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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 471/04, A61K 31/435 — A1

(11) International Publication Number: WO 99/55705

(43) International Publication Date: 4 November 1999 (04.11.99)

(21) International Application Number: PCT/SE99/00662

(22) International Filing Date: 23 April 1999 (23.04.99)

(30) Priority Data:
9801526-6 29 April 1998 (29.04.98) SE

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), *Eurasian patent* (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

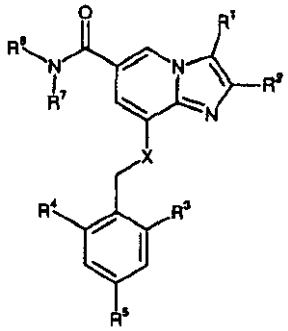
Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

Under Rule 91.1(f), with a request for rectification.

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



(I)

(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 carboxamide 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.

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IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

TECHNICAL FIELD

The present invention relates to novel compounds, and pharmaceutically 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 pharmaceutically 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).

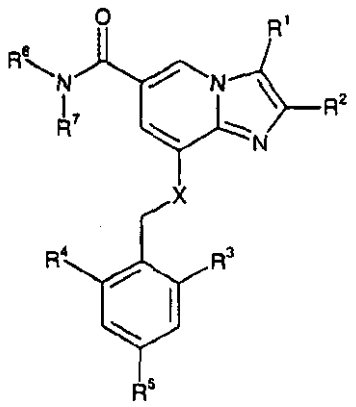
For a review of the pharmacology of the gastric acid pump (the H^+, K^+-ATPase), see Sachs et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

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. The carboxamide group in 6-position is optionally selected to give compounds of Formula I a molecular weight ≤ 600.

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, or

(b) CH_2CH_3;

R^3 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(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 and R^7 are independently selected substituents, comprising C, H, N, O, S , Se , P and Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, provided that at least one of R^6 and R^7 can not be H, C_1–C_6 alkyl, hydroxylated C_1–C_6 alkyl,or C_1–C_6 alkoxy-substituted C_1–C_6 alkyl, and

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.

The substitutents R^6 and R^7 are defined as independently selected substituents, comprising C, H, N, O, S , Se , P or Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, which is a definition easily understood by a person skilled in the art.

Examples of substituents that fall within the scope of this definition includes, but is not limited to,

(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,

(e) C_2–C_6 alkenyl,

(f) C_2–C_6 alkynyl,

(g) halogenated C_1–C_6 alkyl,

(h) C_3–C_8 cycloalkyl,

(i) cycloalkyl-substituted C_1–C_6 alkyl,

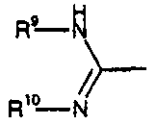
(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl. naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, or CN or NH_2SO_2,

(k) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl , optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN or NH_2SO_2,

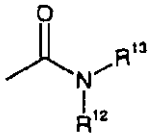
(l) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, NH_2SO_2–, C_1–C_6 alkyl–SO_2NH–, $ArSO_2NH$–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–SO_2–, C_1–C_6 alkyl–C=O–, NH_2–, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$N–, ArCONH–, Ar(C_1-C_6 alkyl)CONH, $ArNHSO_2$–, (Ar)$_2$–N–SO_2–, C_1–C_6 alkyl–$NHSO_2$–, ArS–, ArSO–, $ArSO_2$–, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–, Ar–O– , Ar–NH– , Ar(C_1–C_6 alkyl)N– , (C_1–C_6 alkyl)$_2$$NSO_2$– , hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN, nitro, amino, C_1–C_6 alkyl–NH–, or (C_1–C_6 alkyl)$_2$N–.

(m) C_7-C_{12} .

(n) OH, O-C_1–C_6 alkyl, or O-hydroxylated C_1–C_6 alkyl,

o)  wherein R^9 and R^{10} are independently H or C_1-C_6 alkyl,

p) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, C_1-C_6 alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12}, R^{13} are the same or different H, or C_1-C_6 alkyl

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline);

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 pharmaceutically 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; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl):

(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,

(e) C_2–C_6 alkenyl,

(f) C_2–C_6 alkynyl,

(g) halogenated C_1–C_6 alkyl,

(h) C_3–C_8 cycloalkyl,

(i) cycloalkyl-substituted C_1–C_6 alkyl,

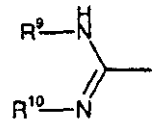
(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, or CN or NH_2SO_2,

(k) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl , optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN or NH_2SO_2,

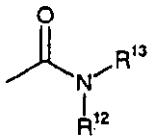
(l) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, NH_2SO_2–, C_1–C_6 alkyl–SO_2NH–, $ArSO_2$NH–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–SO_2–, C_1–C_6 alkyl–C=O–, NH_2–, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$N–, ArCONH–, Ar(C_1-C_6 alkyl)CONH, $ArNHSO_2$–, (Ar)$_2$–N–SO_2–, C_1–C_6 alkyl–$NHSO_2$–, ArS–, ArSO–, $ArSO_2$–, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–, (C_1–C_6 alkyl)$_2$–N–SO_2– , Ar–O– , Ar–NH– , Ar(C_1–C_6 alkyl)N– , (C_1–C_6 alkyl)$_2$$NSO_2$– , hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl. C_1–C_6 alkoxy, CF_3, OH, CN, nitro, amino, C_1–C_6 alkyl–NH–, or (C_1–C_6 alkyl)$_2$N–,

(m) C_7-C_{12} ,

(n) OH, O-C_1–C_6 alkyl, or O-hydroxylated C_1–C_6 alkyl,

(o)  wherein R^9 and R^{10} are independently H or C_1-C_6 alkyl,

(p) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, C_1-C_6 alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12}, R^{13} are the same or different H, or C_1-C_6 alkyl

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline);

More 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, 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; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl)

:

(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,

(e) halogenated C_1–C_6 alkyl,

(f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, or CN;

(g) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, or OH.

(h) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–C=O–,-ArCONH–, Ar(C_1-C_6 alkyl)CONH, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–,hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN,

(i) C_7-C_{12} alkyl.

(j) OH ,

(k) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, or C_1-C_6 alkyl-OOC

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline)

Most preferred compounds according to the invention are:

- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine
- N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[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
- (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone
- 1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin -6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide
- 8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

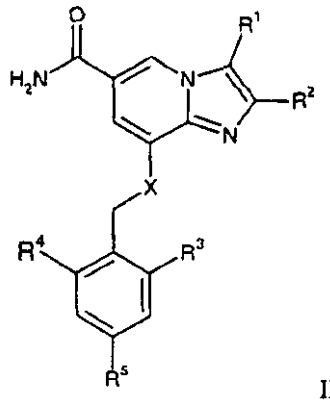
- (2-ethyl-6 methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-hydroxy-1-pyrrolidinyl)methanone
- N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine
- N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine
- 4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid

Preparation

The present invention also provides the following process for the manufacture of compounds with the general Formula I.

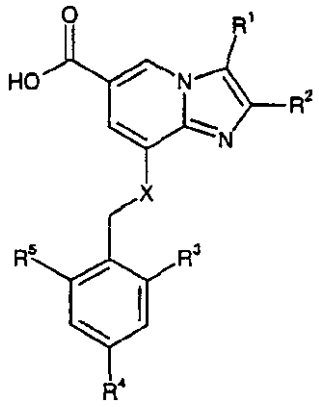
A process for manufacture of compounds with the general Formula I comprises the following steps:

a) Compounds of Formula II



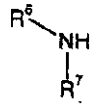
II

wherein R^1, R^2, R^3, R^4, R^5, and X are as defined in Formula I , can be hydrolyzed under standard conditions to the corresponding carboxylic acid to the corresponding carboxylic acid compounds of Formula III



III

b) Compounds of the Formula III wherein R^1, R^2, R^3, R^4, R^5 and X is as defined in Formula I can be reacted with amino compounds of Formula IV



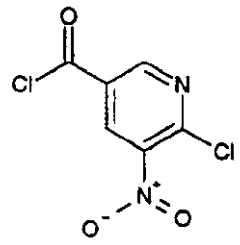
IV

wherein R^6 and R^7 are as defined for Formula I, 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.

The present invention also provides the following process for the manufacture of intermediate compounds with the general Formula II.

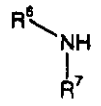
A process for manufacture of compounds with the general Formula II wherein X is NH comprises the following steps:

a) Compounds of the general Formula V



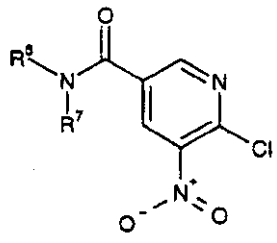
V

can be reacted with amino compounds of the general Formula IV



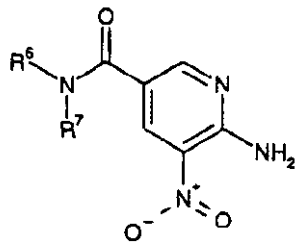
IV

wherein R^6 and R^7 are both hydrogen, to the corresponding amide of the Formula VI. The reaction can be carried out in standard conditions in an inert solvent.



VI

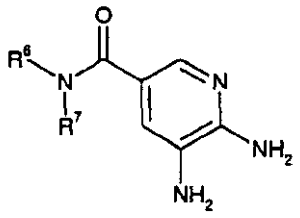
b) Compounds of the general Formula VI can be reacted with ammonia to compounds of the general Formula VII



VII

wherein R^6 and R^7 are both hydrogen. The reactions can be carried out under standard conditions in an inert solvent.

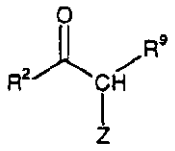
c) Compounds of the Formula VII can be reduced e.g. by using hydrogen and a catalyst such as Pd/C to compounds of the Formula VIII



VIII

wherein R^6 and R^7 are both hydrogen. The reaction can be carried out under standard conditions in an inert solvent.

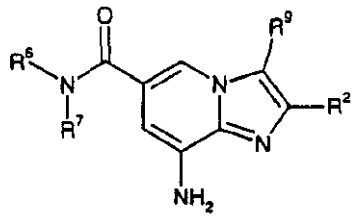
d) The imidazo[1,2-a]pyridine compounds of the Formula X can be prepared by reacting compounds of the general Formula VIII with compounds of the general Formula IX



IX

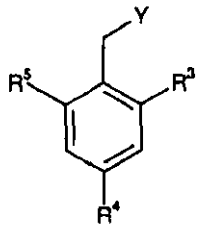
wherein R^2 is as defined for Formula I and Z is a leaving group such as halogen, mesyl. tosyl and R^9 represents H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$ etc.

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



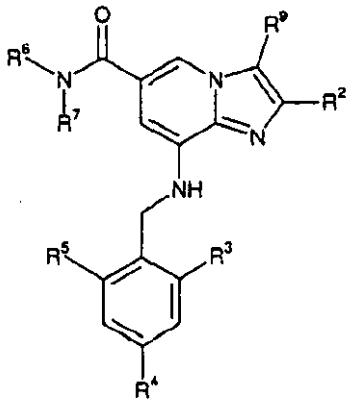
X

e) Compounds of the Formula X can be reacted with compounds of the Formula XI



XI

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 XII.



XII

wherein R^2, R^3, R^4, and R^5 are as defined for Formula I and R^6 and R^7 both hydrogen 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 XII 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 and R6 and R7 are both hydrogen.

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 pharmaceutically 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.

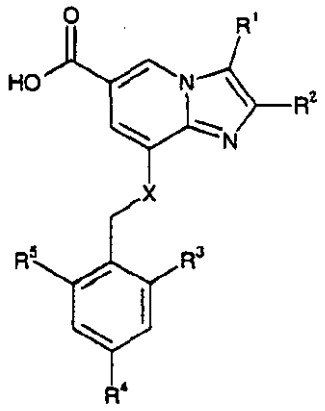
The compounds according to the present invention can also be used together or in combination for simultaneous, separate or sequential use with antacids such as aluminium hydroxide, magnesium carbonate and magnesium hydroxid or alginic acid, or together or in combination for simultaneous, separate or 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

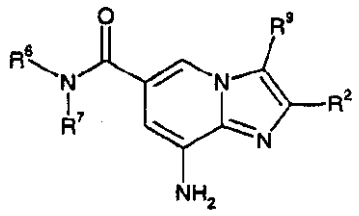
(a) a compound of the formula XVIII



XVIII

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

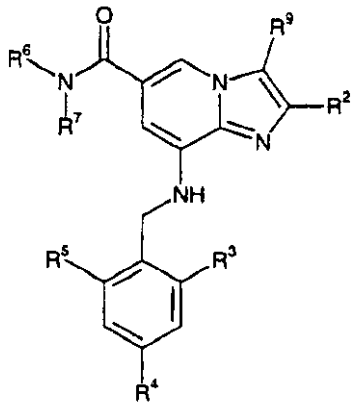
(b) a compound of the formula VIII



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.;

(c) a compound of the formula X



X

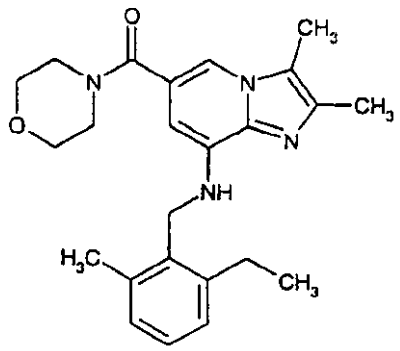
wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for Formula I, and R^9 is an ester group such as $COOCH_3$, $COOC_2H_5$ etc.;

EXAMPLES

1. PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

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

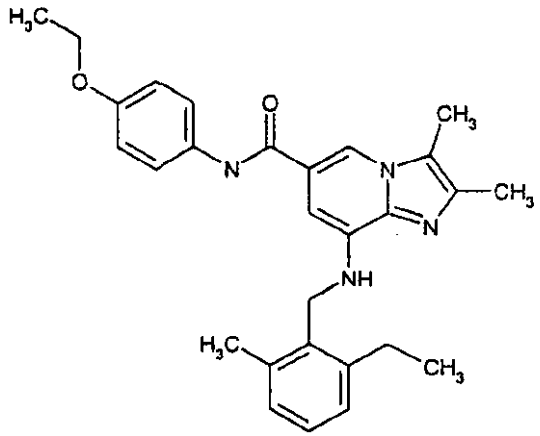


2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). Morpholine (0.12 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was added to a column with silica gel and purification by chromatography using ethylacetate : methylene chloride (1:1) as eluent gave 0.12 g (66%) of the desired product.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 2.7 (q, 2H), 3.7 (s, 8H), 4.35 (d, 2H), 4.95 (bs, 1H), 6.15 (s, 1H), 7.0-7.2 (m, 3H), 7.4 (s, 1H)

Example 1.2

Synthesis of N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide



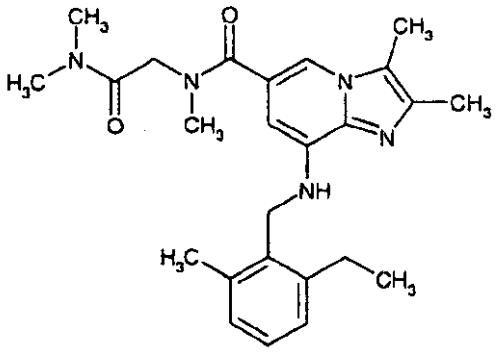
2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). 4-ethoxyanilin(0.19 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 72 h. The solvent was evaporated under reduced pressure and the residue was added to a column with silica gel and was purified by chromatography using methylene chloride : methanol (95:5) as eluent. The residue was treated with a hot mixture

of hexane : ethyl acetate (2:1) and the product was filtered off and dried to obtain 0.14 g (74 %) of the desired compound as white crystals.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 1.4 (t,3H), 2.35 (s, 9H), 2.65 (q, 2H), 4.0 (q, 2H), 4.35 (d, 2H), 4.9 (t, 1H), 6.55 (s, 1H), 6.85 (d, 2H), 7.0-7.2 (m, 3H), 7.5 (d, 2H), 7.9 (s, 1H), 8.15 (s, 1H)

Example 1.3

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

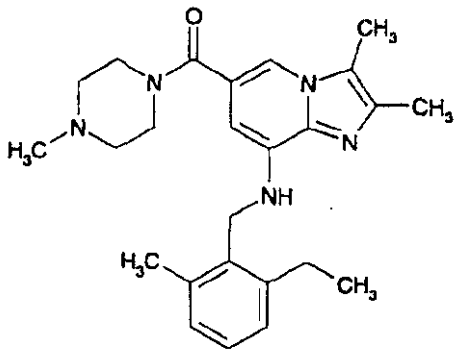


2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.13 g, 0.38 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.12 g, 0.38 mmol) were added to methylene chloride (10 ml). N,N.Dimethyl-2-methylamino-acetamide (0.088 g, 0.38 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using methylene chloride : methanol as eluent (95:5) which gave 80 mg (48 %) of the title product.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.3 (s, 6H), 2.35 (s, 3H), 2.65 (q, 2H), 2.75 (s, 6H), 2.95 (s, 3H), 3.15 (s, 2H), 4.35 (bs, 2H), 4.85 (bs, 1H), 6.25 (s, 1H), 7.0-7.2 (m, 3H), 7.45 (s, 1H).

