 mmol)并回流该反应混合物 5 小时. 冷却后过滤出固体. 将该固体加入到二氯甲烷(150 ml)、 甲醇(150 ml)和碳酸钾(22 g, 160 mmol)中并搅拌 30 分钟. 过滤除去固体并在减压下蒸发溶剂, 得到油状残余物. 用二氯甲烷:甲醇(5:1)作为洗脱剂, 在硅胶上经柱层析纯化得到 3.3 g (20 %)的标题化合物.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H), 2.35 (s, 3H), 5.6 (s, 2H), 6.65 (s, 1H), 7.15(bs, 1H), 7.85 (bs, 1H), 8.05 (s, 1H).

实施例 2.11

8-氨基-6-(氨基羰基)-2-甲基咪唑并[1,2-a]吡啶-3-甲酸乙酯的合成

将 5,6-二氨基烟酰胺(2.0 g, 13.4mmol)、 2-氯代乙酰乙酸乙酯(2.38

g, 14.4 mmol)和乙醇(40 ml)回流 20 小时. 经过滤分离该沉淀物并用乙醇和乙醚洗涤. 将该固体悬浮在水中, 用氢氧化钠溶液碱化并过滤分离. 用水和乙醚洗涤该固体得到 0.42 g (12 %)的所需产物.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.4 (t, 3H), 2.6 (s, 3H), 4.35 (q, 2H), 5.95(bs, 2H), 6.9(s, 1H), 7.35(bs, 1H), 8.0 (bs, 1H) , 9.0(s, 1H).

实施例 2.12

6-(氨基羰基)-8-(2-乙基-6-甲基苄氨基)-2-甲基咪唑并[1,2-a]吡啶-3-甲酸乙酯的合成

将 8-氨基-6-(氨基羰基)-2-甲基咪唑并[1,2-a]吡啶-3-甲酸乙酯(0.41 g, 1.6 mmol)、 2-乙基-6-甲基苄基氯、碳酸钠(0.7 g, 6.6mmol)、碘化钠(0.15 g, 1.0 mmol)和丙酮(20 ml)回流 44 小时. 加入二氯甲烷并经过滤除去固体. 在减压下蒸发滤液并用二氯甲烷:甲醇(100:4)作为洗脱剂, 在硅胶上经柱层析纯化该残余物得到 0.35 g (56 %)的标题化合物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H), 1.45 (t, 3H), 2.35 (s, 3H), 3.65(s, 3H), 2.7(q, 2H), 4.4-4.45(m, 4H), 5.0(t, 1H), 6.95(s, 1H), 7.0-7.2 (m, 3H) , 9.2(s, 1H).

实施例 2.13

8-氨基-2-甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐的合成

将 5,6-二氨基烟酰胺(10 g, 66 mmol)、氯代丙酮(6.1 g, 66mmol)和碳酸氢钠(11.2 g, 132 mmol)加入到二甲基甲酰胺(200 ml)中并在室温下将该混合物搅拌 72 小时. 在减压下蒸发大部分溶剂并加入甲磺酸(6 g, 63 mmol). 在真空下蒸发大部分溶剂并将乙醇加入到该残余物中. 将该混合物加热到 60 ℃后, 产物以盐的形式结晶, 过滤得到 6 g (32 %)的标题化合物.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.3 (s, 6H), 7.25(s, 1H), 7.4(s, 1H), 7.6(s, 1H), 7.75 (s, 1H), 7.85 (s, 1H), 7.9(s, 1H), 8.15(s, 1H), 8.6(s, 1H).

实施例 2.14

1-溴代-2-异丙基-6-甲基苯的合成

将 2-异丙基-6-甲基苯胺(14.9 g, 0.1 mol)溶于浓氢溴酸(40 ml)中并将该混合物冷却至 5 ℃. 加入溶于水(15 ml)中的亚硝酸钠(7.0 g, 0.1 mol)以致温度在 10 ℃以下. 将溶于浓氢溴酸(10 ml)中的溴化铜(I)溶液加入到该反应混合物中, 使温度升至室温. 将该混合物在室温下搅拌 1 小时并在 40 ℃下搅拌 30 分钟. 加入己烷, 分离有机层并在减压下蒸发. 用己烷作为洗脱剂, 在硅胶上经柱层析纯化得到 6.9 g (32 %)的标题化合物, 为一种油.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.23 (d, 6H), 2.43(s, 3H), 3.4-3.55(m, 1H), 7.05-7.2(m, 3H).