Example 1.4

Synthesis of (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone

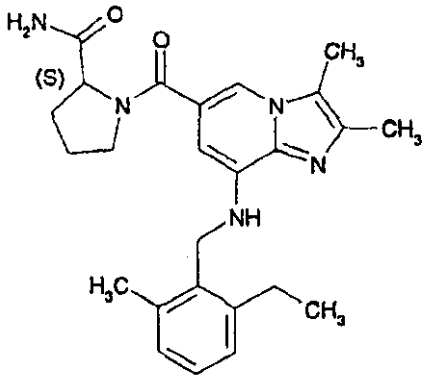


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.5 g, 1.48 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.48 g, 0.1.5 mmol) were added to methylene chloride (20 ml) and the mixture was stirred for 5 min. N-methylpiperazine (0.16g, 1.6 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent gave 0.46 g (74 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.22 (t, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.47 (bs, 4H), 2.71 (q, 2H), 2.80 (s, 3H), 3.65 (bs, 4H), 4.36 (d, 2H), 4.94 (t, 1H), 6.19 (s, 1H), 7.04-7.18 (m, 3H), 7.42 (s, 1H)

Example 1.5

Synthesis of 1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin -6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide

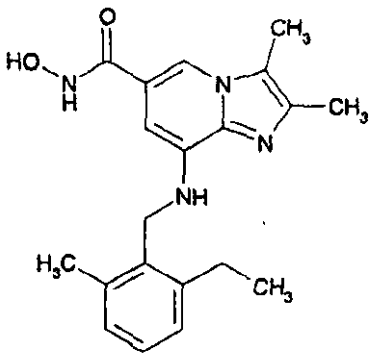


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.45 mmol) and triethylamine (0.05 g, 0.5 mmol) were added to methylene chloride (10 ml) and the mixture was stirred for 10 min.(*S*)-prolinamide (0.016 g, 0.45 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent and crystallization from diethyl ether gave 0.07 g (36 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.21 (t, 3H), 2.1-2.2 (m, 4H), 2.33 (s, 3H), 2.35 (s ,3H), 2.37 (s, 3H), 2.70 (q, 2H), 3.65-3.75 (m, 2H), 4.36 (d, 2H), 4.80 (bs, 1H), 4.94 (bs (1H), 5.88 (s, 1H), 6.33 (s, 1H), 6.98 (s, 1H), 7.04-7.19 (m,3H), 7.54 (s, 1H)

Example 1.6

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



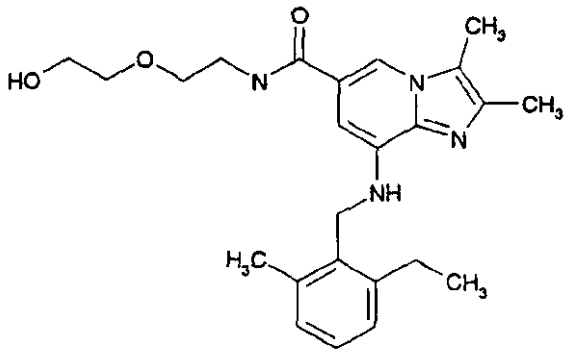
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.45 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.45 mmol), triethylamine (0.1 g, 0.99 mmol) and hydroxylamine hydrochloride (0.031 g, 0.46 mmol) in dimethylformamide (5 ml).

The title compound were prepared according to Example 1.5 (Yield: 0.016 g, 10 %)

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.15 (bs, 3H), 2,25 (bs, 9H), 2.6 (bs, 2H), 4.25 (bs, 2H), 4.95 (bs, 1H), 6.45 (bs, 1H), 6.9-7.1 (m, 3H), 7.75 (bs, 1H)

Example 1.7

Synthesis of (2-ethyl-6 methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-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

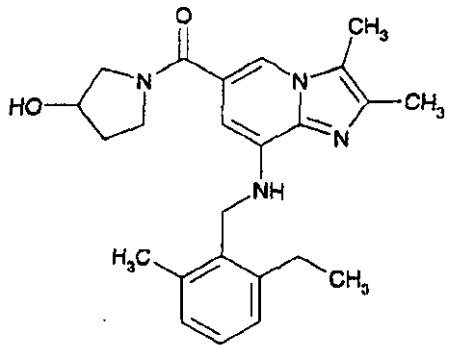
(TBTU)(0.29 g, 0.90 mmol) and 2-(2-aminoethoxy)ethanol (0.2 g, 1.9 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.5 (Yield: 0.24 g, 80 %)

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.25 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 3.4-3.45 (m, 2H), 3.55-3.7 (m, 6H), 4.35 (d, 2H), 5.05 (t, 1H), 6.45 (s, 1H), 7.0-7.2 (m, 4H), 7.5 (s, 1H)

Example 1.8

Synthesis of (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-hydroxy-1-pyrrolidinyl)methanone



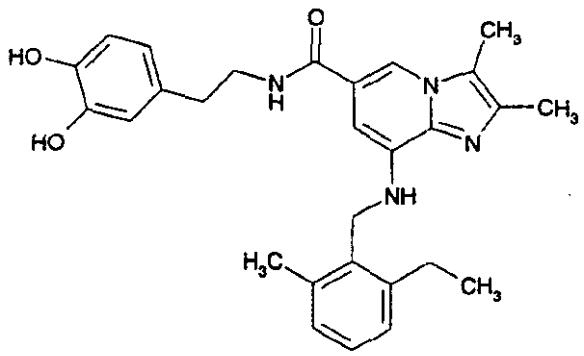
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) and 3-pyrrolidinol (0.12 g, 1.4 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.4. Crystallization from ethylacetate:hexane (2:1) (Yield: 0.24 g, 80 %)

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.23 (t, 3H), 1.93 (bs, 2H), 2.33 (s, 3H), 2.34 (s,3H), 2.41 (s, 3H), 2.70 (q, 2H), 3.51-3.89 (m, 4H), 4.35 (d, 2H), 4.38-4.55 (m, 1H), 5.04 (bs, 1H), 6.35 (s, 1H), 7.01-7.16 (m, 3H), 7.51 (s, 1H)

Example 1.9

Synthesis of N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

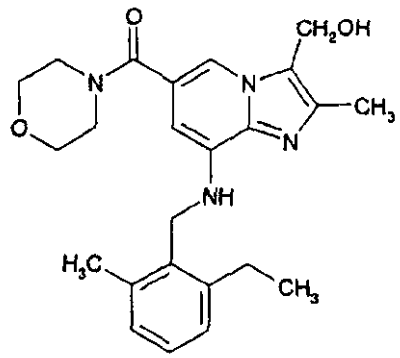


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.45 mmol) were added to dimethylformamide(10 ml) and the mixture was stirred for 5 min. 3,4-dihydroxyphenetylamin (0.27 g 1.4 mmol) and triethylamine (0.28 g, 1.4 mmol) were added was added and the reaction mixture was stirred at ambient temperature for 72 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent and crystallization from acetonitrile gave 0.059 g (28 %) of the title compound.

^{1}H-NMR (400 MHz,DMSO-d_6): δ 1.15 (t, 1H), 2.22 (s, 3H), 2.33 (s, 3H), 2.37 (s, 3H), 2.65-2.74 (m, 4H), 3.41 (q, 2H), 4.37 (d, 2H), 4.85 (t, 1H), 6.48 (dd, 1H), 6.63-6.66 (m, 2H), 6.70 (d, 1H), 7.07-7.21 (m, 3H), 8.04 (d, 1H), 8.49 (t, 1H), 8.63 (s, 1H), 8.75 (s, 1H)

Example 1.10

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



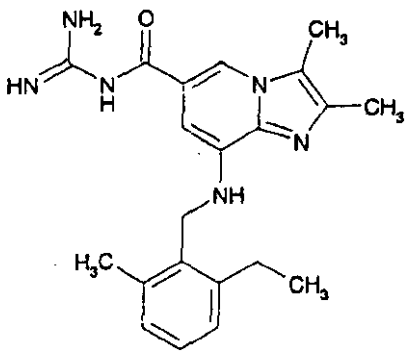
8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxylic acid (0.012 g, 0.034 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.011 g, 0.034 mmol) and morpholine (0.009 g, 0.1 mmol) in methylene chloride (1 ml)

The title compound were prepared according to Example 1.1. (Yield: 0.008 g, 56 %)

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.23 (t, 3H), 2.33 (s, 3H), 2.39 (s, 3H), 2.72 (q, 2H), 3.74 (bs, 8H), 4.37 (d, 2H), 4.85 (s, 2H), 5.02 (t, 1H), 6.27 (d, 1H), 7.06-7.22 (m, 3H), 7.75 (d, 1H)

Example 1.86

Synthesis of N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine

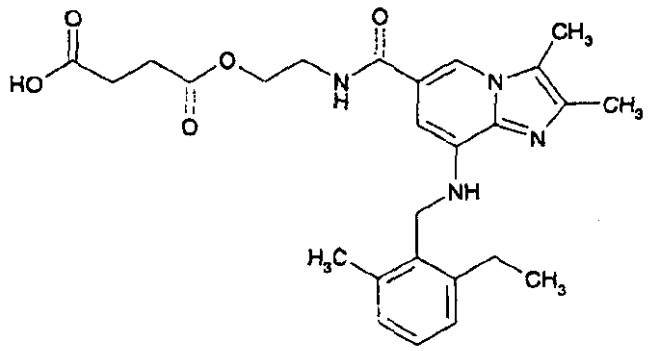


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.5 g, 1.5 mmol) , diisopropyethylamin (0.57 g, 1.5 mmol) and guanidine carbonate (0.53 g, 2.9 mmol) were added to dimethylformamide (10 ml). o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.48 g, 1.5 mmol) was added and the reaction mixture was stirred at 50 °C for 3 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (100:15) as eluent and crystallization from diethyl ether gave 0.12 g (21 %) of the title compound.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.1 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.35 (d, 2H), 4.8 (bs, 1H), 6.9 (s, 1H), 7.05-7.2 (m, 3H), 8.25 (s, 1H)

Example 1.87

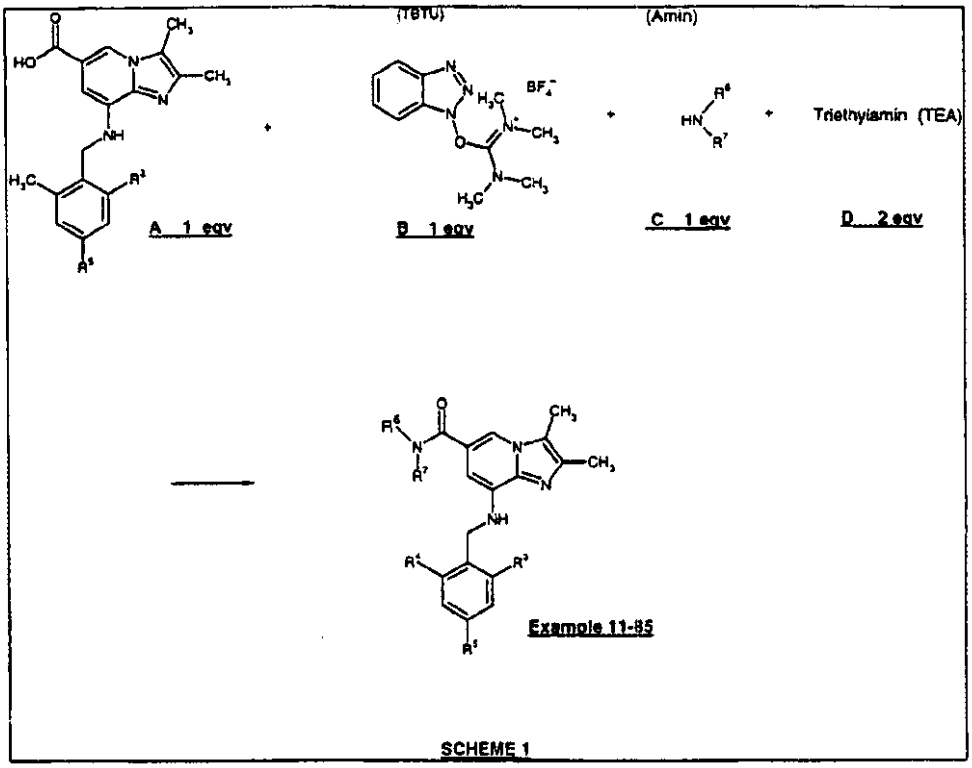
Synthesis of 4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid.



2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide (250 mg, 0.263 mmol) and succinic anhydride (100 mg, 1.00 mmol) were added to 7 ml of acetone. The mixture was refluxed for 48 h. The presiptated product was filtered off and washed with acetone and ether to give 288 mg (91%) of the title compound.

^{1}H-NMR (500 MHz, DMSO): δ 1.16 (t, 3H), 2.24 (s, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 2.48-2.58 (m, 4H), 2.70 (q, 2H), 3.54 (q, 2H), 4.19 (t, 2H), 4.39 (d, 2H), 4.90 (t, 1H), 6.72 (s, 1H), 7.09-7.22 (m, 3H), 8.08 (s, 1H), 8.59 (t, 1H), 12.25 (s, 1H).