实施例 2.15

2-异丙基-6-甲基苯甲醛的合成

向溶于乙醚(50 ml)中的 1-溴代-2-异丙基-6-甲基苯(6.9 g, 32.4 mmol)的溶液中加入镁屑(0.9 g, 37 mmol)并在氮气氛下回流该混合物直到反应开始, 然后在室温下搅拌过夜. 在 10 分钟内滴加二甲基甲酰胺(4 ml)并搅拌该混合物 30 分钟. 加入饱和的氯化铵溶液(30 ml)并将该混合物搅拌 1 小时. 分离有机层, 过滤并在减压下蒸发. 用己烷:二氯甲烷(3:2)作为洗脱剂, 在硅胶上经柱层析纯化得到 1.75 g (33 %)的标题化合物.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (d, 6H), 2.55(s, 3H), 3.7-3.8(m, 1H), 7.1-7.4(m, 3H), 10.65 (s, 1H).

实施例 2.16

2-异丙基-6-甲基苄醇的合成

向溶于甲醇(15 ml)中的 2-异丙基-6-甲基苯甲醛(1.75 g, 10.8 mmol)的溶液中加入硼氢化钠(0.35 g, 9.5 mmol)并在室温下搅拌该混合物 1 小

时．在减压下蒸发溶剂并向该残余物中加入己烷和水．分离有机层并在减压下蒸发得到 1.73 g (98 %)的标题化合物，为一种油．

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (d, 6H), 2.45(s, 3H), 3.3-3.4(m, 1H), 4.8 (s, 2H), 7.05-7.2(m, 3H).

实施例 2.17

2-异丙基-6-甲基苄基氯的合成

向溶于二氯甲烷(20 ml)中的 2-异丙基-6-甲基苄醇(1.7 g, 10.4 mmol)的溶液中加入亚硫酰氯(1.7 g, 14 mmol)并在室温下搅拌该反应物 1 小时．在减压下蒸发溶剂,用二氯甲烷作为洗脱剂，通过硅胶过滤该残余物．在减压下蒸发溶剂得到 1.83 g (96 %)的标题化合物，为一种油．

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (d, 6H), 2.45(s, 3H), 3.25-3.35(m, 1H), 4.75 (s, 2H), 7.05-7.25(m, 3H).

实施例 2.18

2-溴代-6-甲基苄基溴的合成

将 3-溴代-邻-二甲苯(15 g, 81 mmol)、 N-溴代琥珀酰亚胺(15.1 g, 85.1 mmol)、过氧化二苯甲酰(0.65 g)和四氯化碳(150 ml)的混合物回流 5 小时．过滤后，用亚硫酸氢钠和水洗涤滤液．用硫酸钠干燥有机层并在真空中蒸发．层析(SiO_2) (石油醚:乙酸乙酯, 100:4)得到 16.8 g 含有 45 %标题化合物的混合物部分．该混合物没有进一步纯化而使用．

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.5 (s, 3H), 4.65(s, 2H), 7.05-7.45(m, 3H).

实施例 2.19

2-(2-溴代-3-甲基苯基)乙腈的合成

将2-溴代-1-(溴代甲基)-3-甲基苯(15 g, 0.057 mmol)和氰化钾(9.6 g,

0.148 mol)加入到二甲基甲酰胺(75 ml)中并在 90 ℃下搅拌过夜. 在减压下蒸发溶剂并将该残余物分配在水(150 ml)和二氯甲烷之间. 用二氯甲烷萃取该含水层两次, 分离有机萃取液, 用水洗两次并在减压下蒸发. 用庚烷:二氯甲烷(3:7)作为洗脱剂, 在硅胶上经柱层析纯化该残余物得到 8.0 g (67 %)的标题化合物.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.86(s, 2H), 7.22-7.37(m, 3H).