Example 11-85 was prepared by parallell-synthesis using the following method:



SCHEME 1

Solution A : 0.149 mmol in 1 ml dimethylformamide

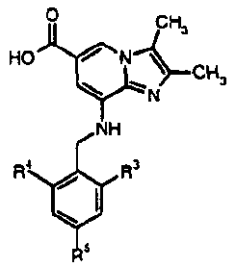
Solution B (TBTU): 0.297 mmol in 1 ml dimethylformamide

Solution C + D: Amin (C) (0.297 mmol in 1 ml dimethylformamide) + TEA (D) (0.594 mmol in 1 ml dimethylamin)

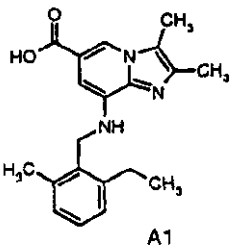
To a solution A (300 µl) were added solution B (150 µl) and solution C+D (150 µl). The reaction was stirred by shaking at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was solved in dichloromethane/methanol (9/1)(600 µl) and was filtred through a plug of silca gel (100 mg) and the gel was washed with dichloromethane/methanol (9/1) (0.5-1.0 ml). The filtrate was evaporated under reduced pressure to give the desired compounds. (If needed the compounds were purified by preparative HPLC.)

The analyses of the examples was made by HPLC and the compounds were identified by LC-mass spectroscopy. All compounds prepared in Example 11-85 showed a mass spectrum that confirmed the proposed structure.

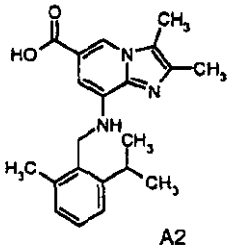
As the starting compound A in the reactions the following compounds were used.



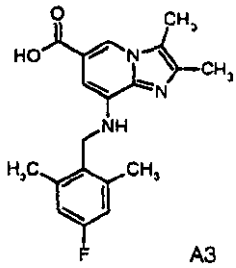
A =



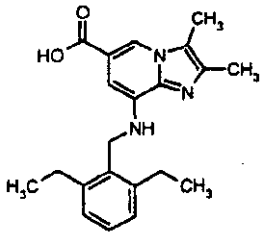
A1



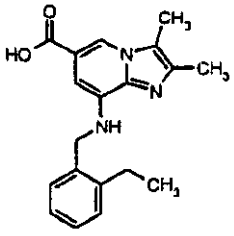
A2



A3



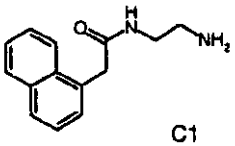
A4



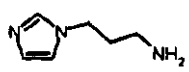
A5

As the starting compound C in the reaction the following amines were used.

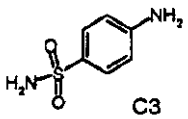
C =



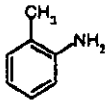
C1



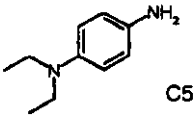
C2



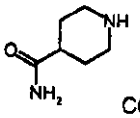
C3



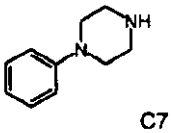
C4



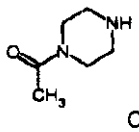
C5



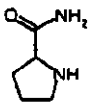
C6



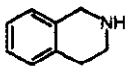
C7



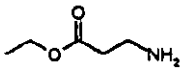
C8



C9

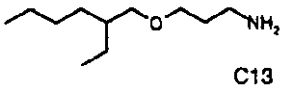


C10

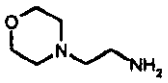


C11

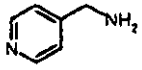
C12



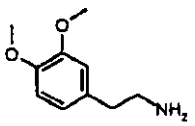
C13



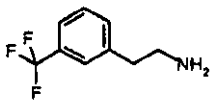
C14



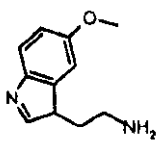
C15



C16



C17

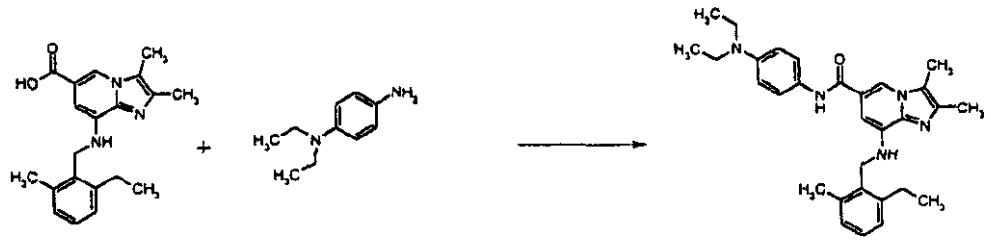


C18

The Examples 11-85 were prepered according to scheme 1

The primary or the secondary amino nitrogen is the nitrogen involved in the reaction.

e.g. A1 + C5 → Example 27



A1 C5 Example 27

$A_n + C_n \rightarrow$ Example 11-85

	A1	A2	A3	A4	A5
C1	Example 11	Example 12	Example 13	Example 14	Example 15
C2	Example 16	Example 17	Example 18	Example 19	Example 20
C3	-	-	-	-	Example 21
C4	Example 22	Example 23	Example 24	Example 25	Example 26
C5	Example 27	Example 28	Example 29	Example 30	Example 31
C6	Example 32	Example 33	Example 34	Example 35	Example 36
C8	Example 37	Example 38	Example 39	Example 40	Example 41
C9	Example 42	Example 43	Example 44	Example 45	Example 46
C10	Example 47	Example 48	Example 49	Example 50	Example 51
C11	-	Example 52	Example 53	Example 54	Example 55
C12	-	Example 56	Example 57	Example 58	Example 59
C13	-	Example 60	Example 61	Example 62	Example 63
C14	-	-	Example 64	Example 65	Example 66
C15	Example 67	Example 68	Example 69	Example 70	Example 71
C16	-	Example 72	Example 73	Example 74	Example 75
C17	Example 76	Example 77	Example 78	Example 79	Example 80
C18	Example 81	Example 82	Example 83	Example 84	Example 85

2. PREPARATION OF INTERMEDIATES

Example 2.1

Synthesis of 8-(2-ethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-ethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (1.0 g, 0.0031 mol) and sodium hydroxide (1.2 g, 0.031 mol) were solved in ethanol (95 %)(30 ml) and

was refluxed overnight. The solvent was evaporated under reduced pressure and to the residue was added water. The pH was adjusted to 7 by addition of conc HCl (2.6 ml) and the solid that precipitated was isolated by filtration, washed with water and dried to give 1.0 g (99 %) of the title compound.

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.2 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.45 (d, 2H), 6.3 (s, 1H), 6.45 (t, 1H), 7.05-7.25 (m, 4H), 7.95 (s, 1H)

Example 2.2

Synthesis of 8-(2,6-diethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2,6-diethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (1.5 g, 0.0043 mol) and sodium hydroxide (1.7 g, 0.043 mol) were solved in ethanol (95 %) (30 ml).
The title compound were prepared according to Example 1.4. (Yield: 1.5 g, 99 %)

^{1}H-NMR (400 MHz,DMSO-d_6): δ 1.14 (t, 6H), 2.22 (s, 3H), 2.37 (s, 3H), 2.67 (q, 4H), 4.37 (d, 2H), 4.89 (t, 1H), 6.68 (s, 1H), 7.11 (d, 2H), 7.23 (t, 1H), 8.09 (s, 1H)

Example 2.3

Synthesis of 8-(2,6-dimethyl-4-fluorobenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2,6-dimethyl-4-fluorobenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.47 g, 0.0034 mol) and sodium hydroxide (1.7 g, 0.034 mol) were solved in ethanol (95 %) (30 ml).
The title compound were prepared according to Example 2.1. (Yield: 1.1 g, 95 %)

^{1}H-NMR (400 MHz,DMSO-d_6): δ 2.23 (s, 3H), 2.34 (s, 6H), 2.36 (s, 3H), 4.31 (d, 2H), 5.04 (bs, 1H), 6.70 (s, 1H), 6.90 (d, 2H), 8.02 (s, 1H)

Example 2.4

Synthesis of 8-(2-isopropyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-isopropyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.2 g, 0.0027 mol) and sodium hydroxide (1.1 g, 0.027mol) were solved in ethanol(95 %) (25 ml).
The title compound were prepared according to Example 2.1. (Yield: 1.1 g, 95 %)

^{1}H-NMR (300 MHz,DMSO-d_6): δ 1.69 (d, 6H), 2.74 (s, 3H), 2.85 (s, 3H), 2.89 (s, 3H), 3.73 (m, 1H), 4.90 (d, 2H), 5.48 (t, 1H), 7.19 (s, 1H), 7.55-7.61 (m, 1H), 7.70-7.76 (m, 2H), 8.60 (s, 1H)

Example 2.5

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

8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (11.0 g, 0.025 mol) and sodium hydroxide (7.0 g, 0.17 mol) were solved in ethanol(95 %) (120 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and to the residue was added water (150 ml). The pH was adjusted to 5 by addition of conc HCl and acetic acid and the solid that precipitated was isolated by filtration, washed with water and acetone, and dried to give 7.6 g (88 %) of the title compound

^{1}H-NMR (500 MHz.DMSO-d_6): δ 1.15 (t, 3H), 2.26 (s, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 2.69 (q, 2H), 4.38 (d, 2H), 5.2 (bs, 1H), 6.73 (s, 1H), 7.07-7.2 (m, 3H), 8.12 (s, 1H)

Example 2.6

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

8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide (0.02 g, 0.057 m mol) and sodium hydroxide (0.02 g, 0.29 mmol) were solved in ethanol (95 %) (1 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and to the residue was added water (1 ml). The pH was adjusted to 5 by addition of acetic acid and the solid that precipitated was isolated by filtration, washed with water and dried to give 0.012 g (60 %) of the title compound.

^{1}H-NMR (300 MHz.DMSO-d_6): δ 1.14 (t, 3H), 2.22 (s, 3H), 2.33 (s, 3H), 2.67 (q, 2H), 4.33 (d, 2H), 4.55 (bs, 1H), 4.67 (s, 2H), 6.83 (s, 1H), 7.06-7.24 (m, 3H), 8.15 (s, 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

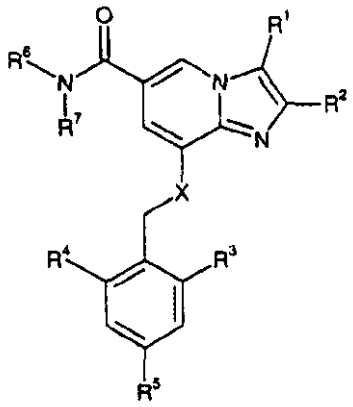
gastric juice collected in consecutive 30-min fractions. Test substance or vehicle is given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered 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, or

(b) CH_2CH_3;

R^3 is

(a) H,

(b) C_1-C_6 alkyl,

(c) hydroxylated C_1-C_6 alkyl, or

(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 and R^7 are independently selected substituents, comprising C, H, N, O, S , Se , P or Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, provided that at least one of R^6 and R^7 can not be H, C_1–C_6 alkyl, hydroxylated C_1–C_6 alkyl.or C_1–C_6 alkoxy-substituted C_1–C_6 alkyl, and

X is

(a) NH, or

(b) O.

2. A compound according to 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; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl)

:

(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,

(e) C_2–C_6 alkenyl,

(f) C_2–C_6 alkynyl,

(g) halogenated C_1–C_6 alkyl,

(h) C_3–C_8 cycloalkyl,

(i) cycloalkyl-substituted C_1–C_6 alkyl,

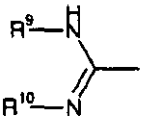
(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, or CN or NH_2SO_2,

(k) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl , optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$–N–, CN or NH_2SO_2,

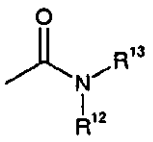
(l) R^8–(C_1-C_6) alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, (C_1–C_6 alkyl)$_2$NC=O–, C_1–C_6 alkyl–OOC–, NH_2SO_2–, C_1–C_6 alkyl–SO_2NH–, $ArSO_2NH$–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–SO_2–, C_1–C_6 alkyl–C=O–, NH_2–, C_1–C_6 alkyl–NH–, (C_1–C_6 alkyl)$_2$N–, ArCONH–, Ar(C_1-C_6 alkyl)CONH, $ArNHSO_2$–, (Ar)$_2$–N–SO_2–, C_1–C_6 alkyl–$NHSO_2$–, ArS–, ArSO–, $ArSO_2$–, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, (C_1–C_6 alkyl)$_2$–NCONH–, ArNHCONH–, (C_1–C_6 alkyl)$_2$–N–SO_2– , Ar–O– , Ar–NH– , Ar(C_1–C_6 alkyl)N– , hydroxylated C1-C6 alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN, nitro, amino, C_1–C_6 alkyl–NH–, or (C_1–C_6 alkyl)$_2$N–,

(m) C_7-C_{12} ,

(n) OH, O-C_1–C_6 alkyl, or O-hydroxylated C_1–C_6 alkyl,

(o)  wherein R^9 and R^{10} are independently H or C_1-C_6 alkyl,

(p) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, C_1-C_6 alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12}, R^{13} are the same or different H, or C_1-C_6 alkyl

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example *morpholine, piperazine, pyrrolidine, piperidine*), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline), or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2 I wherein R^1 is CH_3 or CH_2OH; R^2 is CH_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; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1-C_6 alkyl, hydroxylated C_1-C_6 alkyl or C_1-C_6 alkoxy-substituted C_1-C_6 alkyl).
   (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,
   (e) halogenated C_1–C_6 alkyl,
   (f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted by one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, C_1–C_6 alkyl–NH–, $(C_1$–C_6 alkyl$)_2$–N–, or CN;
   (g) aryl substituted C_1–C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, or OH,
   (h) R^8–$(C_1$-$C_6)$ alkyl-, wherein R^8 is NH_2C=O–, C_1–C_6 alkyl–NHC=O–, $(C_1$–C_6 alkyl$)_2$NC=O–, C_1–C_6 alkyl–OOC–, cyano, C_1–C_6 alkyl–CO–NH–, C_1–C_6 alkyl–OOCNH–, C_1–C_6 alkyl–O–, C_7-C_{12} alkyl-O- C_1–C_6 alkyl–SO–, C_1–C_6 alkyl–S–, C_1–C_6 alkyl–C=O–,-ArCONH–, Ar(C_1-C_6 alkyl)CONH, ArC=O–, NH_2CONH– C_1–C_6 alkyl–NHCONH–, $(C_1$–C_6 alkyl$)_2$–NCONH–, ArNHCONH–,hydroxylated C1-C6

alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, CN,

(i) C_7-C_{12} alkyl

(j) OH ,

(k) R^{11}-(C_1-C_6) alkyl-COO-(C_1-C_6) alkyl- wherein R^{11} is HOOC-, or C_1-C_6 alkyl - OOC,

R^6 and R^7, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1–C_6 alkyl, C_1–C_6 alkoxy, CF_3, OH, nitro, amino, CN ,NH_2SO_2, phenyl, NH_2CO-, C_1-C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline)

4. The compound according to claims 1 to 3 being;

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

N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[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,

(8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone,

1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin -6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide,

8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

(2-ethyl-6 methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

(8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-

hydroxy-1-pyrrolidinyl)methanone,

N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

8-(2-ethyl-6-methylbenzylamino-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine,

N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine,

4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid,

or a pharmaceutically acceptable salt thereof.

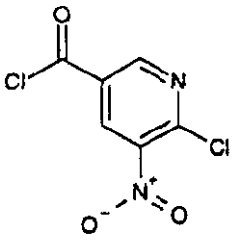
5. A compound according to any of claims 1-4 as a hydrochloride or mesylate salt.

6. Products containing a compound according to any of claims 1-5 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 a compound according to any of claims 1-5 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.

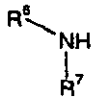
8. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH, comprising

(a) reacting a compound of the Formula II



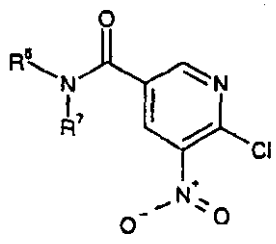
II

with a compound of the Formula III



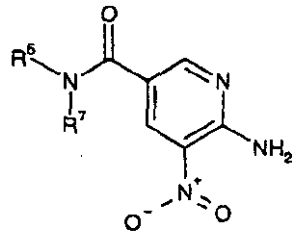
III

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



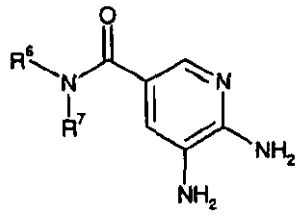
IV

(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



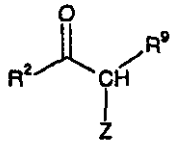
V

(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



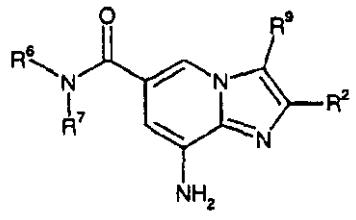
VI

(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



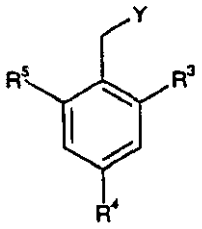
VII

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



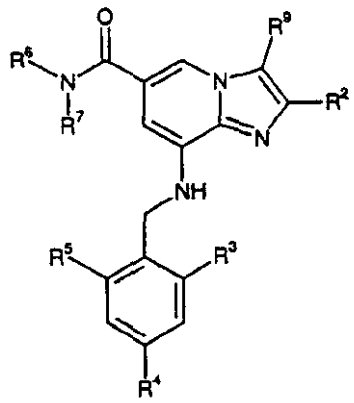
VIII

(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

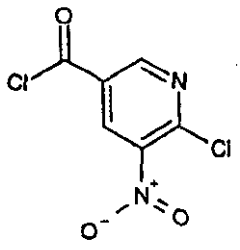


X

(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.

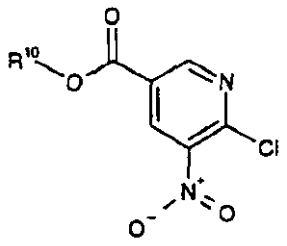
9. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH and R^1 is H or CH_3, comprising

(a) reacting a compound of the Formula II



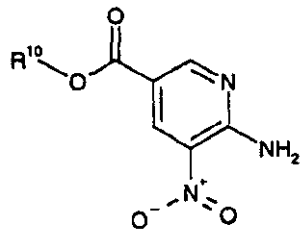
II

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



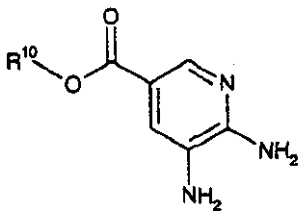
XI

(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



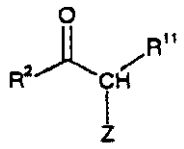
XII

(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



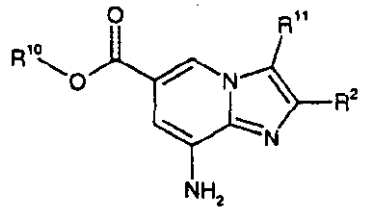
XIII

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



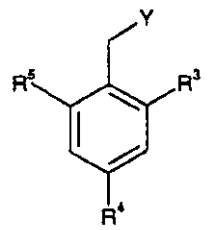
XIV

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



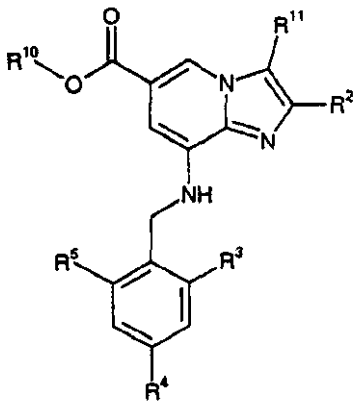
XV

(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



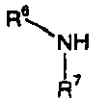
IX

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

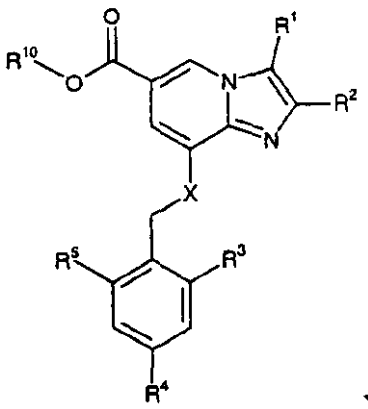


III

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.

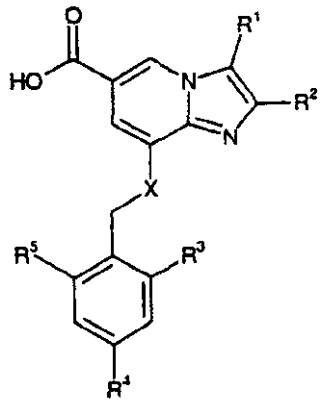
10. A process for the preparation of a compound according to any one of claims 1 to 5 comprising

(a) treating a compound of Formula XVII



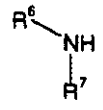
XVII

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

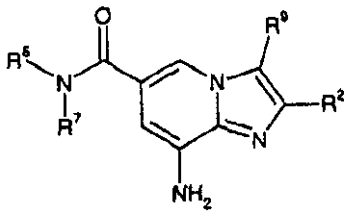
compound as claimed in any one of claims 1 to 5, wherein the said salt is administered in combination with at least one antimicrobial agent.

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.

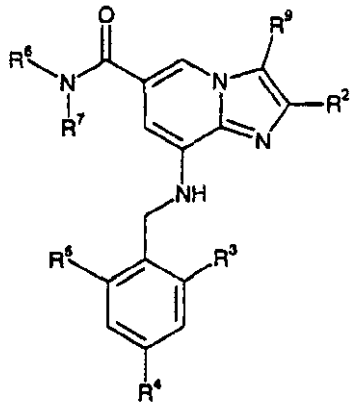
22. A compound of the formula VIII



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.

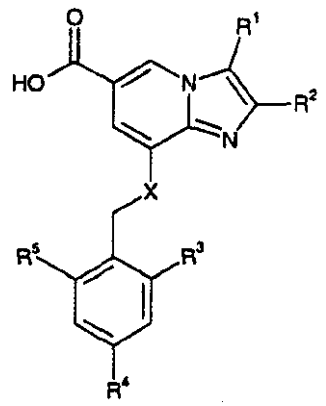
23. A compound of the formula X



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



XVIII

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

[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
C07D471/04
A61K 31/435

[12]发明专利申请公开说明书

[21]申请号 99807799.2

[43]公开日 2001年8月1日

[11]公开号 CN 1306533A

[22]申请日 1999.4.23 [21]申请号 99807799.2
[30]优先权
[32]1998.4.29 [33]SE [31]9801526-6
[86]国际申请 PCT/SE99/00662 1999.4.23
[87]国际公布 WO99/55705 英 1999.11.4
[85]进入国家阶段日期 2000.12.25
[71]申请人 阿斯特拉曾尼卡有限公司
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P·诺尔贝里
I·斯塔克
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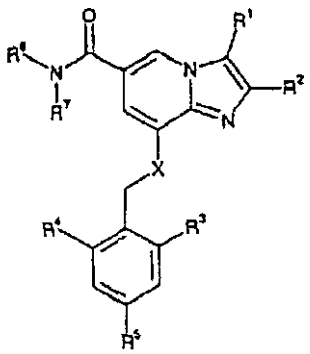
权利要求书13页 说明书33页 附图页数0页

[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,其中所述苯基部分被取代的和其中 所述咪唑并吡啶部分在6-位由甲酰胺基取代,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。



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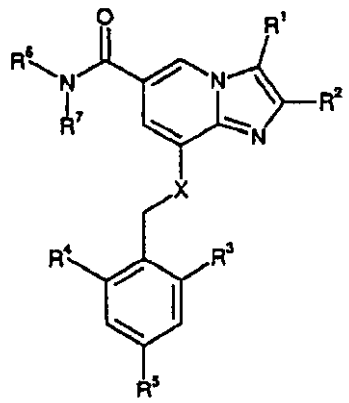
ISSN1008-4274

00.12.25

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，或

(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，或

(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和R^7是可独立选择的取代基，包含C、H、N、O、S、Se、P或卤原子，其提供≤600的分子量的式I化合物，前提为R^6和R^7中至少一个不能是H、C_1-C_6烷基、羟基化的C_1-C_6烷基或C_1-C_6烷氧基-取代的C_1-C_6烷基，和

X是

(a) NH，或

(b) O.

2. 根据式I的化合物或其药学上可接受的盐，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; R^6和R^7独立是(前提为R^6和R^7中至少一个不能是H、C_1-C_6烷基、羟基化的C_1-C_6烷基或C_1-C_6烷氧基-取代的C_1-C_6烷基):

(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，

(e) C_2-C_6链烯基，

(f) C_2-C_6链炔基，

(g) 卤代的C_1-C_6烷基，

(h) C_3-C_8环烷基，

(i) 环烷基-取代的C_1-C_6烷基，

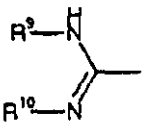
(j) 芳基，其中芳基代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、OH、硝基、氨基、C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-或CN或NH_2SO_2，

(k) 芳基取代的 C_1-C_6 烷基，其中芳基代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、CF_3、OH、硝基、氨基、C_1-C_6 烷基-NH-、(C_1-C_6 烷基)$_2$-N-、CN 或 NH_2SO_2，

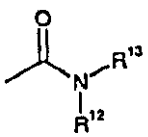
(l) R^8-(C_1-C_6)烷基-，其中 R^8 是 NH_2C=O-、C_1-C_6 烷基-NHC=O-、(C_1-C_6 烷基)$_2$NC=O-、C_1-C_6 烷基-OOC-、NH_2SO_2-、C_1-C_6 烷基-SO_2NH-、$ArSO_2NH$-、氰基、C_1-C_6 烷基-CO-NH-、C_1-C_6 烷基-OOCNH-、C_1-C_6 烷基-O-、C_7-C_{12} 烷基-O-、C_1-C_6 烷基-SO-、C_1-C_6 烷基-S-、C_1-C_6 烷基-SO_2-、C_1-C_6 烷基-C=O-、NH_2-、C_1-C_6 烷基-NH-、(C_1-C_6 烷基)$_2$N-、ArCONH-、Ar(C_1-C_6 烷基)CONH、$ArNHSO_2$-、(Ar)$_2$-N-SO_2-、C_1-C_6 烷基-$NHSO_2$-、ArS-、ArSO-、$ArSO_2$-、ArC=O-、NH_2CONH-、C_1-C_6 烷基-NHCONH-、(C_1-C_6 烷基)$_2$-NCONH-、ArNHCONH-、(C_1-C_6 烷基)$_2$-N-SO_2-、Ar-O-、Ar-NH-、Ar(C_1-C_6 烷基)N-、羟基化的 C_1-C_6 烷基-O-或吗啉基；其中 Ar 代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、CF_3、OH、CN、硝基、氨基、C_1-C_6 烷基-NH-或(C_1-C_6 烷基)$_2$N-，

(m) C_7-C_{12}，

(n) OH、O-C_1-C_6 烷基或 O-羟基化的 C_1-C_6 烷基，

(o)  其中 R^9 和 R^{10} 独立为 H 或 C_1-C_6 烷基，

(p) R^{11}-(C_1-C_6)烷基-COO-(C_1-C_6)烷基-，其中 R^{11} 是 HOOC-、C_1-C_6 烷基-OOC-或具有下式的氨基羰基：



其中 R^{12}、R^{13} 为相同或不同的 H 或 C_1-C_6 烷基，

R^6 和 R^7 与它们所连接的氮原子一起形成任选含有一个或多个另外的

杂原子的饱和或不饱和环(例如吗啉、哌嗪、吡咯烷、哌啶)，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、OH、硝基、氨基、C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-、CN、NH_2SO_2、苯基、NH_2CO-、C_1-C_6烷基-CO-，所述环可与芳环稠合(例如四氢喹啉)。

3. 根据权利要求1或2的化合物，其中R^1是CH_3或CH_2OH；R^2是CH_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；R^6和R^7独立是(前提为R^6和R^7中至少一个不能是H、C_1-C_6烷基、羟基化的C_1-C_6烷基或C_1-C_6烷氧基-取代的C_1-C_6烷基)：

(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，

(e) 卤代的C_1-C_6烷基，

(f) 芳基，其中芳基代表苯基、吡啶基、咪唑基、吲哚基或萘基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、OH、C_1-C_6烷基-MH-、(C_1-C_6烷基)$_2$-N-或CN，

(g) C_1-C_6烷基取代的芳基，其中芳基代表苯基、吡啶基、咪唑基、吲哚基或萘基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3或OH，

(h) R^8-(C_1-C_6)烷基-，其中R^8是NH_2C=O-、C_1-C_6烷基-NHC=O-、(C_1-C_6-烷基)$_2$NC=O-、C_1-C_6烷基-OOC-、氰基、C_1-C_6烷基-CO-NH-、C_1-C_6烷基-OOCNH-、C_1-C_6烷基-O-、C_7-C_{12}烷基-O-、C_1-C_6烷基-SO-、C_1-C_6烷基-S-、C_1-C_6烷基-C=O-、ArCONH-、Ar(C_1-C_6烷基)CONH、ArC=O-、NH_2CONH-、C_1-C_6烷基-NHCONH-、(C_1-C_6烷基)$_2$-NCONH-、ArNHCONH-、羟基化的C_1-C_6烷基-O-或吗啉基；其中Ar代表苯基、吡啶基、咪唑基、吲哚基或萘基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、

OH、 CN，

(i) C_7-C_{12}烷基，

(j) OH，

(k) R^{11}-(C_1-C_6)烷基-COO-(C_1-C_6)烷基-，其中R^{11}是HOOC或C_1-C_6烷基-OOC，

R^6和R^7与它们所连接的氮原子一起形成任选含有一个或多个另外的杂原子的饱和或不饱和环(例如吗啉、哌嗪、吡咯烷、哌啶)，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、OH、硝基、氨基、CN、NH_2SO_2、苯基、NH_2CO-、C_1-C_6烷基-CO-，所述环可与芳环稠合(例如四氢喹啉).