实施例 2.20

2-(2-溴代-3-甲基苯基)乙酸的合成

将 2-(2-溴代-3-甲基苯基)乙腈(8.0 g, 0.038 mol)加入到水(60 ml)和硫酸(50 ml)的混合物中并将该混合物回流过夜. 冷却至室温后, 加入水(200 ml)并用二氯甲烷萃取该混合物两次. 合并二氯甲烷萃取液, 用水洗涤两次, 干燥并在减压下蒸发得到 7.9 g (90.8 %)的标题化合物.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.86(s, 2H), 7.09-7.18(m, 3H).

实施例 2.21

2-(2-溴代-3-甲基苯基)乙酸乙酯的合成

将 2-(2-溴代-3-甲基苯基)乙酸(7.9 g, 0.034 mol)和硫酸(0.1 ml)加入到乙醇(25 ml)中并将该混合物回流过夜. 蒸发溶剂并将饱和的碳酸钠加入该残余物中. 用乙醚萃取该含水溶液两次, 合并有机萃取液, 用水洗涤两次, 干燥并在减压下蒸发得到所需产物, 为一种油. (8.5 g, 97.7 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (t, 3H), 2.40(s, 3H), 3.78 (s, 3H), 4.16 (q, 2H), 7.06-7.14(m, 3H).

实施例 2.22

2-(2-溴代-3-甲基苯基)-1-乙醇的合成

在氩气氛中，将 $LiAlH_4$ (3.1 g, 0.083 mol)悬浮在干燥的四氢呋喃(100 ml)中．加入溶于干燥的四氢呋喃(50 ml)中的 2-(2-溴代-3-甲基苯基)乙酸乙酯(8.5 g, 0.033 mol)并将该混合物在室温下搅拌 4 小时．将该混合物在冰上冷却并滴加 3.1 ml 的水，然后加入 3.1 ml 的 15%氢氧化钠，然后加入 9.3 ml 水． 15 小时后，过滤出固体并用四氢呋喃充分洗涤．在减压下除去滤液．用二氯甲烷:甲醇 (9:1)作为洗脱剂，通过硅胶过滤纯化该残余物得到 7.0 g (98.6 %)的标题化合物，为一种油．

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.00(t, 2H), 3.81 (t, 2H), 7.04-7.10(m, 3H).

实施例 2.23

苄基 2-溴代-3-甲基苯乙基醚的合成

在氩气氛中，将氢化钠(50 % 在油中) (1.7 g, 0.036 mol)悬浮在干燥的四氢呋喃(75 ml)中．在室温下，在 30 分钟内滴加溶于四氢呋喃(25 ml)中的 2-(2-溴代-3-甲基苯基)-1-乙醇(7.0 g, 0.033 mol)．加入苄基溴(6.2 g, 0.036 mol)并将该混合物在室温下搅拌过夜．小心地加入水(1.0 ml)并在减压下蒸发溶剂．将该残余物分配于水和乙醚之间并用乙醚萃取该水层两次．并合该醚萃取液，用水洗涤两次，在减压下蒸发．用庚烷:二氯甲烷(7:3)作为洗脱剂，在硅胶上经柱层析纯化该残余物得到 7.5 g (74.3 %)的标题化合物．

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.10(t, 2H), 3.69 (t, 2H), 4.51 (s, 2H), 7.04-7.08(m, 3H) , 7.21-7.30(m, 5H).

实施例 2.24

2-[2-(苄氧基)乙基]-6-甲基苯甲醛的合成

在氮气氛中，在-65 ℃下，向溶于干燥的四氢呋喃中的苄基 2-溴

代-3-甲基苯乙基醚(3.2 g, 0.0105 mol)的溶液中加入叔-丁基锂(1.7 M，在戊烷中)(10.5 ml, 0.018 mol)，在-20 ℃下搅拌该混合物 30 分钟．在-65 ℃下滴加二甲基甲酰胺(1.5 g, 0.021 mol)，在-20 ℃下搅拌该混合物 30 分钟并在室温下搅拌 1 小时．向该溶液中小心地加入水和 2M HCl 使其酸化并搅拌该混合物 30 分钟．向该混合物中加入乙醚(50 ml)，分离有机层，用饱和的碳酸钠和水洗涤．分离有机层、干燥并在减压下蒸发．用庚烷:二氯甲烷(2:8)作为洗脱剂，在硅胶上经柱层析纯化该残余物得到 1.0 g (38.5 %)的标题化合物．

1H-NMR (300 MHz, $CDCl_3$): δ 2.55 (s, 3H), 3.23(t, 2H), 3.66 (t, 2H), 4.46 (s, 2H), 7.05-7.31(s, 8H), 10.54(s, 1H).