4. 根据权利要求1-3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-甲基苄氨基)-6-(吗啉代羰基)-咪唑并[1,2-a]吡啶,

N-(4-乙氧基苯基)-8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[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)-2,3-二甲基咪唑并[1,2-a]吡啶-基)(4-甲基哌嗪基)甲酮,

1-((8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)-2-(s)-吡咯烷甲酰胺,

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

(2-乙基-6-甲基苄氨基)-N-(2-(2-羟基乙氧基)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)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)(3-羟基-1-吡咯烷基)甲酮,

N-(3,4-二羟基苯乙基)-8-(2-乙基-6-甲基苄氨基)-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-3-(羟甲基)-2-甲基-6-(吗啉基羰基)-咪唑并[1,2-a]吡啶,

N-((8-(2-乙基-6-甲基苄基)氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)胍,

4-(2-(((8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)氨基)乙氧基)-4-氧代丁酸.

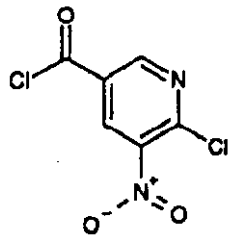
5. 根据权利要求 1-4 中任一项的化合物为盐酸盐或甲磺酸盐.

6. 含有根据权利要求 1-5 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. 含有根据权利要求 1-5 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. 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，包括:

(a)使式 II 化合物

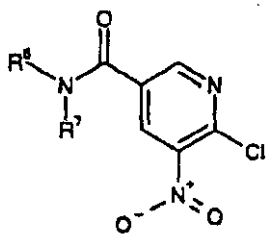


II

与式 III 化合物

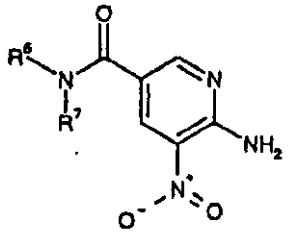
III

其中 R^6 和 R^7 如式 I 所定义，在惰性溶剂中反应得到通式 IV 化合物，



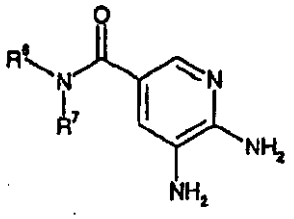
IV

(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，



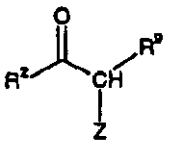
V

(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，



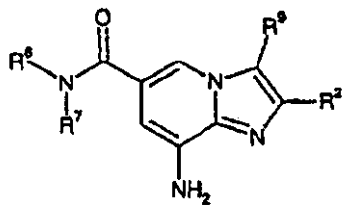
VI

(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

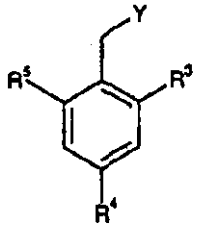
其中 R^2 如权利要求 1 中所定义，Z 是离去基团和 R^9 代表 H、CH_3 或酯基，在惰性溶剂中，在有碱或没有碱存在下反应得到式 VIII 化合物，



VIII

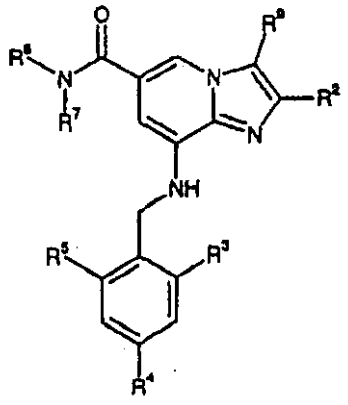
(e)使式 XIII 化合物，其中 R^6、R^7 和 R^2 如权利要求 1 中所定义和

R^9是H、 CH_3或酯基，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，

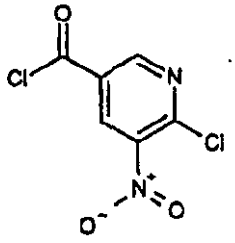


X

(f)将式X化合物，其中R^9是酯基，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．

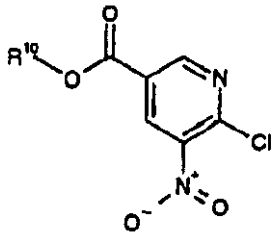
9. 制备根据权利要求1-5中任一项的化合物的方法，其中X是NH和R^1是H或CH_3，包括:

(a)使式II化合物



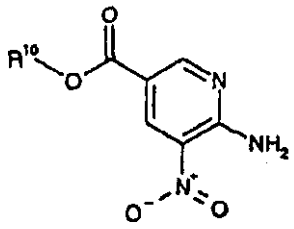
II

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，



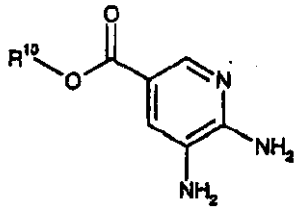
XI

(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，



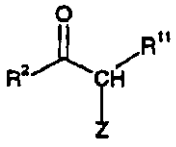
XII

(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，



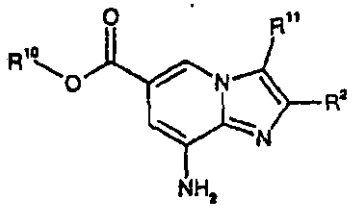
XIII

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



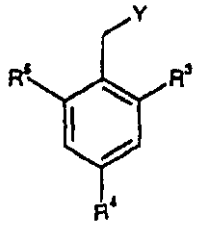
XIV

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，



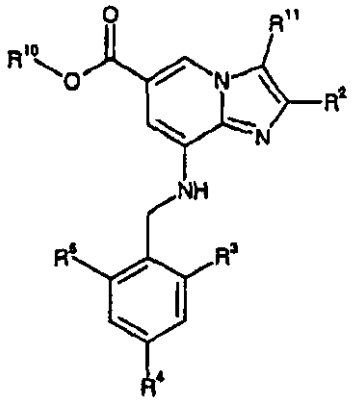
XV

(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



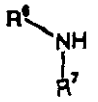
IX

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 如权利要求 I 中所定义，R^{10} 是烷基和 R^{11} 是 H 或 CH_3，与式 III 化合物

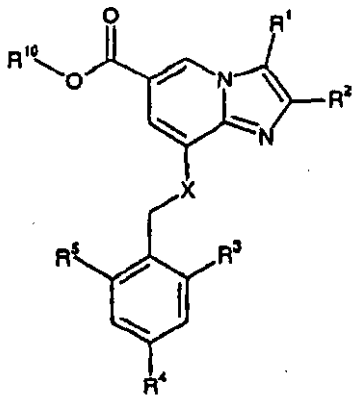


III

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

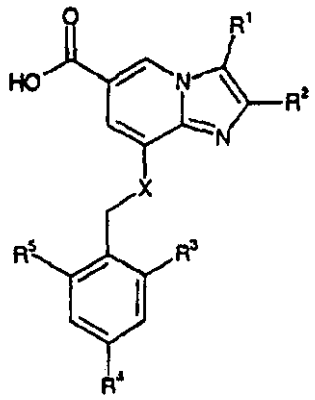
10. 制备根据权利要求 1-5 任一项的化合物的方法，包括:

(a)用酸或碱，在标准条件下处理式 XVII 化合物



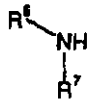
XVII

其中 R^1、R^2、R^3、R^4、R^5和 X 如权利要求 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 如权利要求 1 中所定义，与式 III 化合物



III

其中 R^6和 R^7如权利要求 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(Helicobacter 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. 抑制胃酸分泌的方法，该方法包括给予需要此抑制作用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. 治疗胃肠炎性疾病的方法，该方法包括给予需要此治疗作用

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.

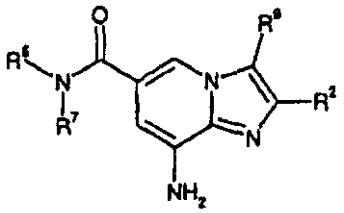
18. 治疗或预防由人胃粘膜幽门螺旋菌感染所引起的疾病的方法，该方法包括给予需要此治疗作用的哺乳动物包括人有效量的根据权利要求 1-5 中任一项的化合物，其中所述盐与至少一种抗菌剂组合给药.

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.

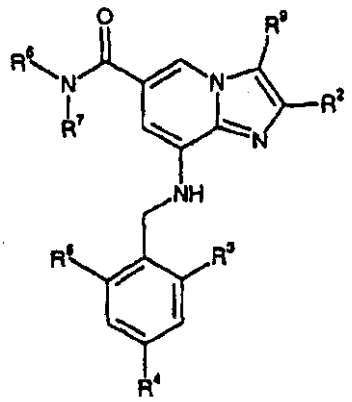
22. 式 VIII 化合物



VIII

其中 R^2、R^6和 R^7如权利要求 1 中所定义，R^9是 H、CH_3或酯基.

23. 式 X 化合物

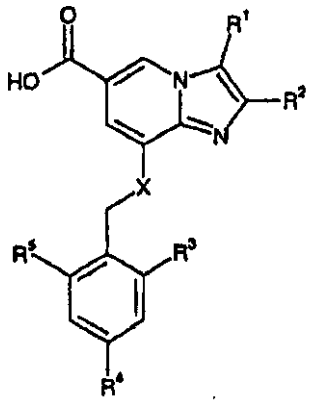


X

其中 R^2、R^3、R^4、R^5、R^6和 R^7如权利要求 1 中所定义，和 R^9是酯基.

00.12.25

24. 下式化合物



XVIII

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

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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药学上可接受的盐，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药学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

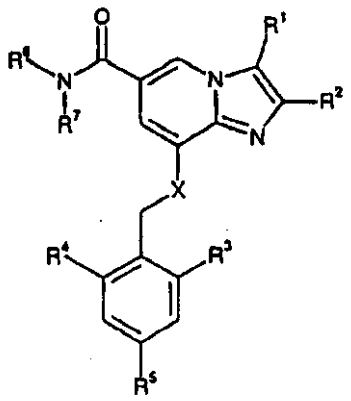
用于治疗消化性溃疡疾病的取代的咪唑并[1,2-a]吡啶为本领域内已知的化合物，例如可从 EP-B-0033094 和 US 4,450,164 (Schering Corporation)中；从 EP-B-0204285 和 US 4,725,601(Fujisawa Pharmaceutical Co.)中；和从 J.J.Kaminski 等在药物化学杂志(28 卷, 876-892, 1985; 30 卷, 2031-2046, 1987; 30 卷, 2047-2051, 1987; 32 卷, 1686-1700, 1989 和 34 卷, 533-541, 1991)中所发表的内容得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

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。在 6-位上的甲酰胺基可任意选择以便提供≤600 的分子量的式 I 化合物。

因此，在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，或

(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，或

(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和R^7是可独立选择的取代基，包含C、H、N、O、S、Se、P和卤原子，它提供≤600的分子量的式I化合物，前提为R^6和R^7中至少一个不能是H、C_1-C_6烷基、羟基化的C_1-C_6烷基或C_1-C_6烷氧基-取代的C_1-C_6烷基，和

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。

取代基R^6和R^7定义为独立选择的取代基，包含C、H、N、O、S、Se、P或卤原子，它们提供≤600的分子量的式I化合物，此定义本领域技术人员很容易理解。

在该定义的范围内的取代基实例包括，但不限于：

(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，

(e)C_2-C_6链烯基，

(f)C_2-C_6链炔基，

(g)卤代的C_1-C_6烷基，

(h)C_3-C_8环烷基，

(i)环烷基-取代的C_1-C_6烷基，

(j)芳基，其中芳基代表苯基、吡啶基、嘧吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、

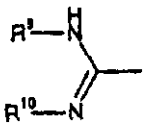
C_1-C_6烷基、 C_1-C_6烷氧基、 CF_3、 OH、硝基、氨基、 C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-或 CN 或 NH_2SO_2，

(k)C_1-C_6烷基取代的芳基，其中芳基代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、 C_1-C_6烷基、 C_1-C_6烷氧基、 CF_3、 OH、硝基、氨基、 C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-、 CN 或 NH_2SO_2，

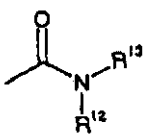
(l)R^8-(C_1-C_6)烷基-，其中 R^8 是 NH_2C=O-、 C_1-C_6烷基-NHC=O-、(C_1-C_6烷基)$_2$NC=O-、 C_1-C_6烷基-OOC-、 NH_2SO_2-、 C_1-C_6烷基-SO_2NH-、 $ArSO_2NH$-、氰基、 C_1-C_6烷基-CO-NH-、 C_1-C_6烷基-OOCNH-、 C_1-C_6烷基-O-、 C_7-C_{12}烷基-O-、 C_1-C_6烷基-SO-、 C_1-C_6烷基-S-、 C_1-C_6烷基-SO_2-、 C_1-C_6烷基-C=O-、 NH_2-、 C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$N-、 ArCONH-、 Ar(C_1-C_6烷基)CONH、 $ArNHSO_2$-、 (Ar)$_2$-N-SO_2-、 C_1-C_6烷基-$NHSO_2$-、 ArS-、 ArSO-、 $ArSO_2$-、 ArC=O-、 NH_2CONH-、 C_1-C_6烷基-NHCONH-、(C_1-C_6烷基)$_2$-NCONH-、 ArNHCONH-、 Ar-O-、 Ar-NH-、 Ar(C_1-C_6烷基)N-、(C_1-C_6烷基)$_2NSO_2$-、羟基化的 C_1-C_6烷基-O-或吗啉基；其中 Ar 代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、 C_1-C_6烷基、 C_1-C_6烷氧基、 CF_3、 OH、 CN、硝基、氨基、 C_1-C_6烷基-NH-或(C_1-C_6烷基)$_2$N-，

(m)C_7-C_{12}，

(n)OH、 O-C_1-C_6烷基或 O-羟基化的 C_1-C_6烷基，

(o)  其中 R^9 和 R^{10} 各独立为 H 或 C_1-C_6烷基，

(p)R^{11}-(C_1-C_6)烷基-COO-(C_1-C_6)烷基-，其中 R^{11} 是 HOOC、 C_1-C_6烷基-OOC-或具有下式的氨基羰基：



其中 R^{12}、R^{13} 为相同或不同的 H 或 C_1-C_6 烷基，

R^6 和 R^7 与它们所连接的氮原子一起形成任选含有一个或多个另外的杂原子的饱和或不饱和环(例如吗啉、哌嗪、吡咯烷、哌啶)，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6 烷基、C_1-C_6 烷氧基、CF_3、OH、硝基、氨基、C_1-C_6 烷基-NH-、$(C_1$-C_6 烷基$)_2$-N-、CN、NH_2SO_2、苯基、NH_2CO-、C_1-C_6 烷基-CO-，所述环可与芳环稠合(例如四氢喹啉)。

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，优选使用适合形成药学上可接受的盐的酸。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。

根据本发明优选的化合物是式 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; R^6和R^7独立是(前提为R^6和R^7中至少一个不能是H、 C_1-C_6烷基、羟基化的C_1-C_6烷基或C_1-C_6烷氧基-取代的C_1-C_6烷基):

(a)H，

(b)C_1-C_6烷基，

(c)羟基化C_1-C_6烷基，

(d)C_1-C_6烷氧基-取代的C_1-C_6烷基，

(e)C_2-C_6链烯基，

(f)C_2-C_6链炔基，

(g)卤代的C_1-C_6烷基，

(h)C_3-C_8环烷基，

(i)环烷基-取代的C_1-C_6烷基，

(j)芳基，其中芳基代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、 OH、硝基、氨基、C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-或CN或NH_2SO_2，