实施例 2.25

8-((2-[2-(苄氧基)乙基]-6-甲基苄基)氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成

在氮气氛中，向溶于甲醇(20 ml)中的 8-氨基-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(1.4 g, 0.0038 mol)的溶液中加入溶于甲醇(10 ml)中的氯化锌(1.0 g, 0.0039 mol)并搅拌该混合物 30 分钟．向该混合物中加入 2-[2-(苄氧基)乙基]-6-甲基苯甲醛(1.0 g, 0.0039 mol)和氰基硼氢化钠(0.48 g, 0.0076 mol)并将该混合物回流过夜．将该反应混合物冷却至室温，加入三乙胺(4 ml)，将该混合物搅拌 30 分钟并在减压下蒸发溶剂．用二氯甲烷:甲醇(9:1)作为洗脱剂，在硅胶上经柱层析纯化该残余物．将该残余物溶于乙醚中，用乙醚/HCl 处理，滤出为 HCl 盐的沉淀产物．将该盐溶于二氯甲烷中并用饱和的碳酸钠洗涤．分离有机层，用水洗涤，干燥并在减压下蒸发得到 0.13 g (7.7g)的标题化合物．

1H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.33(s, 3H), 2.34 (s, 3H), 2.98 (t, 2H), 3.66 (t, 2H), 4.37 (d, 2H), 4.46(s, 2H), 5.02(bs, 1H), 6.29 (bs, 2H), 6.47 (s, 1H), 7.03-7.26(m, 8H), 7.91(s, 1H).

实施例 2.26

2-乙基-6-甲基苄基-5-(2-乙基-6-甲基苄氧基)-6-硝基烟酸酯的合成

将 5-羟基-6-硝基烟酸(1 g, 5 mmol)、 2-乙基-6-甲基苄基氯(1.85 g, 11 mmol)、 N,N-二异丙胺(1.75 g, 14 mmol)和碘化四丁基铵(0.1 g)加入到乙腈(10 ml)中并回流 3 小时. 在减压下蒸发溶剂并将该残余物溶于二氯甲烷中并用水洗涤. 分离有机层、干燥和减压下蒸发. 用己烷:二氯甲烷 (1:1)作为洗脱剂, 在硅胶上经柱层析纯化该残余物得到 0.7 g (29 %)的标题化合物.

1H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 1.25 (t, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 2.7 (q, 2H), 2.8(q, 2H), 5.25 (s, 2H), 5.55 (s, 2H), 7.05-7.3(m, 6H), 8.2(s, 1H) , 8.65 (s, 1H).

实施例 2.27

6-氨基-5-(2-乙基-6-甲基苄氧基)烟酰胺的合成

将 2-乙基-6-甲基苄基 5-(2-乙基-6-甲基苄氧基)-6-硝基烟酸酯(0.7 g, 2 mmol)加入到 5-10 %的氨的甲醇溶液(40 ml)中, 并在 35 ℃下搅拌该混合物 96 小时. 在减压下蒸发溶剂. 用己酸乙酯:二氯甲烷 (1:1)和甲醇:二氯甲烷(1:9)作为洗脱剂, 在硅胶上经柱层析纯化该残余物两次得到 0.14 g (31 %)的标题化合物.

1H-NMR (500 MHz, $CDCl_3$): δ 1.21 (t, 3H), 1.87 (s, 2H), 2.37 (s, 3H), 2.72 (q, 2H), 5.11 (s, 2H), 5.99 (bs, 2H), 7.1-7.3(m, 3H), 7.67(d, 1H) , 8.09 (d, 1H).

生物试验

1.体外实验

在离体的兔胃腺中抑制酸分泌

对体外离体的兔胃腺酸分泌的抑制作用的测定如 Berglindh 等 (1976) Acta Physiol . Scand. 97, 401-414 中所叙述进行.