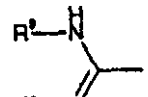
(k)C_1-C_6烷基取代的芳基，其中芳基代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、 OH、硝基、氨基、C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-、 CN或NH_2SO_2，

(l)R^8-(C_1-C_6)烷基-，其中R^8是NH_2C=O-、 C_1-C_6烷基-NHC=O-、(C_1-C_6烷基)$_2$NC=O-、 C_1-C_6烷基-OOC-、 NH_2SO_2-、 C_1-C_6烷基-SO_2NH-、 $ArSO_2$NH-、氰基、 C_1-C_6烷基-CO-NH-、 C_1-C_6烷基-OOCNH-、 C_1-C_6烷基-O-、 C_7-C_{12}烷基-O-、 C_1-C_6烷基-SO-、 C_1-C_6烷基-S-、 C_1-C_6烷基-SO_2-、 C_1-C_6烷基-C=O-、 NH_2-、 C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$N-、 ArCONH-、 Ar(C_1-C_6烷基)CONH、$ArNHSO_2$-、(Ar)$_2$-N-SO_2-、 C_1-C_6烷基-$NHSO_2$-、 ArS-、 ArSO-、

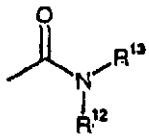
$ArSO_2$-、 ArC=O-、 NH_2CONH-、 C_1-C_6烷基-NHCONH-、(C_1-C_6烷基)$_2$-NCONH-、 ArNHCONH-、(C_1-C_6烷基)$_2$-N-SO_2-、 Ar-O-、 Ar-NH-、 Ar(C_1-C_6烷基)N-、(C_1-C_6烷基)$_2$NSO_2-、羟基化的 C_1-C_6烷基-O-或吗啉基；其中 Ar 代表苯基、吡啶基、噻吩基、咪唑基、吲哚基、萘基或呋喃基，任选由选自以下的一个或多个取代基取代：卤素、 C_1-C_6烷基、 C_1-C_6烷氧基、 CF_3、 OH、 CN、硝基、氨基、 C_1-C_6烷基-NH-或(C_1-C_6烷基)$_2$N-，

(m)C_7-C_{12}，

(n)OH、 O-C_1-C_6烷基或 O-羟基化的 C_1-C_6烷基，

(o)  其中 R^9和 R^{10}各独立为 H 或 C_1-C_6烷基，

(p)R^{11}-(C_1-C_6)烷基-COO-(C_1-C_6)烷基-，其中 R^{11}是 HOOC-、 C_1-C_6烷基-OOC-或具有下式的氨基羰基：



其中 R^{12}、 R^{13}为相同或不同的 H 或 C_1-C_6烷基，

R^6和 R^7与它们所连接的氮原子一起形成任选含有一个或多个另外的杂原子的饱和或不饱和环(例如吗啉、哌嗪、吡咯烷、哌啶)，任选由选自以下的一个或多个取代基取代：卤素、 C_1-C_6烷基、 C_1-C_6烷氧基、 CF_3、 OH、硝基、氨基、 C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-、 CN、 NH_2SO_2、苯基、 NH_2CO-、 C_1-C_6烷基-CO-，所述环可与芳环稠合(例如四氢喹啉)。

根据本发明更优选的化合物是式 I 化合物，其中 R^1是 CH_3或 CH_2OH; R^2是 CH_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; R^6和 R^7独立是(前提为 R^6和 R^7中至少一个不能是 H、 C_1-C_6烷基、羟基化的 C_1-C_6烷基或 C_1-C_6烷氧基-取代的 C_1-C_6烷基)：

(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，

(e)卤代的C_2-C_6烷基，

(f)芳基，其中芳基代表苯基、吡啶基、咪唑基、吲哚基或萘基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、OH、C_1-C_6烷基-NH-、(C_1-C_6烷基)$_2$-N-或CN，

(g)C_1-C_6烷基取代的芳基，其中芳基代表苯基、吡啶基、咪唑基、吲哚基或萘基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3或OH，

(h) R^8-(C_1-C_6)烷基-，其中R^8是NH_2C=O-、C_1-C_6烷基-NHC=O-、(C_1-C_6-烷基)$_2$NC=O-、C_1-C_6烷基-OOC-、氰基、C_1-C_6烷基-CO-NH-、C_1-C_6烷基-OOCNH-、C_1-C_6烷基-O-、C_7-C_{12}烷基-O-、C_1-C_6烷基-SO-、C_1-C_6烷基-S-、C_1-C_6烷基-C=O-、-ArCONH-、Ar(C_1-C_6烷基)CONH、ArC=O-、NH_2CONH-、C_1-C_6烷基-NHCONH-、(C_1-C_6烷基)$_2$-NCONH-、ArNHCONH-、羟基化的C_1-C_6烷基-O-或吗啉基；其中Ar代表苯基、吡啶基、咪唑基、吲哚基或萘基，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、OH、CN，

(i) C_7-C_{12}烷基，

(j) OH，

(k) R^{11}-(C_1-C_6)烷基-COO-(C_1-C_6)烷基-，其中R^{11}是HOOC-或C_1-C_6烷基-OOC，

R^6和R^7与它们所连接的氮原子一起形成任选含有一个或多个另外的杂原子的饱和或不饱和环(例如吗啉、哌嗪、吡咯烷、哌啶)，任选由选自以下的一个或多个取代基取代：卤素、C_1-C_6烷基、C_1-C_6烷氧基、CF_3、OH、硝基、氨基、CN、NH_2SO_2、苯基、NH_2CO-、C_1-C_6

烷基-CO-，所述环可与芳环稠合(例如四氢喹啉).

根据本发明最优选的化合物是:

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-6-(吗啉代羰基)-咪唑并[1,2-a]吡啶

N-(4-乙氧基苯基)-8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[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)-2,3-二甲基咪唑并[1,2-a]吡啶-基)(4-甲基哌嗪基)甲酮

1-((8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)-2-(s)-吡咯烷甲酰胺

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

(2-乙基-6-甲基苄氨基)-N-(2-(2-羟乙氧基)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)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)(3-羟基-1-吡咯烷基)甲酮

N-(3,4-二羟基苯乙基)-8-(2-乙基-6-甲基苄氨基)-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-3-(羟甲基)-2-甲基-6-(吗啉代羰基)-咪唑并[1,2-a]吡啶

N-((8-(2-乙基-6-甲基苄基)氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)胍

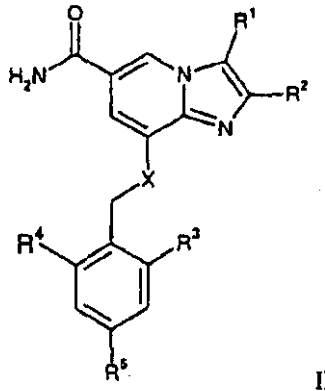
4-(2-(((8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)氨基)乙氧基)-4-氧代丁酸.

制备

本发明也提供下列制备通式I化合物的方法.

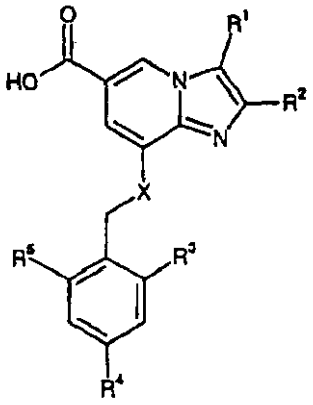
用于制备通式I化合物的方法包括以下步骤:

a)式II化合物



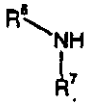
II

其中R^1、R^2、R^3、R^4、R^5和X如在式I中所定义，在标准条件下可被水解得到相应的羧酸得到相应的式III羧酸化合物，



III

b)式III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，可与式IV氨基化合物



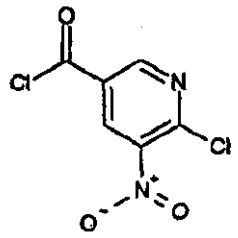
IV

其中R^6和R^7如在式I中所定义，在偶合试剂存在下反应得到相应的式I酰胺化合物．该反应可在惰性溶剂中，在标准条件下进行．

本发明也提供以下制备通式II的中间体化合物的方法．

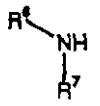
制备通式II化合物的方法，其中X是NH，包括以下步骤:

(a)使通式V化合物



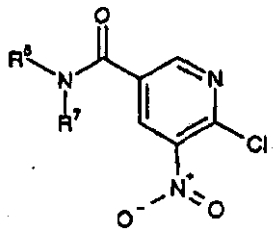
V

与通式 IV 的氨基化合物反应



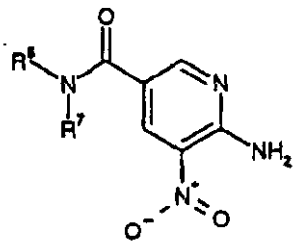
IV

其中 R^6 和 R^7 都是氢，得到相应的式 VI 酰胺. 该反应可在标准条件下，在惰性溶剂中进行，



VI

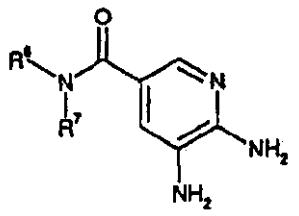
b)通式 VI 化合物可与氨反应得到通式 VII 化合物



VII

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

c) 通过使用氢和催化剂如 Pd/c，可以将式 VII 化合物还原为式 VIII 化合物

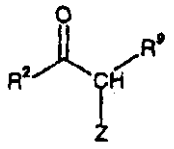


VIII

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

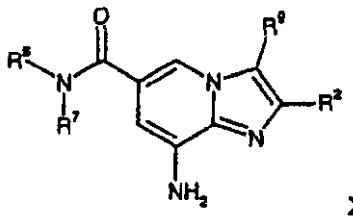
d) 式 X 化合物咪唑并[1,2-a]吡啶可通过式 VIII 化合物与式 IX 化

合物反应制备



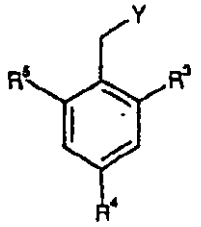
IX

其中 R^2 如在式 I 中所定义，Z 是离去基团，例如卤素、甲磺酰基、甲苯磺酰基，R^9 代表 H、CH_3 或酯基例如 $COOCH_3$、$COOC_2H_5$ 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，



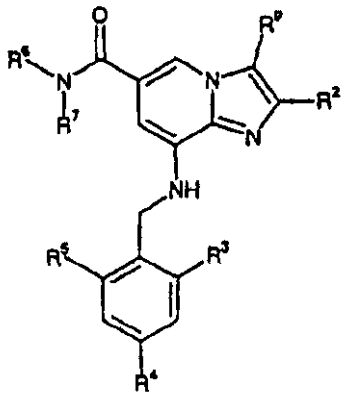
X

e)式 X 化合物可与式 XI 化合物反应



XI

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



XII

其中 R^2、R^3、R^4 和 R^5 如式 I 中所定义，R^6 和 R^7 都是氢，R^9 是 H、CH_3 或酯基如 $COOCH_3$、$COOC_2H_5$ 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，在有或没有碱存在下进行反应．该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)例如通过使用硼氢化锂在惰性溶剂例如四氢呋喃或乙醚中，还原通式XII化合物，其中R^9是酯基，得到为通式I的化合物，其中R^1是CH_2OH，R^6和R^7都是氢．

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药学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．所述载体可以是固体、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)感染所引起的疾病. 其它活性成分可以是抗菌剂，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.

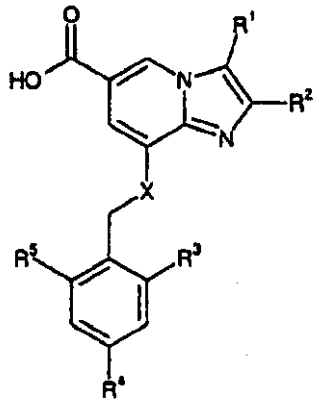
根据本发明的化合物可与解酸药例如氢氧化铝、碳酸镁和氢氧化镁或藻酸一起或以组合的形式同时、分别或按顺序使用，或者与抑制胃酸分泌的药物例如 H2-受体阻断剂(例如西米替丁、雷尼替丁)、H^+/K^+-ATP 酶抑制剂(例如奥美拉唑、泮托拉唑、兰索拉唑或雷贝拉唑)一起或以组合的形式同时、分别或按顺序使用,或者与胃动力药(gastroprokinetics) (例如西沙必利、莫沙必利) 一起或以组合的形式同时、分别或按顺序使用.

中间体

本发明的另一方面是用于合成根据本发明的化合物中的新的中间体化合物.

因此，本发明包括:

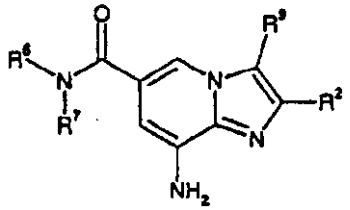
(a)式 XVIII 化合物



XVIII

其中 R^1、R^2、R^3、R^4、R^5和 X 如式 I 所定义;

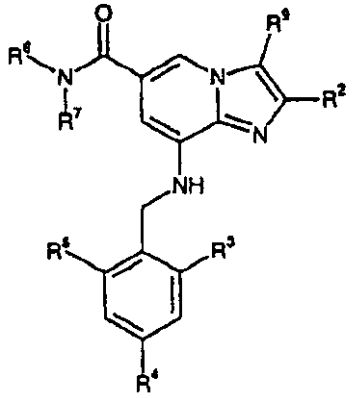
(b)式 VIII 化合物



VIII

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

(c)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是酯基例如 $COOCH_3$、$COOC_2H_5$等.

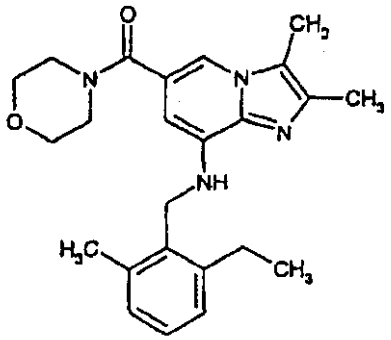
实施例

1.本发明化合物的制备

00.12.25

实施例 1.1

2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-6-(吗啉代羰基)-咪唑并[1,2-a]吡啶的合成

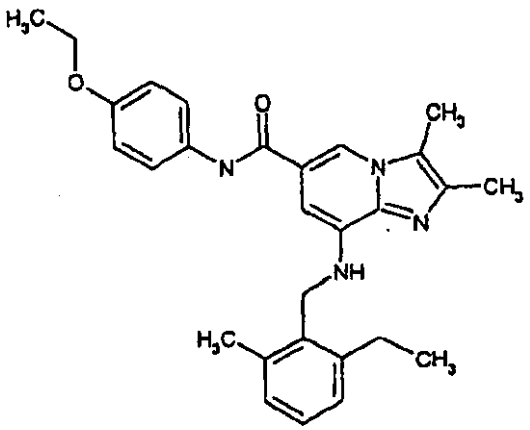


将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.15 g, 0.44 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓(uronium)四氟硼酸盐(TBTU)(0.14g, 0.44 mmol)加入到二氯甲烷(10 ml)中. 加入吗啉(0.12 g, 1.4 mmol)并在室温下搅拌该反应混合物 1.5 小时. 将该反应混合物与硅胶一起加入到柱中, 用乙酸乙酯:二氯甲烷(1:1)作为洗脱剂, 经层析纯化得到 0.12 g(66 %)所需产物.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.32 (s, 3H), 2.35(s, 3H), 2.37(s, 3H), 2.7(q, 2H), 3.7 (s, 8H), 4.35 (d, 2H), 4.95 (bs, 1H), 6.15 (s, 1H), 7.0-7.2(m, 3H), 7.4(s, 1H).

实施例 1.2

N-(4-乙氧基苯基)-8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成

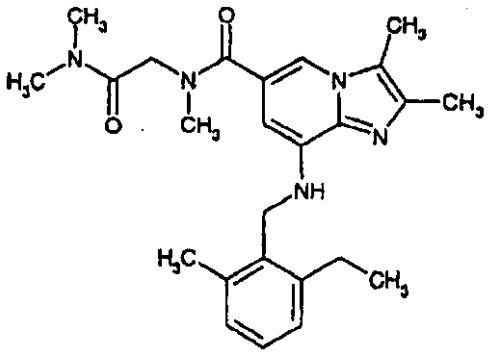


将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.15 g, 0.44 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.14g, 0.44 mmol)加入到二氯甲烷(10 ml)中. 加入 4-乙氧基苯胺(0.19 g, 1.4 mmol)并将该反应混合物在室温下搅拌 72 小时. 在减压下蒸发溶剂并将残余物与硅胶一起加入到柱中, 用二氯甲烷:甲醇(95:5)为洗脱剂, 经层析纯化. 用热的己烷:乙酸乙酯(2:1)的混合物处理该残余物, 滤出产物并干燥得到 0.14 g(74 %)所需的产物, 为白色结晶.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.2(t, 3H), 1.4 (s, 3H,), 2.35 (s, 9H), 2.65 (q, 2H), 4.0(q, 2H), 4.35 (d, 2H), 4.9(t, 1H), 6.55 (s, 1H), 6.85 (d, 2H), 7.0-7.2 (m, 3H), 7.5 (d, 2H), 7.9 (s, 1H), 8.15 (s, 1H).

实施例 1.3

N-[2-(二甲基胺)-2-氧代乙基]-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



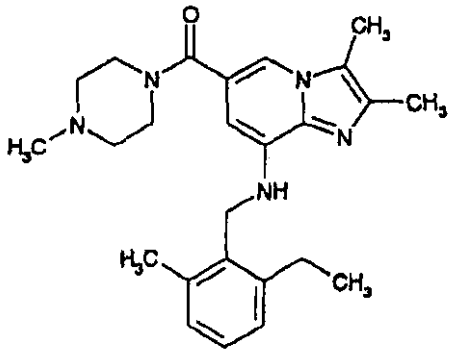
将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.13 g, 0.38 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.12g, 0.38 mmol)加入到二氯甲烷(10 ml)中. 加入 N,N-二甲基-2-甲基氨基-乙酰胺(0.088g, 0.38 mmol)并将该反应混合物在室温下搅拌 1 小时. 在减压下蒸发溶剂并用二氯甲烷:甲醇(95:5)为洗脱剂, 经柱层析纯化该残余物得到 80 mg(48 %)的标题产物.

^{1}H-NMR (500 MHz,$CDCl_3$): δ 1.2(t, 3H), 2.3 (s, 6H), 2.35 (s, 3H), 2.65(q, 2H), 2.75(s, 6H), 2.95 (s, 3H), 3.15(s, 2H), 4.35 (bs, 2H), 4.85 (bs,

1H), 6.25 (s, 1H), 7.0-7.2 (m, 3H), 7.45 (s, 1H).

实施例 1.4

(8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-基)(4-甲基哌嗪基)甲酮的合成

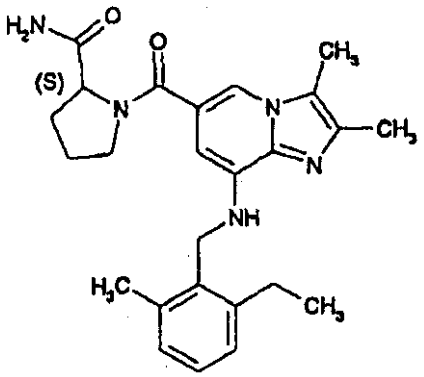


将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.5 g, 1.48 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.48g, 0.15 mmol)加入到二氯甲烷(20 ml)中并将该混合物搅拌 5 分钟. 加入 N-甲基哌嗪(0.16 g, 1.6 mmol)并在室温下搅拌该反应混合物过夜. 在减压下蒸发溶剂, 用二氯甲烷:甲醇(9:1)为洗脱剂在硅胶上用柱层析纯化该残余物得到 0.46g(74%)的标题化合物.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.22 (t, 3H), 2.34 (s, 3H), 2.36(s, 3H), 2.38(s,3H), 2.47(bs, 4H), 2.71(q, 2H), 2.80 (s, 3H), 3.65 (bs, 4H), 4.36 (d, 2H), 4.94 (t, 1H), 6.19 (s, 1H), 7.04-7.18(m, 3H), 7.42(s, 1H).

实施例 1.5

1-((8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)-2-(s)-吡咯烷甲酰胺的合成

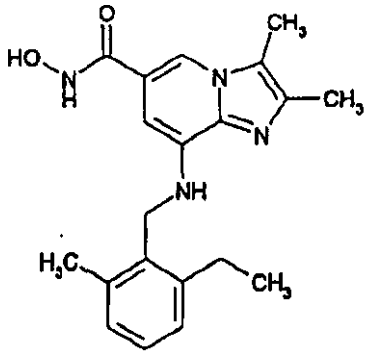


将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.15 g, 0.44 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.14g, 0.45 mmol)和三乙胺(0.05 g, 0.5 mmol)加入到二氯甲烷(10 ml)中并将该混合物搅拌 10 分钟. 加入(s)-脯氨酰胺(0.016 g, 0.45 mmol)并在室温下搅拌该反应混合物 1 小时. 在减压下蒸发溶剂, 用二氯甲烷:甲醇(9:1)为洗脱剂在硅胶上用柱层析纯化该残余物并从乙醚中结晶得到 0.07g(36%)标题化合物.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.21 (t, 3H), 2.1-2.2 (m, 4H), 2.33 (s, 3H), 2.35(s, 3H), 2.37(s, 3H), 2.70(q, 2H), 3.65-3.75(m, 2H), 4.36 (d, 2H), 4.80 (bs, 1H), 4.94 (bs, 1H), 5.88 (s, 1H), 6.33 (s, 1H), 6.98 (s, 1H), 7.04-7.19(m, 3H), 7.54(s, 1H).

实施例 1.6

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



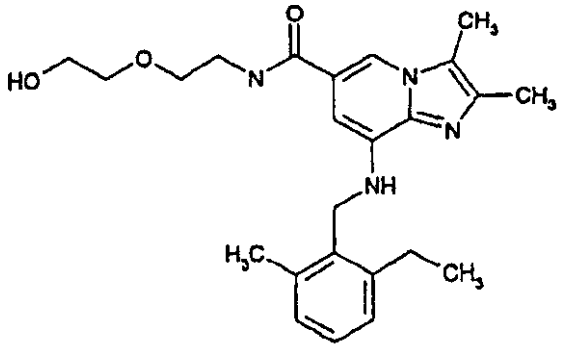
溶于二甲基甲酰胺(5 ml)中的 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.15 g, 0.45 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.14g, 0.45 mmol)、三乙胺(0.1 g, 0 . 99 mmol)和盐酸羟胺(0.031 g, 0.46 mmol).

根据实施例 1.5 制备标题化合物(产率:0.016 g, 10 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.15 (bs, 3H), 2.25 (bs, 9H), 2.6(bs, 2H), 4.25(bs, 2H), 4.95(bs, 1H), 6.45 (bs, 1H), 6.9-7.1 (m, 3H), 7.75 (bs, 1H).

实施例 1.7

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



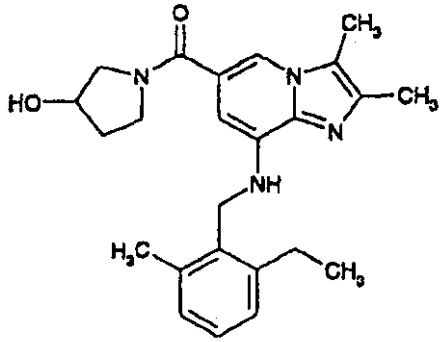
溶于二氯甲烷(10 ml)中的 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.3 g, 0.88 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.29g, 0.90 mmol)和 2-(2-氨基乙氧基)乙醇(0.2 g, 1.9 mmol).

根据实施例 1.5 制备标题化合物(产率:0.24 g, 80 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (t, 3H), 2.25 (s, 3H), 2.3(s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 3.4-3.45 (m, 2H), 3.55-3.7 (m, 6H), 4.35 (d, 2H), 5.05 (t, 1H), 6.45 (s, 1H), 7.0-7.2(m, 4H), 7.5(s, 1H).

实施例 1.8

(8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)(3-羟基-1-吡咯烷基)甲酮的合成



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-

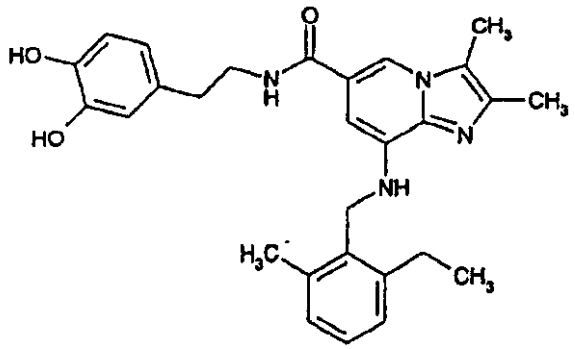
N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.14g, 0.44 mmol)和 3-吡咯烷醇(0.12 g, 1.4 mmol).

根据实施例 1.4 制备标题化合物. 从乙酸乙酯:己烷(2:1)中结晶(产率: 0.24 g, 80 %).

^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.23 (t, 3H), 1.93 (bs, 2H), 2.33(s, 3H), 2.34 (s, 3H), 2.41 (s, 3H), 2.70 (q, 2H), 3.51-3.89 (m, 4H), 4.35 (d, 2H), 4.38-4.55 (m, 1H), 5.04 (bs, 1H), 6.35(s, 1H), 7.01-7.16(m, 3H) , 7.51(s, 1H).

实施例 1.9

N-(3,4-二羟基苯乙基)-8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺的合成



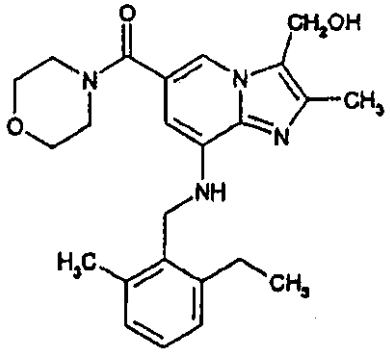
将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.15 g, 0.44 mmol)和 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.14g, 0.45 mmol)加入到二甲基甲酰胺(10 ml)中并将该混合物搅拌 5 分钟. 加入 3,4-二羟基苯乙胺(0.27g, 1.4mmol)和三乙胺(0.28 g, 1.4 mmol)并在室温下搅拌该反应混合物 72 小时. 在减压下蒸发溶剂 , 用二氯甲烷:甲醇(9:1)为洗脱剂在硅胶上用柱层析纯化该残余物并从乙腈中结晶得到 0.059g(28%)标题化合物.

^{1}H-NMR (400 MHz, DMSO-d_6): δ1.15 (t, 1H), 2.22 (s, 3H), 2.33 (s, 3H), 2.37 (s, 3H), 2.65-2.74 (m, 4H), 3.41 (q, 2H), 4.37 (d, 2H), 4.85 (t, 1H), 6.48 (dd, 1H), 6.63-6.66(m, 2H), 6.70(d, 1H), 7.07-7.21(m, 3H) 8.04(d, 1H), 8.49(t, 1H), 8.63(s, 1H), 8.75(s, 1H).

00.12.25

实施例 1.10

8-(2-乙基-6-甲基苄氨基-3-(羟基甲基)-2-甲基-6-(吗啉代羰基)-咪唑并[1,2-a]吡啶的合成



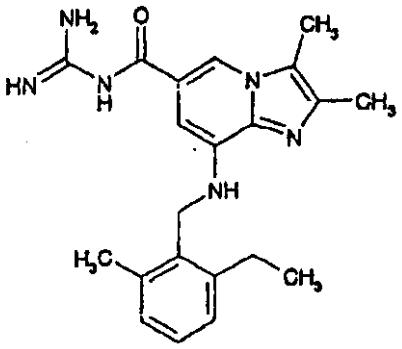
溶于二氯甲烷(1 ml)中的 8-(2-乙基-6-甲基苄氨基)-3-羟基甲基-2-甲基咪唑并[1,2-a]吡啶-6-羧酸(0.012 g, 0.034 mmol)、 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.011g, 0.034 mmol)和吗啉(0.009 g, 0.1 mmol).

根据实施例 1.1 制备标题化合物(产率: 0.008 g, 56 %).

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.23 (t, 3H), 2.33 (s, 3H), 2.39(s, 3H), 2.72 (q, 2H), 3.74 (bs, 8H), 4.37(d, 2H), 4.85(s, 2H), 5.02(t, 1H), 6.27(d, 1H), 7.06-7.22(m, 3H), 7.75(d, 1H).

实施例 1.86

N-((8-(2-乙基-6-甲基苄基)氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)胍的合成



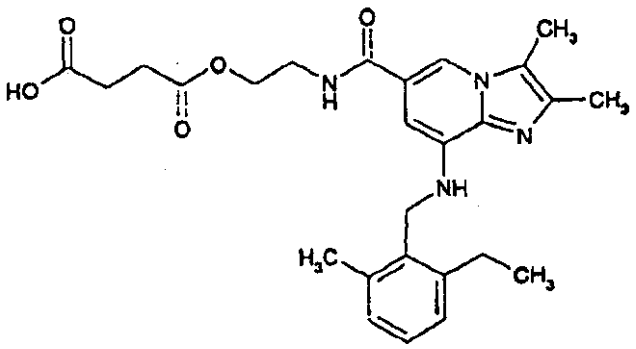
将 2,3-二甲基-8-(2-乙基-6-甲基苄氨基)-咪唑并[1,2-a]吡啶-6-羧酸(0.5 g, 1.5 mmol)、二异丙基乙基胺(0.57g, 1.5 mmol)和碳酸胍(0.53 g, 2.9

mmol)加入到二甲基甲酰胺(10 ml)中，加入 o-苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐(TBTU)(0.48g, 1.5 mmol)并将该反应混合物在 50 ℃下搅拌 3 小时．在减压下蒸发溶剂，用二氯甲烷:甲醇(100:15)为洗脱剂在硅胶上用柱层析纯化该残余物并从乙醚中结晶得到 0.12g(21%)标题化合物．

^{1}H-NMR (500 MHz,$CDCl_3$): δ1.1 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.35 (d, 2H), 4.8 (bs, 1H), 6.9 (s, 1H), 7.05-7.2(m, 3H) 8.25(s, 1H).