H^+,K^+-ATP 酶活性的测定

在 37 ℃下，在含有 2mM $MgCl_2$、 10mM KCl 和 2mM ATP 的 18mM Pipes/ Tris 的缓冲剂(pH 7.4)中，将膜囊泡(2.5-5μg)孵育 15 分钟．如 LeBel 等(1978) Anal . Biochem .85, 86-89 中所述，以从 ATP 中无机磷酸盐的释放来估计 ATP 酶的活性，

2.体内实验

对雌性大鼠酸分泌的抑制作用

使用 Sprague-Dawly 品系的雌性大鼠．在大鼠的胃(腔)和十二指肠上部安插套管瘘管，以便分别用于收集胃分泌物和给予试验物质．试验开始前，术后 14 天为恢复期．

在分泌试验前，使动物禁食但不禁水 20 小时．通过胃插管用自来水(+37 ℃)反复洗胃，经皮下给予 6 ml 的林格-葡萄糖液．在 2.5-4 小时内，经皮下 1.2 ml /小时输注五肽胃泌素和氨甲酰胆碱(分别为 20 和 110 nmol / kg . h)以刺激酸分泌，在此期间，以 30 分钟一份收集胃的分泌物．在刺激(静脉内和十二指肠内给药, 1 ml / kg)开始后 60 分钟，或在刺激(口服, 5 ml / kg ,关闭胃插管)开始以前 2 小时给予试验物质或溶媒．给药和刺激之间的时间间隔可以延长以便研究作用持续时间．用 0.1 M NaOH 滴定胃液样品至 pH 为 7.0，根据产物的滴定体积和浓度计算酸的产量．

进一步的计算基于从 4-6 只大鼠的组平均反应．在刺激期间给药的情况下，在给予试验物质或溶媒后这段时间内的酸产量被表示为分数响应(fractional responses)，设定在 30 分钟的上一给药期间内的酸产量为 1.0．从试验化合物和溶媒引起的分数响应(fractiona responses)计算百分抑制率．在刺激前给药的情况下，抑制百分率直接从给予试验化合物和溶媒后所记录的酸产量来计算．

在大鼠体内的生物利用率

使用成年 Sprague-Dawley 品系大鼠．在实验前 1-3 天，所有大鼠

都在全麻下左颈动脉插管．用于静脉实验的大鼠也在颈静脉插管(Popovic (1960) J. Appl. Physiol. 15,727-728)．插管外置在颈部背面．

给药后，按间隔直到 5.5 小时从颈动脉多次抽取血样(0.1-0.4 g)．冷冻该血样直到分析试验化合物．

计算分别在大鼠或狗(i)十二指肠内(i.d.)或口服(p.o.)给药和(ii)静脉内(i.v.)给药后，血/血浆浓度曲线下面积(AUC)之间的商数来评估其生物利用率．

通过 log /线性梯形规则测定血浓度与时间曲线下面积 AUC 并通过用在最后阶段中的清除速率常数除最终测得的血浓度将 AUC 外推到无穷大．在十二指肠内或口服给药后的系统的生物利用率(F %)如下计算： F(%)=(AUC (p.o.或 i.d.) / AUC (i.v.) x 100 .

有意识的狗体内胃酸分泌的抑制和生物利用率

使用任意性别的 Labrador 猎犬或 Harrier 狗．给它们十二指肠造瘘管以给予试验化合物或溶媒，制造胃瘘管或 Heidenhaim-陷窝以便收集胃的分泌物．

在分泌试验前，将这些动物禁食约 18 小时，但可自由饮水．以产生约 80 %的个体最大分泌反应的剂量输入二盐酸组胺(12 ml / h)来刺激胃酸分泌达 6.5 小时，以 30 分钟一份连续收集胃液．在开始输入组胺后 1 或 1.5 小时，以 0.5 ml / kg 体重的体积口服、 i.d.或 i.v.给予试验物质或溶媒．应该指出的是，在口服的情况下，将所述试验化合物给到主要分泌酸的狗胃的 Heidenham-陷窝．

经滴定至 pH 为 7.0 来测定胃液样品的酸度并计算酸产量．在给予试验物质或溶媒后，在收集期间的酸产量表示为分数响应，设定在上一份给药期间内的酸产量为 1.0．从试验化合物和溶媒引起的分数响应计算百分抑制率．

在给药后，按间隔直到 4 小时采集血样用于分析血浆中试验化合物的浓度．在采集后 30 分钟内分离血浆并冷冻，然后分析．如上所述，计算大鼠模型口服或 i.d.给药后的系统的生物利用率(F %)．