实施例 1.87

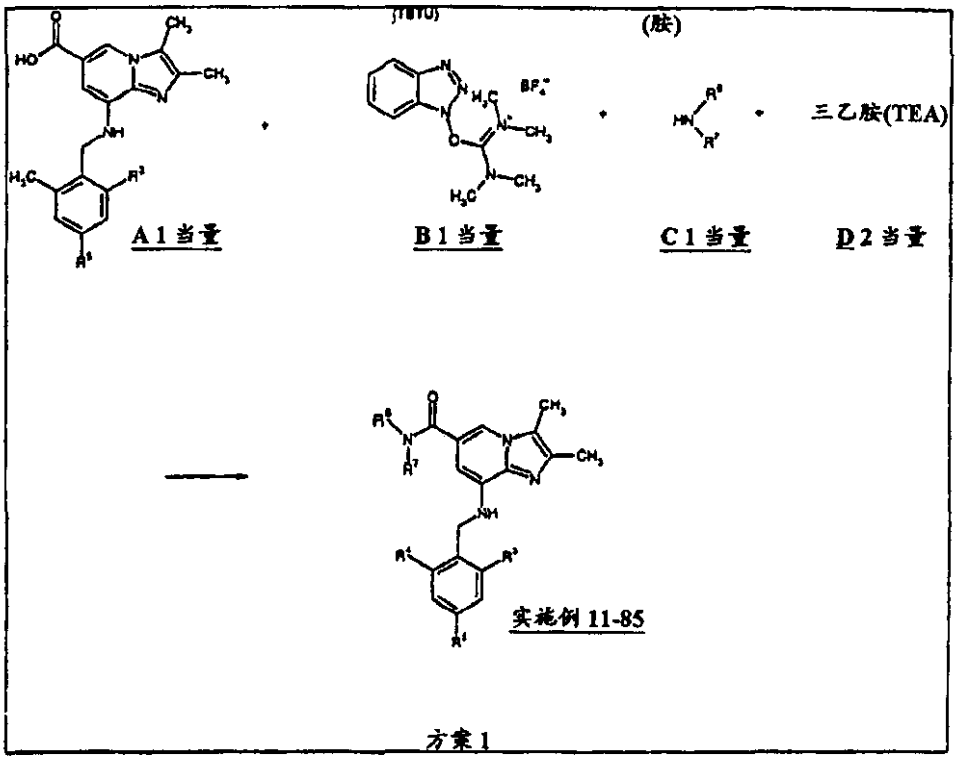
4-(2-(((8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-基)羰基)氨基)乙氧基)-4-氧代丁酸的合成



将 2,3 二甲基-8-(2-乙基-6-甲基苄氨基)-N-羟基乙基-咪唑并[1,2-a]吡啶-6-甲酰胺(250 mg, 0.263 mmol)和琥珀酸酐(100 mg, 1.00 mmol)加入到 7ml 丙酮中．将该混合物回流 48 小时．滤出沉淀的产物并用丙酮和乙醚洗涤得到 288 mg(91 %)的标题化合物．

^{1}H-NMR (500 MHz, DMSO): δ 1.16 (t, 3H), 2.24 (s, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 2.48-2.58(m, 4H), 2.70(q, 2H), 3.54 (q, 2H), 4.19 (t, 2H), 4.39 (d, 2H), 4.90 (t, 1H), 6.72(s, 1H), 7.09-7.22(m, 3H), 8.08(s, 1H), 8.59 (t, 1H), 12.25(s, 1H).

实施例 11-85 用以下方法经平行合成制备:



方案 1

溶液 A: 0.149 mmol 溶于 1 ml 二甲基甲酰胺中

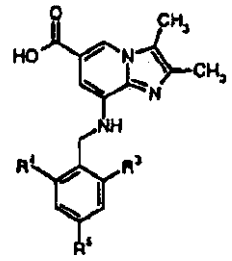
溶液 B (TBTU): 0.297 mmol 溶于 1 ml 二甲基甲酰胺中

溶液 C+D: 胺(C) (0.297 mmol 溶于 1 ml 二甲基甲酰中)+TEA(D) (0.594 mmol 溶于 1 ml 二甲基胺中).

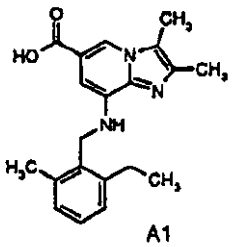
向溶液 A(300 μl)中加入溶液 B(150 μl)和溶液 C+D(150 μl). 在室温下经振动搅拌该反应物过夜. 在减压下蒸发溶剂. 将残余物溶于二氯甲烷/甲醇(9/1)(600 μl)中并通过硅胶(100 mg)塞柱过滤, 用二氯甲烷/甲醇(9/1)(0.5-1.0 ml)洗涤该硅胶. 在减压下蒸发滤液得到所需化合物. (如果需要, 可通过制备性 HPLC 纯化该化合物).

用 HPLC 制备分析样品, 用 LC-质谱鉴定所述化合物. 在实施例 11-85 中制备的所有化合物显示确证所提出结构的质谱.

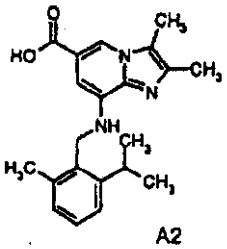
作为所述反应中的起始化合物 A，使用以下化合物.



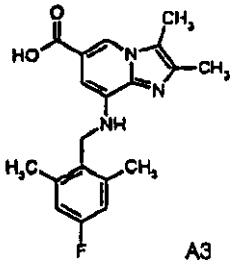
A =



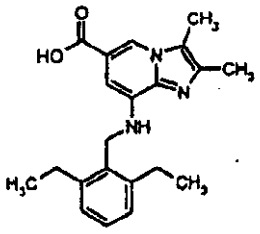
A1



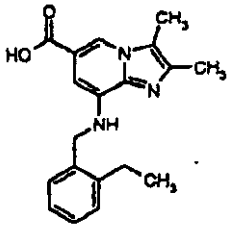
A2



A3

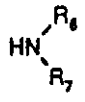


A4

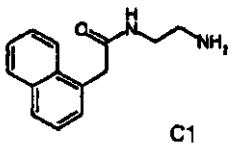


A5

作为反应中的起始化合物C，使用以下胺。

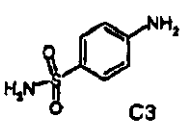


C =

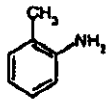


C1

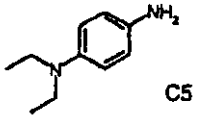
C2



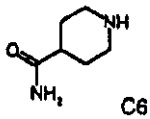
C3



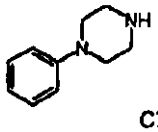
C4



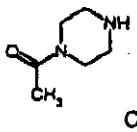
C5



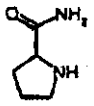
C6



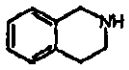
C7



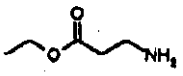
C8



C9

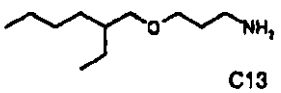


C10

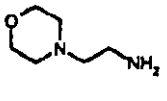


C11

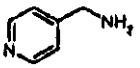
C12



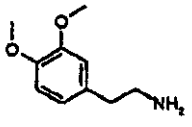
C13



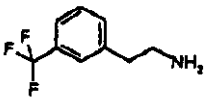
C14



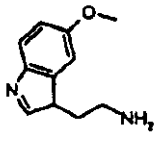
C15



C16



C17

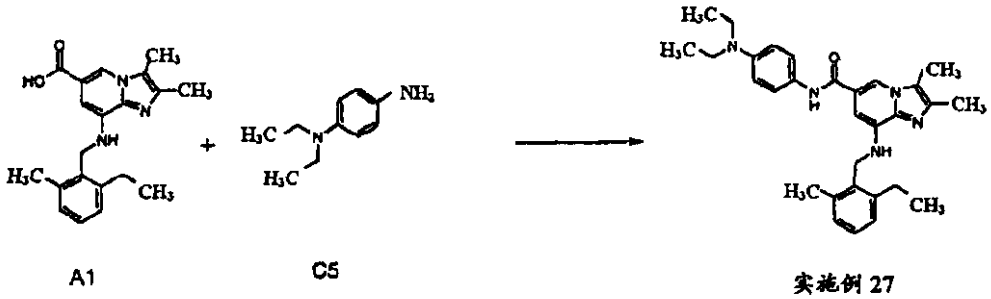


C18

根据方案 1 制备实施例 11-85 .

伯或仲氨基氮为在反应中涉及的氮.

例如 A1 + C5 → 实施例 27



A1 C5 实施例 27

An + Cn → 实施例 11-85

	A1	A2	A3	A4	A5
C1	实施例 11	实施例 12	实施例 13	实施例 14	实施例 15
C2	实施例 16	实施例 17	实施例 18	实施例 19	实施例 20
C3	-	-	-	-	实施例 21
C4	实施例 22	实施例 23	实施例 24	实施例 25	实施例 26
C5	实施例 27	实施例 28	实施例 29	实施例 30	实施例 31
C6	实施例 32	实施例 33	实施例 34	实施例 35	实施例 36
C8	实施例 37	实施例 38	实施例 39	实施例 40	实施例 41
C9	实施例 42	实施例 43	实施例 44	实施例 45	实施例 46
C10	实施例 47	实施例 48	实施例 49	实施例 50	实施例 51
C11	-	实施例 52	实施例 53	实施例 54	实施例 55
C12	-	实施例 56	实施例 57	实施例 58	实施例 59
C13	-	实施例 60	实施例 61	实施例 62	实施例 63
C14	-	-	实施例 64	实施例 65	实施例 66
C15	实施例 67	实施例 68	实施例 69	实施例 70	实施例 71
C16	-	实施例 72	实施例 73	实施例 74	实施例 75
C17	实施例 76	实施例 77	实施例 78	实施例 79	实施例 80
C18	实施例 81	实施例 82	实施例 83	实施例 84	实施例 85

2. 中间体的制备

实施例 2.1

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

将 8-(2-乙基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺(1.0 g, 0.0031 mol)和氢氧化钠(1.2g, 0.031 mol)溶于乙醇(95 %)(30 ml)中并回流过夜. 在减压下蒸发溶剂并向该残余物中加入水. 通过加入浓 HCl(2.6 ml)将 pH 调到 7，经过滤分离出沉淀的固体，用水洗涤并干燥得到 1.0 g (99 %)的标题化合物.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.2 (t, 3H), 2.25 (s, 3H), 2.35(s, 3H), 2.7(q, 2H), 4.45(d, 2H), 6.3(s, 1H), 6.45(t, 1H), 7.05-7.25 (m, 4H), 7.95 (s, 1H).

实施例 2.2

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

将 8-(2,6-二乙基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺(1.5 g, 0.0043 mol)和氢氧化钠(1.7g, 0.043 mol)溶于乙醇(95 %)(30 ml)中.

根据实施例 1.4 制备标题化合物(产率: 1.5 g, 99 %).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 6H), 2.22 (s, 3H), 2.37(s, 3H), 2.67 (q, 4H), 4.37(d, 2H), 4.89 (t, 1H), 6.68(s, 1H), 7.11 (d, 2H), 7.23 (t, 1H), 8.09 (s, 1H).

实施例 2.3

8-(2,6-二甲基-4-氟代苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-羧酸的合成

将 8-(2,6-二甲基-4-氟代苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(1.47 g, 0.0034 mol)和氢氧化钠(1.7g, 0.034 mol)溶于乙醇(95 %)(30 ml)中.

根据实施例 2.1 制备标题化合物(产率: 1.1 g, 95 %).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 2.34(s, 6H), 2.36 (s,

3H), 4.31(d, 2H), 5.04 (bs, 1H), 6.70(s, 1H), 6.90 (d, 2H), 8.02 (s, 1H).

实施例 2.4

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

将 8-(2-异丙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(1.2 g, 0.0027 mol)和氢氧化钠(1.1g, 0.027 mol)溶于乙醇(95 %)(25 ml)中.

根据实施例 2.1 制备标题化合物(产率: 1.1 g, 95 %).

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.69 (d, 6H), 2.74(s, 3H), 2.85 (s, 3H), 2.89 (s, 3H), 3.73 (m, 1H), 4.90(d, 2H), 5.48 (t, 1H), 7.19(s, 1H), 7.55-7.61(m, 1H), 7.70-7.76(m, 2H), 8.60 (s, 1H).

实施例 2.5

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

将 8-(2-乙基-6-甲基苄氨基)-2,3-二甲基咪唑并[1,2-a]吡啶-6-甲酰胺甲磺酸盐(11.0 g, 0.025 mol)和氢氧化钠(7.0g, 0.17 mol)溶于乙醇(95 %)(120 ml)中并回流 20 小时. 在减压下蒸发溶剂并向该残余物中加入水(150 ml). 通过加入浓 HCl 和乙酸将 pH 调到 5，经过滤分离出沉淀的固体，用水和丙酮洗涤，干燥得到 7.6 g (88 %)的标题化合物.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.15 (t, 3H), 2.26 (s, 3H), 2.34(s, 3H), 2.39 (s, 3H), 2.69 (q, 2H), 4.38(d, 2H), 5.2 (bs, 1H), 6.73(s, 1H), 7.07-7.2 (m, 3H), 8.12 (s, 1H).

实施例 2.6

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-羧酸的合成

将 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(0.02 g, 0.057 mmol)和氢氧化钠(0.02g, 0.29 mmol)溶于乙醇(95 %)(1 ml)中并回流 20 小时. 在减压下蒸发溶剂并向该残余物中加入

水(1 ml). 通过加入乙酸将 pH 调到 5，经过滤分离出沉淀的固体，用水洗涤，干燥得到 0.012 g (60 %)的标题化合物.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.14 (t, 3H), 2.22 (s, 3H), 2.33(s, 3H), 2.67 (q, 2H), 4.33(d, 2H), 4.55 (bs, 1H), 4.67(s, 2H), 6.83 (s, 1H), 7.06-7.24 (m, 3H), 8.15 (s, 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，根据产物滴定的体积和浓

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.

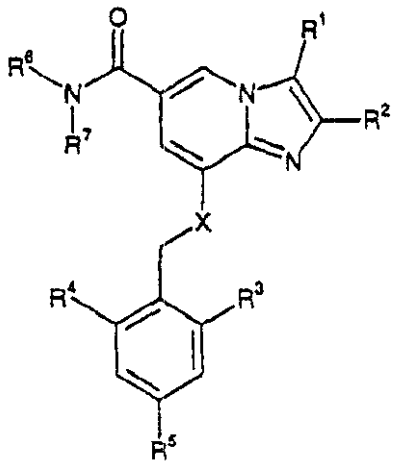
经滴定至 pH 为 7.0 来测定胃液样品的酸度并计算酸产量. 在给予试验物质或溶媒后，在收集期间的酸产量表示为分数响应，设定在上一份给药期间内的酸产量为 1.0 . 从试验化合物和溶媒引起的分数响应计算百分抑制率.

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 %).

HKP0121810

IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

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 carboxamide group in 6-position, which inhibit exogenously or endogeneously stimulated gastric acid secretion and thus ca be used in the prevention and treatment of gastrointestinal inflammatory diseases.



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